Improving the Success of Kidney Transplants

Recent results suggest that blood transfusions reduce the risk of kidney graft rejection even more than does a good tissue match

One of the recent findings in studies of kidney transplantation is that tissue matching, as it is routinely done in this country, is of relatively little value in predicting kidney graft survival. Perhaps even more surprising is the finding that transplantation success is much better in recipients who had previously received blood transfusions than in those who had not. In fact, in some circumstances the transfusion effect can override whatever bad effects might otherwise be attributable to a poor tissue match.

According to G. Melville Williams of the Johns Hopkins University Medical School, "It is no longer justified to give a kidney transplant to an individual who is not transfused. The data are overwhelming." This position marks a complete turnabout from that prevailing in the early 1970's, when transfusion was considered a contraindication for kidney transplantation.

Two large multi-institutional studies, one conducted by the Southeastern Organ Procurement Foundation (SEOPF) and the other carried out under the aegis of the National Institute of Allergy and Infectious Diseases (NIAID), are among those providing the evidence on blood transfusions. The SEOPF study included more than 1200 patients from 39 medical centers, who had received transplants of kidneys taken from cadaver donors.

The success rate of these grafts often leaves much to be desired. As few as 30 percent may still be functioning after 1 year, with the average about 45 percent. In contrast, grafts of kidneys donated by living relatives succeed 80 to 90 percent of the time. Nevertheless, many patients do not have relatives who are suitable—and willing—donors, and about 70 percent of all transplantations use kidneys taken from individuals who have died. Last year, a total of more than 4200 persons in the United States received new kidneys.

According to Williams, who presented some of the SEOPF data at the 7th International Convocation on Immunology,* "The outlook for the nontransfused patient [who received a cadaver kidney] was dismal, even with a good match for the A and B HLA antigens." In order to prevent rejection of the transplanted kidney by the patient's immune system, the surgeon tries to ensure that it matches the recipient's tissues as much as possible. The HLA-A and -B antigens of the tissues are the ones that are normally matched.

The genes for the HLA antigens (also called histocompatibility antigens) are located in a group—the major histocompatibility complex—on human chromosome 6. So far, four gene sites, designated A, B, C, and D, have been identified in the complex. Genes for some 20 to 30 different histocompatibility antigens can occur at the A and B sites, which is what makes finding a histocompatible kidney for each potential recipient such a difficult business.

In the SEOPF study, only 29 percent of kidneys well matched for the HLA-A and -B antigens survived for 12 months in nontransfused patients. The comparable survival rate for poorly matched kidneys was 27 percent.

But the situation was much improved for patients who had received at least one blood transfusion before the transplant operation. In that event, 55 percent of well matched and 49 percent of poorly matched kidneys continued to function for 12 months. Overall, the study data showed that transfusion makes an independent contribution of about a 20 percent increase to 1-year kidney graft survival rates.

The NIAID study, which included more than 1500 patients and some 40 cooperating medical centers, also showed a relatively large effect of transfusion. According to Henry Krakauer of NIAID, the 1-year graft survival increased from 37 percent in patients who had received no transfusions to 50 percent in patients who had received one to five transfusions, and to 56 percent in patients who had had six to ten transfusions before the transplant operation. Additional increases in the number of transfusions did not produce further improvement in the graft survival rate. (Patients who are on kidney dialysis for long periods, as many transplant recipients are, often become anemic and consequently need many transfusions.)

The role of tissue matching in the transplantation of cadaver kidneys has been a subject of controversy for perhaps 10 years. Early reports, especially from European centers, usually found that a good match for the HLA-A and -B antigens improved graft survival. But investigators in this country, including Paul Terasaki and Gerhart Opelz of the University of California Medical School at Los Angeles, often could find no such correlation. The difference may be related to the fact that European populations are far more homogeneous than those of the United States.

What the SEOPF study is now showing is a small, but still significant, improvement of about 9 percent in 1-year kidney survival rates, when there is a good match of the HLA-A and -B antigens of the donor and recipients. If anything, the NIAID study shows an even smaller effect of matching for the A and B HLA antigens than did the SEOPF study. "Some improvement was seen with a good match," says Krakauer, "but it was not quite statistically significant." These results may not totally resolve the controversy, but there is growing agreement that the effect of A and B matching in this country is small at best.

The SEOPF and NIAID studies differed on the effectiveness of the use of anti-lymphocyte serum to retard graft rejection in kidney transplant recipients. The theory is that this serum, which contains antibodies against lymphocytes, might increase graft survival by destroying the recipient's lymphocytes, immune cells that participate in the attack on the foreign tissue. The SEOPF study found that anti-lymphocyte serum improved kidney graft survival at 1 year by 15 percent, whereas the NIAID study found that it had no significant effect. Since the use of this serum is still in an early stage of development, with different preparations and treatment schedules being tried, additional work will clearly be re-

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quired to determine whether or not it works.

