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Evaluation of the permissible mismatch concept

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Abstract Maruya et al. described a method of separating one HLA-A+B+DR mismatched transplants into permissible and immunogenic categories (published in Clinical Transplants 1993). For the permissible subgroup, they observed an outcome similar to that of zero-A+B+DR mismatched transplants. The classification was based on the HLA type combination of donor and recipient. We evaluated this concept with the data of the Collaborative Transplant Study (CTS). We did not obtain significant differences between the outcome of immunogenic and permissible mismatched transplants. The pairwise *p*-values for the comparison of zero-mismatched with permissible mismatched transplants are significant for cadaver transplants. The indifferent results obtained in our analysis do not support the concept of permissible mismatches. A more restrictive definition of the permissible mismatches might be helpful. The current method appears to be of insufficient reliability due to the relatively small numbers of transplants in the individual subgroups used to identify permissible combinations.

Key words HLA compatibility · Permissible mismatch

Introduction

There have been extensive discussions recently concerning the report by the University of California at Los Angeles (UCLA) registry that, depending on the recipient's human lymphocyte antigen (HLA) profile, certain HLA mismatches may be *permissible* and thus not have a negative impact on graft survival [1]. It was proposed that this concept could be transformed into an improved algorithm for the allocation of cadaver kidneys. We re-examined the attractive UCLA concept based on an analysis of the larger Collaborative Transplant Study (CTS) data base in order to determine whether such an approach would indeed allow an identification of HLA mismatches that could safely be ignored. The implications, of course, are important, because it would be easier to find tissue-compatible donor-recipient combinations.

Methods

A total of 15915 cadaver and 4470 living related donor transplants performed in North America and 40333 cadaver and 2397 living related donor transplants performed in Europe were analyzed. We followed the exact specifications for the identification of *permissible* and *immunogenic* mismatches published by the UCLA group [1]. Actuarial rates of graft survival were computed according to the method of Kaplan and Meier.

Results

The original UCLA study in which *permissible* profiles were identified was based on an analysis of related donor transplants. Indeed, when the CTS data for related transplants reported from North America were analyzed, a confirmatory trend was observed. Transplants with one HLA mismatch that were categorized as *permissible* did as well as zero-mismatch transplants, and

Table 1 Graft survival rates with the permissible mismatch concept. (*HLA* Human lymphocyte antigen)

HLA mismatches	Graft survival in North America		Graft survival in Europe	
	Related (1 year/3 years)	Cadaver (1 year/3 years)	Related (1 year/3 years)	Cadaver (1 year/3 years)
Zero A + B + DR	95 %/91 % (n = 1269)	91 %/83 % (n = 719)	93 %/87 % (n = 422)	86 %/79 % (n = 2137)
One permissible	98 %/90 % (n = 112)	83 %/74 % (n = 157)	90 %/78 % (n = 78)	84 %/74 % (n = 1403)
One immunogenic	91 %/86 % (n = 252)	84 %/73 % (n = 397)	90 %/86 % (n = 167)	83 %/74 % (n = 2101)

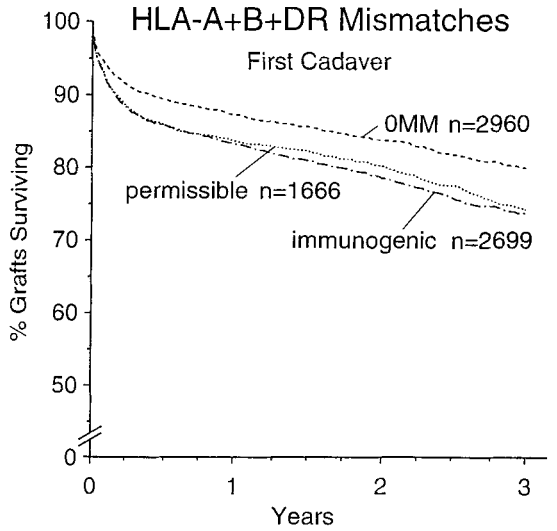

Fig. 1 Graft survival analysis of first cadaver kidney transplants according to whether grafts had no mismatches on the human lymphocyte antigen (HLA)-A, HLA-B and HLA-DR loci *(0 MM)*, or whether one mismatch was present which was defined as *permissible* or *immunogenic*. The numbers of patients studied are indicated. The one-mismatch grafts had significantly lower survival rates than the zero-mismatch grafts, regardless of whether the mismatch was *permissible* or *immunogenic*

better than transplants with one HLA mismatch categorized as *immunogenic* (Table 1).

When the same type of analysis was performed on related donor transplants reported from Europe, however, the improved outcome of grafts with one *permissible* mismatch could not be confirmed. Because the number of related grafts available for analysis from North America was much larger than that from Europe, this result was not considered too disturbing. More critical was the following analysis of cadaver donor transplants, since the UCLA inference was that cadaver organs could be allocated better by considering certain HLA mismatches as *permissible*.

Among first cadaver transplants done in North America, grafts with one HLA mismatch did worse than zero-mismatch grafts, regardless of whether the one mismatch was *permissible* or *immunogenic* ($P < 0.02$). When the same type of analysis was performed for European cadaver transplants, there was no difference at all between the survival rates of *permissible* and *immunogenic* mismatches. The outcome of both one-mismatch groups was significantly inferior to that of true zero-mismatch grafts ($P < 0.006$). An analysis of the total CTS file, including transplants from all geographical regions of the world, also failed to show an advantage of transplants with permissible mismatches. True zero-mismatch transplants did significantly better ($P < 0.0001$) than either the permissible or the immunogenic one-mismatch groups (Fig. 1).

Discussion

It is evident from this analysis that the permissible mismatch concept cannot be confirmed, at least not as proposed by the UCLA group. Of course, the concept itself, of identifying certain HLA mismatches as non-deleterious, remains attractive. Most of us have observed that some poorly matched transplants function very well. However, the likelihood of good graft outcome is much greater for a good match than for a poor match, especially when long-term survival is considered.

When the UCLA group analyzed the influence on overall graft survival, the results of the conventional and the current UCLA method were better than those obtained with the permissible matching scheme [2, 3]. Even a refinement of this concept was not considered as satisfactory by the authors [4].

At present, we know of no reliable method that would allow a prediction of good graft survival in the presence of several HLA mismatches. Unfortunately, the permissible mismatch concept, as currently proposed, does not appear to hold its promise in this respect.

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