The Application of Xenotransplantation In Humans—Reasons to Delay

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INTRODUCTION

There is consensus, among those involved in the field of clinical transplantation, that a need exists for a larger pool of organ donors. Efforts to enlarge the current pool of cadaver organ donors have not alleviated what has now become a critical shortage of donors. As a result, substantial numbers of patients with end stage disease of vital organs, 2,359 in 1991—an increase of 20 percent over the previous year (according to the most recently available UNOS figures)—are dying while awaiting transplantation (DHHS 1993). Those on the waiting list are waiting longer for their organs, and even if efforts currently in place were able to maximize the pool of cadaver donors, there would still be a shortfall in meeting potential demand. This situation is particularly frustrating to clinicians given the high rate of successful outcome in those transplants that do occur.

For these reasons interest is focused on xenogeneic tissue as an alternative for those requiring transplantation. The progress made in the field of experimental xenotransplantation over the past few years has further encouraged clinicians, particularly the measurable success that has been achieved in the survival of transplanted xenogeneic organs under certain circumstances, most notably in concordant rodent species (Hassan and others 1992). However, the barriers to successful clinical xenotransplantation are much greater than those to allogeneic transplantation, and clinically successful xenotransplantation has yet to be achieved.

CLINICAL EXPERIENCE

Previous clinical experience in xenotransplantation is summarized in Table 1. In all more than 20 patients have received xenografts. Although all these experiments have been failures in the sense that long-term organ survival was not achieved, they were able to show that xenogeneic tissue is able to support human life for a period of time. Rejection of xenogeneic tissue was both humoral and cellular and was more difficult to control than allograft rejection, although in the short term, it could be controlled with conventional immunosuppressants, albeit in large doses.

Over and above the immunological and physiological barriers to xenotransplantation, these early cases raised a number of other issues. They included: the rights of humans to use animals to suit their best interests, particularly in the case of primate donors (Singer 1992); concerns about the possibility of transmission of xenotransplant associated zoonoses to recipients under immunosuppression (Michaels 1994); ethical questions regarding the rights of patients, and the performance of extreme medical interventions, in those with reduced life expectancy (Caplan 1992). While it is important that these concerns be addressed when considering clinical xenotransplantation, we believe that none of them represent a barrier to it as such, and that it is reasonable to consider xenotransplantation because too many patients are dying while waiting for an organ. There are, however, other fundamental reasons for not yet performing this procedure. These include a lack of data in support of long-term engraftment, the considerable immunosuppression required to prevent rejection of xenogeneic tissue, and the inability to select appropriate recipients from those currently awaiting allotransplantation. Thus we tend to see the issue as primarily scientific and logistical, rather than ethical.

STATUS OF CURRENT EXPERIMENTATION

Much of the current enthusiasm for clinical xenotransplantation is based on the potential for success indicated by
research advances achieved in the field over the past few years. However, many of these advances have been made in rodents and do not provide an adequate basis for human experimentation. At the same time, investigators are reporting increased survival times for solid organ transplantation in certain concordant and some discordant species involving nonhuman primate recipients. Monkey to baboon heart transplants have survived for months, and in the case of one group of investigators for more than a year (Michler 1987; Sadeghi and others 1987). Recipients also survived after the heart xenograft was removed and replaced by an allograft in an experiment aimed at proving that a xenograft may be used as a bridge to allotransplantation (Alonso de Begona and others 1992). However, the data for orthotopic heart transplantation in primates are not as encouraging as for heterotopic heart transplantation, and the immunosuppression used was quite toxic in those models documenting long-term successful outcomes (Sadeghi and others 1987).

The animal research data reported to date highlights several important issues relevant to xenotransplantation. For instance, sudden rejection of the Pittsburgh groups most recently performed baboon liver transplant was thought to be due to activation of complement in the recipient, possibly provoked by the transfusion of blood products. Uncontrolled activation of complement will occur in a setting where complement, and the regulators of complement activation, originate from different species (Starzl and others 1994).

In addition, a role for induced antibodies in the rejection of concordant xenograft tissue appears likely. Although treatment strategies have been developed against induced antibody responses, these strategies have involved the use of large doses of cyclophosphamide and other drugs, with resultant severe immunosuppression, to the detriment of the recipient in at least one of the most recently performed baboon-to-human liver transplants (Starzl and others 1994).

Alternative, less toxic, therapies are needed to deal with this problem. Finally, rapid humoral rejection of both concordant and discordant xenografts has in the past limited the ability of investigators to study the mechanisms of cellular rejection in vivo. However, essentially every direct comparison of cell-mediated xenograft compared with allograft rejection has indicated that larger doses of nonspecific immunosuppressive drugs are needed to control cell-mediated xenograft rejection. Recent in vitro evidence showing intact direct recognition of discordant xenogeneic tissue, coupled with in vivo work in those concordant transplants with prolonged survival times, will allow further clarification of the role of cellular xenogeneic rejection, and the interventions necessary for its control (Murray and others 1994; Auchincloss 1994).

