PAPER NO. IV-1 BY NORIKO MURASE, M.D.
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DISCUSSION

DR. AUCHINCLOSS (Boston, Massachusetts): Do you think the two drugs are prolonging survival more effectively than one alone because they're acting synergistically on a single mechanism of rejection, or are they working on two different mechanisms of rejection?

One way of examining that question would be to test the two drugs together in allograft combinations. Do you see the same synergistic effect when using an allograft?

DR. MURASE: In the allograft system we have a different experiment because we use a very low dose of FK506. With antiproliferative drugs at these low doses, an additive or synergistic effect is observed on allograft survival.

DR. AUCHINCLOSS: I'm sorry, you do see synergistic effect?

DR. MURASE: Yes.

DR. SOLLINGER (Madison, Wisconsin): This is the longest graft survival ever reported using drug therapy in this xenograft model.

I have two questions. What did the histology show in your cardiac model? How about FK506 plus Brequinar versus FK506 and RS61443? I am particularly interested in the histology of the coronary arteries.

The second question is if you would have a choice clinically to use either RS61443 or Brequinar in conjunction with FK506, what would you recommend?

DR. MURASE: We have histology for the greater than 100 day survivors. This was reviewed by Dr. Jake Demetris, who found no coronary artery changes.

Perhaps Dr. Starzl should answer the second question.

DR. STARZL (Pittsburgh, Pennsylvania): I think that any of the drugs you mentioned would be fine. My impression is that there is a wider margin of acceptable drug dose with the RS61443 than with Brequinar, which really has to be used right at the 3.5 to 4 mg/kg range. Whereas with RS61443, one can see an effective dose range all the way from just above 10 mg/kg up to 60 mg/kg.

However, I think it's worth pointing out that Cytoxan does the same thing. Although less efficient, methotrexate seems similar. The important point is that Dr. Murase has exposed a generic discovery, not an advocacy of a particular drug. Thus, several of the antimetabolites can be used as an adjuvant to "jump-start" maintenance treatment with FK506. Because of anxiety on the part of the drug companies about using experimental drugs together, it seems likely that a drug like Cytoxan will be used first with FK506 if clinical trials are attempted.

DR. AUCHINCLOSS: Dr. Starzl, you're the only person who has put an animal liver into a human being. With these new drugs now becoming available, are you prepared to do that again?

DR. STARZL: That's a policy decision that I wouldn't care to make myself. It involves the institutional IRBs and it involves the FDA and the NIH. There would have to be a substantial consensus before anyone would want to attempt such a trial. I have the impression, because of the delicate nature of the undertaking, that there will only be one or two opportunities to do it, so it's rather important that it succeed.

However, the basic tools to make it succeed are within our hands. In 1963, we transplanted six baboon-to-human kidney heterografts. None hyperacutely rejected. They all functioned for more than six days, to a maximum of 60 days. All grafts were eventually lost because of the syndrome that Dr. Murase has been able to interdict, that is, the delayed humoral rejection.

I don't know of any undertaking in clinical transplantation that is more thoroughly supported than a potential trial of xenotransplantation. With Dr. Murase's model, which is a very difficult one, she has been consistently able to get better results than most people 6 to 12 months ago could do with a whole variety of fairly difficult allograft models. It is a stunning set of data; except for the FK506, the achievement is not particularly drug specific.

It's like getting to a precious jewel encased in an impermeable shell. She has broken the shell with the antiproliferative drugs. It's quite an amazing story.

DR. AUCHINCLOSS: I agree entirely.

DR. STARZL: Can I just add one thing, because I think Dr. Murase said this in a way that might be misunderstood. At 100 days, the pathology in most of these hearts was absolutely normal. That is, when specimens were presented to Dr. Demetris as unknowns, he had trouble determining which was the xenograft heart and which was the native heart.

DR. BACH (New York, New York): Could you explain what you meant when you say that the heart is simply a vascular form of rejection, whereas the liver is the combination of vascular and cellular? I ask this especially when you show us that at least by the assay you used for natural antibodies, that they go up very much with the combined treatment of FK506, and either Brequinar or RS61443. Yet you get survival despite that.

DR. STARZL: The phenomenon is, of course, one which you have given the name "accommodation." When you and I last discussed this, it was in terms of transfection of human genes into xenograft endothelium. If you can succeed for a while, and it looks as if the magic time is 13 or 14 days, the continuing presence of these preformed antibodies may no do harm. This would not be without precedent, since it has been observed in recipients of allografts who "ride out" preformed cytotoxic antibodies.

But I'm only expressing my own particular brand of wonderment about the fact that enormous delayed rises in titer don't kill the graft.

The differentiation, between humoral and cellular rejection is made possible with 2 different kinds of organ grafts. On one hand, the heart xenograft at three days in untreated rats, or at four days in rats treated with FK506-with no histopathologic evidence of cellular rejection. Also, the liver, known to be relatively resistant to humoral rejection, survives long enough to identify a cell mediated component along with the characteristic changes of humoral rejection in the blood vessels. The cellular component by this time is very aggressive. This combination lesion is not unfamiliar. We have often seen it in allografts.

DR. BACH: That is precisely why I asked the question. It seems that is not induction of accommodation, it is accommodation!

My concern, is that we don't know as much about a combination, such as hamster-to-rat, as we do, for instance about pig-to-nonhuman primate. As such, I'm not quite sure how to think about antibody, complement, or other factors in the vascular rejection.

DR. STARZL: Thank you for putting the question that way. We think the barriers are the same; they differ only quantitatively. At a practical level, what is required to win in a human situation is to pick a species combination where you do not get hyperacute rejection within minutes before you can do something to break through the antibody barrier. With hyperacute rejection, the game is over.

By empirical experience, there are at least 3 animal-human combinations that qualify: the baboon-to-human (the kidney experience of 1963 and the Baby Faye case of 1984), the chimpanzee to human experience of Reemtsma, and the Rhesus monkey experience of Reemtsma. The Rhesus monkey was the least satisfactory because it was fiercely rejected after about three days, but hyperacute rejection did not occur. The best donor, the chimpanzee, cannot be used again because this is an endangered species. This appears to leave us with the baboon.

The work being done at Duke and at your place looking at in vitro antibody reactivities may well be predictive of other interspecies possibilities, but right now it seems to me that the pig-to-human is too tough.

More than 25 years ago, René Kuss of Paris tried a pig-to-human kidney xenotransplant, under Imuran and prednisone, at a time when dialysis was not available. Kuss has described to me in detail how the kidney was hyperacutely rejected in about 15 minutes. Thus the pig cannot qualify unless, or until, we can do something to move that antibody barrier back.