time, reduced ischemic injury) may counterbalance the poor HLA matching in the ULD group.

Although the arguments against the use of living donors must be considered, long-term prospects for kidney donors is reassuring provided there is careful evaluation of potential donors and the strict criteria for exclusion are respected [2]. The benefit for the donor must also not be ignored.

Our current policy continues to restrict ULD transplantation to selected cases. In the absence of a compatible living related donor, in order to avoid waiting for a cadaver kidney, and with the full understanding and strong motivation of an 'emotionally' related donor, we find ULD transplantation totally justifiable. It is time to reclaim a discarded opportunity (Levey et al.) [3].

References

Overcoming immunologic barriers to discordant organ xenotransplantation

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The increasing shortage of donor organs is the major barrier to successful application of transplantation for the treatment of end-stage heart, liver, and kidney diseases. Because of this shortage, a high and continuously increasing number of patients who would benefit from organ transplantation die, awaiting the availability of a suitable donor organ.

Despite the historical use of primate donor xenografts as long as 30 years ago, the pig has received the greatest attention over the past few years as a potential donor species for human organ xenotransplantation. Serious ethical, financial, logistic, and infectious problems have essentially excluded the use of primate donors to solve the organ transplant shortage. In contrast, the pig is generally regarded as the most acceptable potential donor species for humans based on these considerations. Nevertheless, at present there remain significant immunological barriers to the clinical use of donor hearts from pigs.

Xenotransplant donors can be divided into those subject to humorally-mediated HAR, termed ‘discordant’ (e.g. pig to human), and those not, termed ‘concordant’ (e.g. chimp to human). Two key factors account for HAR of discordant pig organs into primates. First, is the presence of preformed ‘natural antibody’ in humans, apes, and Old World monkeys that is directed against the terminal disaccharide galactose α 1,3 galactose epitope (‘α gal’) expressed on glycolipids and glycoproteins of other species [1]. This natural antibody, which is predominantly IgM and IgG2 in man [2], binds immediately upon donor organ perfusion causing severe vascular endothelial cell injury, activation of complement (C), platelet aggregation, and leukocyte infiltration, which result in hemorrhage, thrombosis, and infarction of the organ. The second key factor resulting in HAR of discordant xenografts is the inability of key species-specific regulators of C (e.g. decay accelerating factor-DAF, membrane cofactor protein-MCP) which are expressed on donor (e.g. pig) vascular endothelium to inhibit the activation of recipient (e.g. human) C. This antibody independent mechanism alone can yield HAR in some species combinations [3].

At present, three general approaches are being used to overcome the immune barriers to discordant xenotransplantation: endogenous C inhibition using transgenic pig donors [4,5]; endogenous induction of specific host immune unresponsiveness using antibody depletion and mixed xenogeneic chimerism [6,7]; and exogenous inhibition of C at the level of the C3 and C5 convertases, or membrane attack complex [8,9] using agents such as human recombinant soluble C receptor type I (sCR1) and anti-C6 antibodies, respectively. Unfortunately, while each approach has yielded pig to primate xenograft survival for up to 3-7 weeks, long term recipient survival has not been successful to date because of infectious and other complications.

C activation via classical and alternative pathways clearly plays a key role in HAR of discordant organ xenografts. We have used two approaches to study this problem; inhibiting C at the level of terminal component activation, and inhibiting multiple components involved in both pathways. This approach has allowed
a better understanding of the role of several specific C components in mediating HAR and the effects of their inhibition alone and in combination with other immunosuppressive agents in several different models of cardiac xenotransplantation.

Our studies of multiple rat strains to evaluate the relative contribution of C and preformed xenoreactive natural antibody (NAb) to HAR of discordant guinea pig (gp) heart xenografts, revealed a congruent strain of PVG rats with a profound deficiency in C6 (PVG/C—) and, therefore, membrane attack complex (MAC) formation. We found that this specific deficiency is associated with the complete absence of HAR, despite high titers of NAb [9]. Gp heterotopic heart xenografts were rejected by congenic PVG/C+ recipients within 0.5 ± 0.2 h compared to 45 ± 9 h by PVG/C− recipients. The pattern of rejection seen in C− recipients was one of accelerated acute rejection, with abundant neutrophils and platelets.

