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CHAPTER 38

Cyclosporin A and steroids for liver and heart transplantation

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1. Introduction

Combination therapy with Cyclosporin A (CyA) and steroids has improved the course of patients after cadaveric renal transplantation. Application of this therapeutic advance to the transplantation of cadaveric livers and hearts was a natural extension to be described in this communication.

2. Liver transplantation

29 patients were accepted for the clinical trial for the indications listed in Table 1. 8 of the recipients were in the pediatric age group (2–16 years) and the other 21 were 20–56 years old. The liver grafts were preserved with Collins solution for $1\frac{1}{2}$–

TABLE 1: Diagnoses in 29 liver recipients accepted for clinical trial

Chronic active hepatitis	8
Primary hepatic malignancy (3 hepatoma, one intrahepatic duct cell carcinoma)	4
Biliary atresia	4
Budd-Chiari Syndrome	3
Secondary biliary cirrhosis	3
Primary biliary cirrhosis	2
Sclerosing cholangitis (one with duct cell carcinoma)	2
Byler's Syndrome	1
Alpha-1-antitrypsin deficiency and cirrhosis	1
Congenital hepatic cirrhosis	1

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$10\frac{1}{2}$ h and transplanted by the same techniques as have been used in the past (Starzl, 1969; Starzl et al., 1979).

Donor recipient matching for HLA antigens was random. Because of urgent need, two donors were accepted in spite of ABO incompatibility (A to O and A to B). In three more cases, a positive cross match was present with complete killing of donor lymphocytes by pre-existing cytotoxic antibodies in the recipient serum. It is known (Starzl et al., 1979) that the liver is resistant to hyperacute rejection from preformed antibody states.

CyA usually was started a few hours preoperatively at 17.5 mg/kg and continued daily, usually with half the dose every 12 h. The quantities were reduced subsequently if toxic manifestations developed, of which suspected nephrotoxicity (Fig. 1) was the most important.

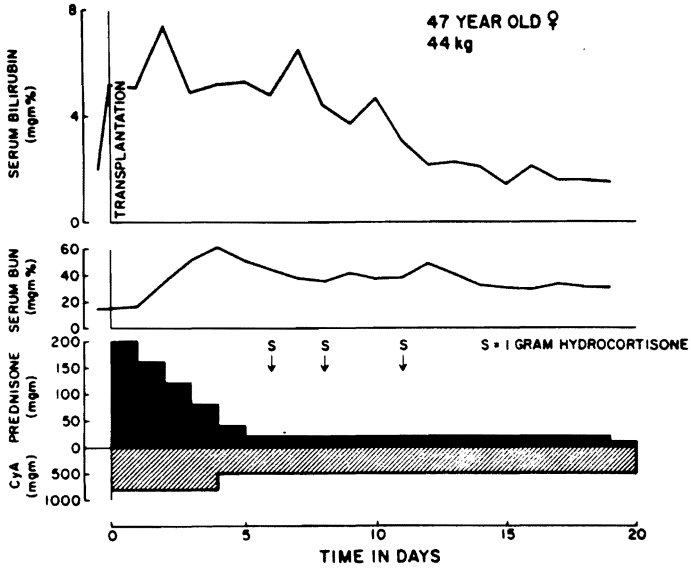

Fig. 1. CyA and steroid therapy in a woman with a hepatoma whose cirrhosis was too severe to permit subtotal hepatic resection. Note the 5 day initial burst of prednisone therapy, and the adjustment of CyA dose as the BUN rose.

In the Colorado part of the series, steroids were not given at first in half of the cases. When it became evident from clinical observations and biopsy evidence that rejection was common, steroids were begun on the day of operation. Adult patients who did not have profound metabolic abnormalities and who left the operating room in good condition were given the 5 day burst of prednisone described elsewhere in this symposium for renal recipients, starting at 200 mg and stopping with a maintenance of 20 mg per day (Fig. 1). Initial and maintenance therapy were scaled down in infants and children. If the patient was in poor condition, high dose initial therapy with steroids was omitted (Fig. 2).

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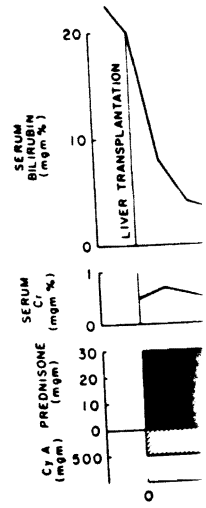

Fig. 2. Omission
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2.1. Colorado series

The 14 patients were operated upon between March and September 1980. Two recipients died on the operating table (Table 2) from technical complications and were not treated with immunosuppression. One of the remaining 12 died 19 days post-operatively of hepatic artery thrombosis.

All of the other 11 patients lived through the first post-operative year. Including the two intra-operative deaths, the one year survival was 78.6%, and excluding them, the one year survival was 92%. Many complications which were treated successfully (Starzl et al., 1981a,b) were the kind which had been almost always lethal under conventional immunosuppression (Starzl et al., 1969, 1979). The ability to maintain good graft function despite low-dose steroid therapy was the distinguishing feature of the CyA series.

Two patients died after a year (12 and 16 months). One had recurrence of a cholangiocarcinoma from her native liver, and the other from recurrent Budd–Chiari syndrome. Nine (64.3%) of the original 14 patients are still alive after $1-1\frac{1}{2}$ years, and all but one have normal or near normal liver function. Of those 12 actually treated with CyA and prednisone, the present survival is 75%.

