

## **HUMAN RETROPLACENTAL GAMMA GLOBULIN: PAST EXPERIENCE AND PROPOSED USE WITH LOW DOSE CYCLOSPORIN A IN CADAVERIC KIDNEY TRANSPLANTATION**

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### **Summary**

Retroplacental gamma globulin, previously shown to enhance cadaver renal allograft survival rates by a factor of 20 per cent, will be adjunctively used with low dose Cyclosporin A (CyA) therapy for the purpose of minimizing the dose-related, adverse side effects of CyA and possibly further enhancing graft survival in this treatment group.

### **Introduction**

The effectiveness of Cyclosporin A as an immunosuppressive agent for use in kidney transplantation is in part compromised by its nephrotoxicity. This adverse effect of the drug becomes manifest early after transplantation and notably so in the presence of acute renal failure. Indeed, long-term graft survival rates are seriously affected by its use in this instance. Perhaps more bothersome than dangerous is the relatively mild to moderate renal insufficiency seen in certain recipients with functioning allografts who have been treated with CyA for several weeks to months. The lack of a clear association between CyA trough concentrations and predictability of interstitial lesions clouds the issue on how to effectively and safely use CyA. In most instances, therefore, we are forced to empirically lower the dose of CyA without knowing if a rejection episode due to suboptimal immunosuppressive therapy is likely to ensue.

We propose an investigation of CyA at reduced dosage, using plasma trough concentrations as a guide, coupled with the adjunctive administration of retroplacental gamma globulin. Our purpose is to prevent rejection from occurring with suboptimal CyA therapy and/or even further enhance graft survival rates obtainable with CyA alone. In the latter instance, we had obtained a 73 per cent one year cadaver graft survival rate with CyA with trough concentrations assiduously maintained in the range of 150 to 200ng/ml. We now plan to maintain trough concentrations between 50 to 100ng/ml while simultaneously administering retroplacental gamma globulin over the first four post-operative months.

## Background

We have previously provided evidence that a pooled, human-source, gamma globulin concentrate (recovered from the retroplacental blood of post-partum women) could enhance the survival rate of cadaver renal transplants when used adjunctively with azathioprine and prednisolone [1,2]. The rationale for its use in transplant recipients was based on the finding that, in contrast to gamma globulin concentrates recovered from non-gravid females, retroplacental gamma globulin effectively suppressed allogeneic proliferative responses in a series of mixed leucocyte culture experiments [3]. Since the mixed leucocyte culture response is thought to be the *in vitro* correlate of immune activation sequencing *in vivo*, we hypothesized that retroplacental gamma globulin might 'block or retard' the rejection process in its early phase of development. We were further encouraged to pursue this concept in transplant recipients because the preparation's content of alloantibodies was similar to that found in graft-enhancing serum preparations used successfully in experimental animal transplant models [4-6]. From the analysis of data obtained from the five year clinical trial in 98 first and second transplants [2], retroplacental gamma globulin enhances the graft survival rate at one year over that obtainable with azathioprine and prednisolone alone by a factor of 20 per cent.

## Revised CyA protocol with retroplacental gamma globulin

Primary and secondary cadaver graft recipients who have previously received one or more third party blood transfusions are eligible for entry into the study. Retroplacental gamma globulin will be administered intravenously (1.6g of retroplacental gamma globulin diluted to 100ml with normal saline): prior to and following transplantation; daily for 29 days; weekly for 12 weeks; then discontinued. Cyclosporin A will start at 10mg/kg/day and will be tapered by 1mg/kg every week thereafter until a maintenance dose of 5mg/kg/day is reached. CyA will be monitored by radioimmunoassay with the goal of maintaining plasma trough concentrations between 50 and 100ng/ml. Alterations in renal function, in the absence of overt renal failure, will be treated as follows: if trough concentrations are acceptable, the patient is pulsed with IV methylprednisolone; if trough concentrations are excessive (>100ng/ml), CyA is maintained and the patient observed.

## Conclusions

Limiting factors in the effective use of CyA include a high incidence of acute renal failure in the post-operative period and modest to significant increases (progressive?) in serum creatinine with its chronic administration. A significant reduction in the amount of CyA used may lessen the incidence and degree of these apparent dose-related adverse effects thus allowing for its continued use in transplant recipients. The concomitant administration of the human-source biological retroplacental gamma globulin may spare the recipient from a rejection process that might unfold with lower CyA blood concentrations or actually

enhance graft survival. This enhancing effect with retroplacental gamma globulin has already been demonstrated in patients who had previously been treated with azathioprine and prednisolone.

## References

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