Attempts to further prolong survival in C6 deficient recipients by inhibition of neutrophil adhesion have been partially successful; use of antibody to CD18b, a component of C receptor 3 (CR3, Mac-1), LFA-1, and gp150,95, showed no benefit [10], whereas treatment with NPC 15669, a leumedin that blocks CR3/Mac-1 upregulation, showed significant prolongation beyond controls [11]. The degree and source of C6 activity required for HAR was examined by transplanting C+ recipients with C− livers, yielding almost complete reconstitution of C6, and reconstituting PVG/C− rats with bone marrow from C+ donors, yielding 10% reconstitution of C6. Hepatic sources of C6 were sufficient to yield HAR, whereas with only extrahepatic sources, HAR was delayed to 9 ± 3 h [12].

Selective depletion of C6 by anti-C6 antibody treatment has reproduced the effect seen in C6 deficient recipients [13]. LEW rats were treated with rat-anti-rat C6 antiserum to deplete C6 prior to gp cardiac xenotransplantation, and afterwards to inhibit natural reconstitution. Treated rats showed abrogation of HAR (38 ± 11 h) compared to normal serum treated controls (1 ± 0.7 h). Use of the purified IgG fraction of the anti-C6 serum likewise prevented HAR. Our findings that C6 deficiency can inhibit acute (and hyperacute) allograft rejection, raises the possibility that this approach may be a useful adjunct in promoting long-term xenograft survival.

A second approach to overcome HAR has been to inhibit both the classical and alternative pathways at steps earlier than C6 using the recombinant soluble form of human C receptor I (sCR1), which has both delay accelerating and co-factor activity [14]. Initial work in the gp to rat cardiac xenograft model demonstrated a dose dependent association between sCR1 treatment and inhibition of HAR [15]. Subsequently, using an ex-vivo model of pig heart perfusion with human blood [16], we found that single dose treatment with sCR1 abrogated C activation and prevented HAR [8]. Likewise, single bolus treatment with sCR1 of cynomolgus monkeys at the time of heterotopic pig heart transplantation, with no other treatment or preparation, resulted in the abrogation of hyperacute rejection compared to vehicle treated controls: 70 ± 18 vs 0.8 ± 0.2 h [8]. At the time of rejection, sCR1 treated recipients showed reconstitution of classical and alternative C pathway activity and elevation of NAb, especially IgG.

Continuous infusion of sCR1 with no other treatment resulted in further prolongation of xenograft function, but ultimately resulted in rejection at 5–7 days despite reduced C activity [17]. At the time of rejection, the graft showed extensive IgM and IgG deposition, with abundant neutrophils and macrophages, but modest T-cell infiltration. NAb levels of both IgG and IgM were both elevated at rejection. A triple therapy protocol of cyclosporine, cyclophosphamide, and high dose steroids was then added to the continuous infusion of sCR1 [18]. The initial recipient treated with this protocol had graft prolongation to 11 days, but developed an IgG and IgM NAb response on days 5–7, with a high titer of each by the time of rejection. The graft showed a rejection pattern similar to that of continuous sCR1 infusion alone. To determine the effect of NAb inhibition, treatment with cyclophosphamide was begun 1 week pretransplantation, which prevented the NAb response post-transplantation, and resulted in graft prolongation beyond three weeks in 2 subsequent monkeys. Neither recipient rejected their graft, but both died of infectious complications. The grafts in both recipients showed abundant IgG and IgM, no C, and rare inflammatory cells. Control monkeys treated with the triple therapy protocol without sCR1 demonstrated HAR within 1 hour [18].

