LIVER TRANSPLANTATION

New Approaches in the Use of Cyclosporine: With Particular Reference to the Liver

T.E. Starzl

THE REVOLUTIONARY influence of cyclosporine (CsA) on liver transplantation is so well known[1] that another article with this message would be a superfluity. Thus, I will talk about our clinical experience only briefly, and then mention some potential future developments that could involve CsA in one way or another.

THE CLINICAL IMPACT OF CYCLOSPORINE

Six weeks ago, Iwatsuki et al[2] summarized at a meeting in Pittsburgh the results with our first 1,000 liver recipients in the so-called CsA era. Life-survival was compared with that of 170 historical controls in whom treatment was with azathioprine (or cyclophosphamide) and prednisone, usually with antilymphocyte globulin (ALG).

The life-survival curve of patients before CsA-steroid therapy showed steep early losses so that $<1/3$ of patients entered (56 of 170) were living at the end of 1 year. Deaths beyond 1 year continued to occur so that at 5 years only 21% were still living (Fig 1). Now, with follow-ups of 7 to 18 years, 28 (16.5%) of the original 170 recipients are still alive.

The 1-year survival with the introduction of CsA in early 1980 was almost immediately doubled. The 1-year advantage gained has not been diluted by the further passage of time, as judged by actual or actuarial statistics. At 3 years and at 5 years, the projected survival has tripled. Thus, the gap is increasing with each year of further followup.

These improved results were obtained in spite of the inclusion for candidacy of an increasing number of high-risk recipients including older patients who were systematically excluded until 1984 and 1985 if they were over 50 years of age. In Fig 2, a year by year account is given of patients undergoing liver transplantation beyond the age of 50. By 1986, almost 35% were in the older age group. Similarly, age restrictions at the lower end were all but eliminated. Our youngest recipient was only 26 days old.

LIMITATIONS OF CYCLOSPORINE

In spite of its great value, CsA has two limitations that have some relationship to each other. First, the drug's nephrotoxicity imposes a dose ceiling. This was surprising in the first clinical trials, since renal injury had not been a striking feature of toxicologic studies in rats, dogs, or rabbits. The practical consequence has been that CsA has been used most efficiently as part of a pharmacologic

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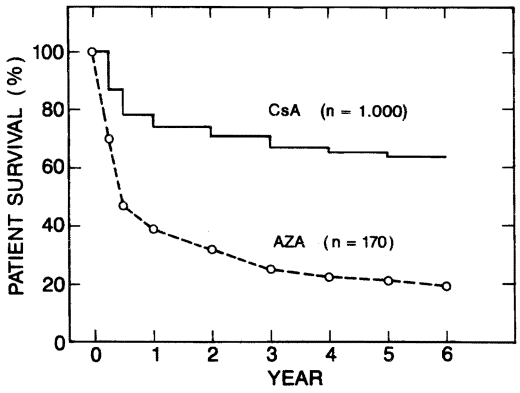

Fig 1. Actuarial survival rates of 1,000 patients treated with CsA/steroid therapy compared with surivial of 170 patients treated with the "conventional" therapy used before 1980.

cocktail, combining it with steroids, azathioprine, or lymphoid-depleting procedures including ALG or thoracic duct drainage.[1] The principle has been to reduce the specific toxicity of individual drugs by using them in smaller amounts. To be effective, this strategy requires that the different drugs in a regimen be at least additive, and optimally they should be synergistic.

Perhaps all rejections could be controlled if CsA could be administered without dose restriction. However, with the regimens that have been evolved, rejections ranging from annoying to irreversible have been seen with

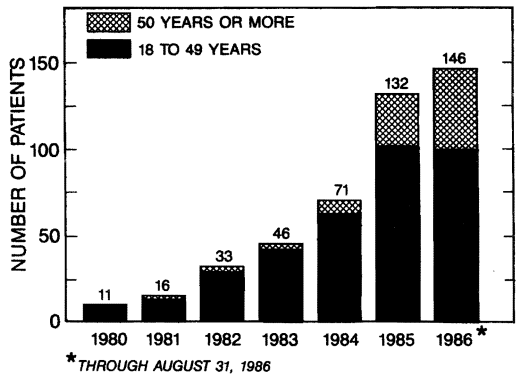

Fig 2. Liver transplantation in adults. Change in pattern of age distribution with recent increased numbers of older recipients. Note that the data for 1986 was for only the first nine months.

the kidney, liver, and other transplanted organs. Thus, failure to control rejection in all cases is the second limitation.

There is no reason to think that CsA is the last development that will occur in immunosuppression, and in fact, other candidates are already lurking in the wings. I will next talk about how research with CsA has paved the way for a search for other drugs, and then I will discuss briefly the most promising of these new agents (FK 506) as it could relate to liver transplantation or the transplantation of other organs in the future.

IN VITRO STUDIES

When CsA was developed, more was accomplished than the mere production of a new and eminently practical agent. Possibly even more importantly, powerful new techniques were developed that made it possible in test tubes or culture media to dissect the mechanisms of drug action as these affected lymphocyte population; to study the intrinsic cytotoxicity of the agents on cell cultures; and to measure in highly quantifiable test systems the interactions (including synergism) of different drugs. These techniques have made it possible with a few days of effort to acquire information that previously was completely inaccessible or that required years to accumulate.