Within the past few years, evidence suggesting that matching for D-related (DR) HLA antigens may turn out to be more important for kidney survival than HLA-A or -B matching has been appearing. For example, Peter Morris and his colleagues at the University of Oxford and John Radcliffe Hospital, found that good DR matching improves graft survival rates at 1 year by approximately 20 percent, an effect about twice as great as that of matching for the other antigens. They, too, noted a beneficial effect of transfusion, but found that matching for the DR antigens could overcome the poorer graft survival of nontransfused patients. According to Morris, who also presented data at the immunology convocation, "The message is that a patient should either get a DR-compatible kidney or be transfused before the graft."

There is some doubt that DR matching will prove to be as effective in the long run as it now appears, however. Krakauer points out that matching for HLA-A and -B seemed to give better graft survival in the early trials than has been the case in the recent studies.

The participants at the International Histocompatibility Antigen Workshop held last February in Los Angeles examined the data from a number of international studies on DR matching. They found, according to Terasaki, the workshop organizer, that it has an effect, although not an overriding one, especially when compared to the effects of transfusion. In Terasaki's view, "DR matching does have an influence, but we have to use many factors to improve transplant success."

Despite the relatively modest effects of A and B matching, no one is currently recommending that it be abandoned. Williams points out that the effects of transfusion and treatment with anti-lymphocyte serum occur primarily in the first 6 months after the transplant surgery, which is the time when about 50 percent of the graft rejections occur. The positive effects of HLA-A and -B matching do not become apparent until 12 to 18 months after transplantation, when a good match appears to have a stabilizing effect on the survival of kidneys that made it through the earlier, more hazardous time.

Even though DR matching may have a more favorable impact on kidney graft survival than matching for the A and B antigens, it is not done routinely in this country, at least partly because funds to pay for the test have been slow in coming. Williams, for one, has been disturbed by the failure of the health insurers, who pay for most kidney transplants, to pick up the tab for DR matching. But this situation appears to be about to change.

The Health Care Financing Administration (HCFA), acting through intermediaries such as Blue Cross, pays for most of the kidney transplants in the United States. (Exact figures are not available, but HCFA pays for transplants for all individuals covered by Social Security.) The intermediaries process and pay each patient's bill, but it is HCFA, which reimburses the intermediaries for their expenses, that determines what items will be covered.

According to P. H. Vandegrift of HCFA's End-Stage Renal Disease Program, the instructions to the intermediaries state that the HCFA will pay for tissue matching, without specifying which histocompatibility antigens are included. But the forms that have been going out with the instructions mention only the A, B, and C antigens, a circumstance that might have led the intermediaries to think only matching for these antigens was covered. The new forms, which are already in the works, will include a space for DR matching, the utility of which only became apparent in the past year or two. "It is a case," Vandegrift explains, "in which technology outstripped our ability to get out the forms."

How much DR matching will add to the expenses of a kidney transplant is unclear. Currently, the average transplant costs approximately $25,000, with about $5,500 of that going for organ procurement, which includes tissue matching. If DR matching does significantly increase graft survival, an overall saving may be realized, especially when dialysis, which costs about $30,000 annually and is required by patients who reject their transplanted kidneys, is considered.

In view of the growing consensus that transfusion can benefit kidney transplant patients, this procedure may be widely adopted in the near future. Nevertheless, no one really knows just how it works.

Some patients who receive transfusions respond by making antibodies that react with cells from potential donors. On the one hand, this could be a disadvantage. It was a major reason why transfusion was previously considered a contraindication for kidney grafting. The standard pretransplant test can detect such antibodies against donor cells. Their presence usually disqualifies a patient as a candidate for the surgery, although Morris has evidence that this is not always necessary. The antibodies that are detected react against a variety of different antigens, not all of which are involved in graft rejection. By a refinement of the test for detecting the antibodies, Morris thinks it may be possible to identify those individuals whose antibodies do not necessarily preclude them from having a kidney transplant.

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On the other hand, transfusion might be a means of identifying individuals who produce extremely strong antibody reactions and might consequently be high-risk graft recipients in the first place. If the antibody response is weaker, it might be a means of selecting more compatible donors, because whatever antibodies were present would be useful for identifying and eliminating less compatible donors from consideration.

More than this kind of selection may be involved, however. Yuichi Iwaki, who is also from Terasaki's laboratory, has evidence that transfusion may stimulate the production of "enhancing" antibodies, which are directed against the antibodies that attack the kidney graft, and thus enhance graft survival.

Terasaki notes that another possible action of transfusion might be the induction of tolerance, a state of immunological nonresponsiveness to an antigen induced by exposing an animal to that antigen. Normally tolerance is induced only in very young, immunologically immature animals. But if a similar condition can occur in adult animals, it might help to explain the effects of transfusion.

Of course, additional immunological effects, which remain to be identified, may also be at work. As Williams sums up the current situation regarding transfusion and kidney transplantation, "The history of transplantation is replete with surgeons doing some crazy things that have turned out to be successful, much to the consternation of the basic scientist."—JEAN L. MARX