Remarkable progress has been made over the past five years in better understanding the mechanisms involved in discordant xenograft rejection, and has lead to the development of strategies of endogenous and exogenous C inhibition, each of which has successfully overcome the critical barrier of HAR. However, it is not yet clear whether any single approach or even combination of approaches will ultimately yield clinical application of discordant organ xenotransplantation. Studies are now in progress with both approaches to reduce and adjust therapy to prevent rejection, but maintain host defense from infection. Likewise, the risks of irreversible acute rejection, delayed xenograft reactions due to endothelial activation, and the potential for severe chronic rejection/accelerated graft arteriosclerosis, have not been fully established, and must potentially be overcome before any preclinical approach is deemed successful to the point of implementing clinical trials.

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Differential drug therapy of hypertension

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In 1977, the NHLBI in the USA called together their first Joint National Committee (JNC) to provide guidelines on the detection, evaluation and management of high blood pressure (BP). This group were responsible for the introduction of the term 'stepped care' to describe the method of adding in drugs sequentially until BP levels were controlled. The first 'step' in terms of drug therapy was identified as diuretic. Through the 1970's and into the early 1980's, the three classic steps — 'triple therapy' — of managing hypertension consisted of adding in a beta-blocker if diuretics were inadequate (step 2) and then a vasodilator such as hydralazine (step 3) should the need arise. However the Clinicians' Manual on Hypertension [1], produced in 1990 on behalf of the International Society of Hypertension, included the statement that: 'the rigid “stepped care” approach, i.e. starting with a diuretic, then adding a beta-blocker and then a vasodilator, has now, in general been abandoned.'

Since then, five sets of national or international guidelines on the management of hypertension have been produced from Canada [2], New Zealand [3], UK [4], USA [5], and the WHO/ISH [6]. Whilst there are many areas of agreement common to all five sets of guidelines, the issue of optimal first line drug therapy remains controversial. The recommendations of JNC V on one hand were to use diuretics and beta-blockers as first line agents except then ineffective or contraindicated. The WHO/ISH document on the other hand stated that any of several classes of agents could be used as first line agents.

The former approach is based on the premise that we should not use drugs unless they have been tried and tested in long term morbidity and mortality trials. Whilst this is theoretically an ideal position to take, inevitably, because of ethical issues and the drugs used in the hypertension trials, the lists of exclusion criteria from trials are extensive, which results in typical hypertensives being greatly under-represented. Conversely therefore trial results usually relate to totally atypical patients, and hence extrapolation from trial data to clinical practice should be done with care.

Even with the benefit of trial data, for example in elderly hypertensives, we are faced with some further reservations about data from randomised controlled trials. Specifically, these reservations include how intention to treat analyses affects the relationship between efficacy and effectiveness, and how the data are interpreted without due consideration of these issues and other important aspects of design such as power.

The alternative approach to drug therapy for hypertension management proposed in the WHO/ISH guidelines acknowledges the shortcomings of currently available data and implies that therapy be tailored to the individual. Tailored therapy in practice involves making a choice of treatment based on the risk profile of the individual patient. Consequently, whilst this appears a logical approach, it does involve taking a much broader view of management than was hitherto the norm. It is based on the belief that the prognosis of hypertensives is not simply a function of lowering BP, but rather is mainly determined by the coexistence of other cardiovascular risk factors and/or target organ damage.

Because long term morbidity and mortality trial data are not yet available to guide us as how best to manage various subgroups of patients — for example those with diabetes or left ventricular hypertrophy — tailoring therapy involves using information from studies of shorter duration which have evaluated the effects of antihypertensive agents on surrogate end points.

In the absence of morbidity and mortality trial data, a best estimate has to be made as to optimal therapy for the many subgroups of hypertensives either totally excluded or under-represented in the trials. An example of how the profiles of the major drug groups might be considered in the context of diabetes is shown in the table. From this, it seems reasonable to infer that diuretics and beta-blockers are unlikely to be optimal drugs for hypertensive diabetics whereas ACE inhibitors, alpha-blockers and calcium channel blockers appear to be preferable agents. Similarly a review of the data regarding optimal drug therapy for patients with left ventricular hypertrophy [7] and hypertension in the elderly [8] appears to challenge the conservative