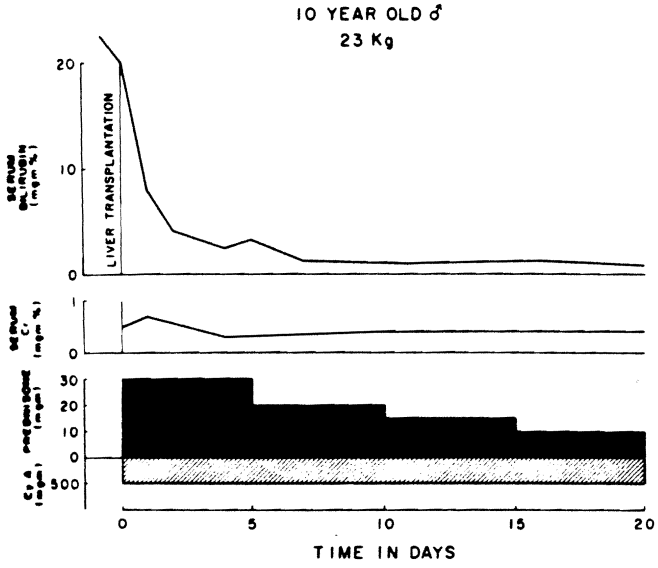


Fig. 2. Omission of steroid burst therapy in a 10-year-old boy who was thought to be at increased risk of pulmonary infection because of a recent gastrointestinal haemorrhage. He was transferred to the University of Pittsburgh from the Intensive Care Unit of a hospital in a distant city. The full dose of CyA has been well tolerated.

TABLE 2: Causes of death in Denver series of liver transplantations in CyA era (14 patients)

Operative	2*
Hepatic artery thrombosis (19 days)	1
Recurrent malignancy (12 months)	1
Recurrent Budd–Chiari Syndrome (16 months)	1

* Not treated with immunosuppression.

TABLE 3: Causes of death in Pittsburgh Series (15 patients)

Poorly preserved livers	4
(with technical errors	2)
(without technical errors	2)
Systemic aspergillosis	1

2.2. Pittsburgh series

15 patients were accepted for the trial. The first 4 (all adults) died after 4 to 16 days (Table 3). A feature common to these consecutive disasters was poor initial liver function including failure of clotting; technical errors in biliary tract reconstruction were also committed in two. Multiple organ failure and uncontrollable infections ensued. At autopsy, the livers had widespread necrosis but little or no evidence of rejection.

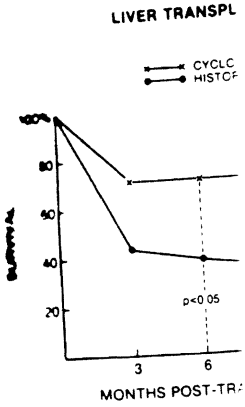
A deviation had been made from the previously standardized harvesting procedure leading to de-emphasis or omission of cooling by the portal venous route, and reliance on in situ hepatic arterial cooling.

After correction of this error, uniformly adequate livers were obtained and 10 of the next 11 recipients have survived for $1-4\frac{1}{2}$ months. All but one have been discharged from the hospital, including a child whose first liver was replaced with another graft after two weeks because of a huge *Candida* abscess which destroyed much of the right lobe. The only death in the last 11 cases was from disseminated aspergillosis at 8 days in a patient who was in Stage 4 hepatic coma prior to operation. Liver function is normal or near normal in the 10 survivors.

Nephrotoxicity of CyA in liver recipients has been studied by Klintmalm et al. (1981). Renal dysfunction was usually correctable by downward adjustments of CyA dosage. However, one patient required hemodialysis. No examples of CyA hepatotoxicity have been recognized.

2.3. Actuarial survival in combined series

Even including the two operative deaths in the Colorado series and the four flawed cases in the Pittsburgh series, the one year life expectancy has been raised to better than 70% in the CyA era, twice as high as in our previous total experience (Fig. 3). Calne et al. (1981) have reported a similar recent improvement corresponding to their use of CyA. Calne et al. (1979) were the first to use CyA in clinical liver transplantation.



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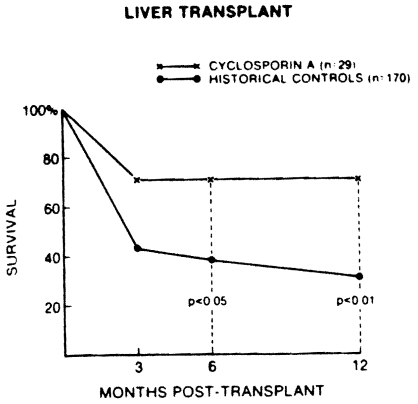

Fig. 3. One year actuarial life survival curve of the last 29 liver recipients, including two who died intraoperatively and 4 who received livers that were damaged by poor preservation. The actual one year survival of historical controls also is shown.

3. Cardiac transplantation

The University of Pittsburgh cardiac transplantation team (H. B. B., R. H., B. G.) performed 7 heart transplantations under CyA and steroid therapy from early April to late July 1981. Because no interval, however brief, of rejection and ineffective cardiac function could be accepted, the steroid withdrawal was done more gradually than that depicted in Fig. 1 in a liver recipient.

These cases, including their special management problems, will be reported separately. 6 of the 7 recipients (all adults) are alive after $1\frac{1}{2}$–5 months. The only death (from infection and heart failure) was at 10 weeks of a 48-year-old woman whose serum contained anti-donor T warm cytotoxic antibodies. The positive crossmatch was not known about in advance. Although the heart escaped hyperacute rejection, it was badly damaged.

4. Discussion and Conclusions

The grafting of organs such as liver and heart has not had the wide application of renal transplantation, in part because artificial life support systems analogous to the artificial kidney did not and do not exist. With the ability to control rejection more predictably as has been made possible with CyA and steroids, interest in transplantation of extra renal organs will surge. Although each organ will have special requirements, the principles of immunosuppression evolved with the simple kidney model will undoubtedly be applicable to all.

Acknowledgements

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I. Introduction

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