These considerations have led us to conclude that the immunological barriers to xenotransplantation are greater than for allotransplantation and, therefore, that higher levels of immunosuppression will be needed to accomplish long-term xenograft survival.

Patient selection for xenotransplantation

In considering all the available data, including previous clinical experiences, it is now apparent that if the large doses of immune suppression are tolerated, some xenogeneic transplants will probably survive in human candidates for a period of time. Assuming that concordant xenotransplantation will work in a given number of cases, and a small percentage of transplants may even achieve prolonged engraftment, the question then is how to identify appropriate recipients for these second best organ transplants.

In the past, selection of patients for xenotransplantation has been based essentially on two criteria (1) the unsuitability of the recipient to receive an allotransplant (e.g. Hepatitis B infected patients for liver transplants because of the high recurrence rate in the allotransplanted organ and the resistance of baboon livers to Hepatitis B virus), or (2) the unavailability of an organ for a dying patient. The exclusion of Hepatitis B infected patients from liver allotransplantation is not absolute and a number of centers will transplant these patients. In fact, the survival rates reported for allotransplantation in these patients with Hepatitis B is superior to that which we could expect from xenotransplantation at this time. Another possible group might be in patients who run out of dialysis options, who have failed previous attempts at allotransplantation, and who are highly sensitized. We do not know, however, whether such patients are also likely to be sensitized to discordant donor antigens.

For organs such as the heart and the liver where there are limited options for chronic replacement therapy other than transplantation, failure to obtain a human organ in time often leads to the patient's demise. However, current policies favoring allotransplantation to the sickest patients, means that even as the patients approach imminent death, they still have a better chance of long-term survival by waiting for a last-minute human organ than by opting for a xenotransplant. Under our current system of organ allocation, some patients waiting for a heart or a liver transplant will die of organ failure while waiting for human organ. The ideal circumstance would be to offer a xenotransplant to those who would die without achieving allotransplantation. However, to achieve this will require changes in our organ allocation policy (Auchincloss 1993).

XENOTRANSPLANTATION AS A BRIDGE TO ALLOTRANSPLANTATION

One intermediate proposal is to use xenotransplantation as a bridge to allotransplantation in patients who are approaching death while waiting for a graft. This proposal is superficially compelling, particularly in the pediatric group, for whom the size of the baboon heart is well suited, and for whom there is not only a waiting list mortality comparable to that of adults, but also some waste of organs due to availability, timing, and size of donors and recipients (Michler and Chen 1994). Once
again though, it is hard to select patients to receive the less favorable option of xenotransplantation, instead of possibly waiting longer for an allotransplant. Furthermore, the performance of two major surgical procedures instead of one (allotransplant following xenotransplant) will diminish survival following the allograft, and the xenogeneic tissue may sensitize the recipient against a future allograft (Sachs and others 1971).

Most importantly, the use of xenografts as a bridge to allografting does not address the fundamental issue of the shortage of human donor organs (Gundry 1994). Indeed, the use of xenografting as a bridge will probably diminish the overall survival of those patients who receive our limited number of human organ transplants. Thus, the use of xenotransplants as a bridge to allotransplants will probably benefit some individual patients and provide valuable information to our society about xenotransplantation in human beings, but at a short-term cost of less good overall survival for patients with organ failure.

AN APPROACH TO CLINICAL XENOTRANSPLANTATION

In order that there be a high likelihood of a successful outcome for the early patients entering a trial of clinical xenotransplantation we would recommend further experimental documentation of successful long-term xenotransplantation using tolerable doses of immunosuppression, in nonhuman primate models. It is accepted that there exists a need for an alternative therapy in a large number of patients who will wait unsuccessfully for a transplant. Even though xenotransplantation offers the potential for an expanded pool of donor organs, which could be obtained electively, it is competing with an established successful therapy, namely allotransplantation. A large part of the problem with xenotransplantation as it currently stands, is that the reduced chances of long-term graft survival compared to allotransplants make it an unacceptable therapeutic option in the clinical setting, most of the time.

For situations where xenografting might be considered, when no other alternative is available for instance, a system needs to be developed so that potential recipients of xenografts can be clearly identified. A solution would be to change allograft allocation policy, such that healthier candidates are more readily able to have access to an allograft, and sicker patients after a defined wait at highest priority, would lose that advantage (as their chances of a successful outcome are reduced). Selected patients from this group might then become candidates for xenotransplantation.

Ultimately, if xenografting can be shown to offer predictable long-term successful outcomes, patient selection for the procedure will be simplified.

CONCLUSION

Clinical xenotransplantation cannot yet be offered as an acceptable form of organ replacement therapy. Fundamental questions remain about the rejection of xenogeneic tissue and how to deliver the least amount of immune suppression safely to prevent rejection. Referral of appropriate candidates for xenotransplantation will remain problematic in this setting. Good animal models exist in which these issues can be investigated, and hopefully solved, so that xenotransplantation could be offered to selected patients with at least the equivalent hope of success of allotransplantation. It would be under these circumstances that this form of treatment should be applied to a patient population to their best advantage.

REFERENCES


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