Controversy

Very short ischaemia is not the answer

Gerhard Opelz

Department of Transplantation Immunology, Institute of Immunology, University of Heidelberg, Germany

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Gillich et al. [1] report on an excellent transplant success rate of 77 kidney grafts performed over a 10-year period, using cadaver donor organs that were obtained and transplanted locally, without taking HLA matching into consideration. They hypothesize that the good result was due to the fact that the kidneys were not exposed to prolonged ischaemic preservation. Paired kidneys that were shipped to other centres via the auspices of Eurotransplant were exposed to cold ischaemia on average 10 h longer. Although the graft success rate of these kidneys was similar, they were transplanted into recipients with significantly fewer HLA mismatches. The authors suggest that the longer exposure of shipped kidneys to cold ischaemia probably abolished any advantages conferred by better HLA compatibility.

The report of Gillich et al. [1] raises a question that is not new but nevertheless highly relevant: would it make sense to concentrate with high priority on keeping the ischaemic preservation time very short, thereby limiting ischaemic damage and allowing the successful transplantation of cadaver kidneys in spite of poor HLA compatibility? If the answer were yes, the implications would be far reaching. Current cadaver kidney allocation practices would have to be revised.

Any decision favouring an overriding importance of short cold ischaemia must be based on solid facts. The study by Gillich et al. [1], although carefully conducted, was based on a rather small number of transplants. On the other hand, as pointed out by the authors, they are not alone with their view and others have argued along similar lines. Against this background, it is useful to examine the available evidence. Data presented here are derived from the Collaborative Transplant Study (CTS), the largest international scientific transplant database [2].

Surprisingly, when the influence of cold ischaemic preservation time on graft survival is examined for cadaver kidney transplants performed from 1985 to 2000, one does not find that graft outcome is directly correlated with the length of ischaemia. While there is a strong general trend towards impaired outcome with increasing preservation times, the very shortest ischaemia category (0–6 h) shows a paradoxical result: graft outcome in this group is significantly worse than that with donor kidneys exposed to 7–24 h of ischaemia ($P < 0.0001$) (Figure 1). This result was consistent in a subset analysis of transplants performed in Europe, North America, or on other continents (not shown). Importantly, the distribution of HLA-A+B+DR mismatches was less favourable in the 0–6 h group than in the 7–24 h group. Among transplants with 0–6 h of cold ischaemia, there were 8.0% grafts with 0–1 mismatches and 22.2% with 5–6 mismatches, whereas the corresponding rates were 15.4% and 13.1%, respectively, among transplants with 7–24 h of cold ischaemia ($P < 0.0001$).

Recent ‘old for old’ donor-recipient age matching strategies prescribe short cold ischaemia for kidneys obtained from elderly donors. This raises the possibility that the relatively poor graft outcome observed with 0–6 h of cold ischaemia may have been due to old donor age. An analysis in which donor age was...
restricted to the ‘ideal’ age bracket of 20–45 years, however, showed that very short ischaemia was associated with less than optimal graft outcome even in these transplants (Figure 2).

A more direct approach is the analysis of HLA matching in transplants with short ischaemic exposure of donor organs. If short ischaemia were able to eliminate the impact of HLA matching, one should not see an effect of matching in these transplants. The result, however, shows that HLA matching has a highly significant impact even with cold ischaemic preservation of only 0–12 h (Figure 3).

The explanation that very short ischaemia may have been the secret behind the high success rate of the 77 transplants reported by Gillich et al. [1] appears therefore unlikely. Possible alternative explanations might be that the kidneys were removed expertly and were of particularly good quality, that prophylactic ATG was administered more often, and that acute rejections, which occurred at a significantly higher frequency among the locally transplanted and HLA poorly matched grafts, were recognized early and treated effectively. One must also consider the likelihood that the result may have been a chance occurrence [3].

A recent CTS evaluation of transplants performed from 1996 to 1999 showed that immunosuppressive treatment with ‘modern drugs’ is able to decrease the early graft failure rate of poorly matched grafts. However, 3 years after transplantation, the effect of HLA matching was just as strong as that seen with application of previously standard medication [4]. In other words, rejection of HLA poorly matched grafts was delayed but not eliminated. Still, the result suggests that improved immunosuppression can overcome the effect of HLA mismatching to a greater extent. In future, the introduction of even more effective immunosuppressive regimens may well make HLA matching superfluous. For the time being, however, a continuation of strategies aimed at obtaining good HLA matches would seem sound. The CTS experience indicates that kidney preservation times in excess of 24 h should be avoided.

References


Editor’s note

Please see also Original Article by Gillich et al., pp. 884–886.