Zeevi and Duquesnoy in Pittsburgh have referred to these techniques as mini-transplant models.[3-5] From biopsies of hearts and livers, they obtained clones of primed lymphocytes that had been exposed to donor-specific antigen by virtue of transplantation (Fig 3). When donor spleen, which is saved at the time of organ harvest and preserved, is added to the recipient lymphocyte culture, the "primed" recipient lymphocytes proliferate (cell expansion) with very little delay (Fig 4). The mechanisms of the expansion can be studied qualitatively and quantatively by collecting interleukin 2 (IL2) or other lymphokines from the culture medium and adding them to IL2-dependent cells. The proliferation or other

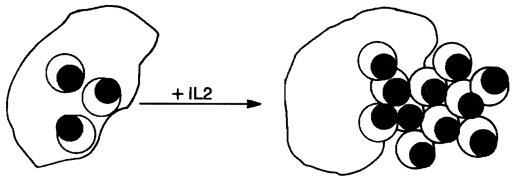

Fig 3. Propagation of activated lymphocytes from human biopsies with interleukin.

response characteristics of these IL2-dependent cells provide an end point for a biologic assay.

The ability of CsA or other drugs to prevent this expansion of a human lymphocyte population is illustrated in Fig 5. In the liver or heart biopsies of patients undergoing severe or even intractable rejection, clones have been found of CsA resistant lymphocytes side-by-side with sensitive clones (Fig 6).[6] In such cases, the new experimental agent, FK 506 (Fujisawa Pharmaceutical Co, Ltd, Osaka, Japan), about which I will say more in a moment, used alone or added to CsA, can eliminate the rogue clones (Fig 7).[7] It is fascinating that CsA, azathioprine, and FK 506 are all synergistic with each other with in vitro[7,8] or in vivo models.[9-11] FK 506 and CsA have an identical or at least almost identical, mechanism, namely inhibition of the production of IL2.[8,12]

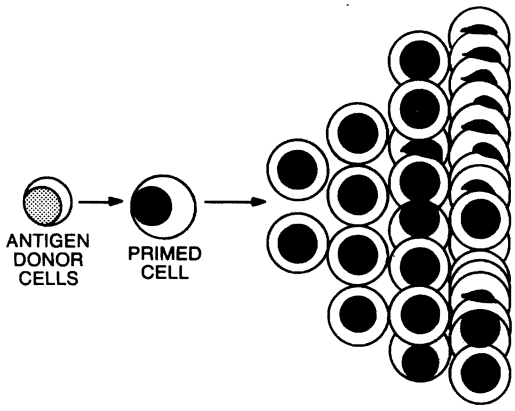

Fig 4. Lymphocyte culture technique in which human lymphocytes obtained from biopsies and cultured are exposed to donor cells. Clonal expansion results.

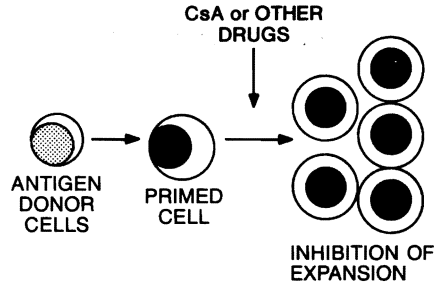

Fig 5. Prevention or inhibition of clonal expansion in primed human lymphocyte cultures by addition of CsA or other drugs.

IN VIVO STUDIES OF NEW DRUGS AND COMBINATIONS

As already mentioned, the most promising of the new drugs is FK 506. This agent, which is derived from a strain of Streptomyces, was reported verbally by Ochiai et al[12] in Helsinki in August 1986. This first description of FK 506's remarkable immunosuppressive properties was published only 8 months ago.[12] Yet, a complete symposium of all that is known of FK 506 was held in Gothenburg, Sweden, by June 1987 and published in a special volume of *Transplantation Proceedings* in October 1987.[13]

In rats submitted to ACI to Lewis heterotopic heart transplantation, the control of rejection with FK 506 has been reliable and with little toxicity.[9,12,14] FK 506 is synergistic in rats with CsA alone and with CsA plus low doses of steroids.[9] Partial tolerance induction, or something resembling it, has been made possible with only three daily doses of FK 506 injected four, five, and six days after transplantation.[9,11]

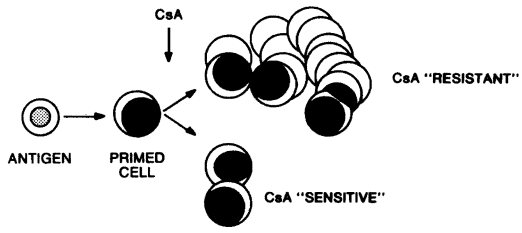

Fig 6. Development of CsA-resistant clones in liver or heart biopsies that were undergoing clinical rejection.

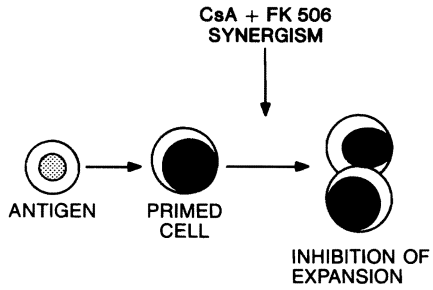

Fig 7. Disappearance of "rogue" clones by the addition of the experimental drug FK 506.

FK 506 is toxic in dogs, causing lethal emaciation and wide-spread vasculitis. In spite of this, the results with canine renal and hepatic transplantation have been comparable with those with CsA. Using CsA and FK 506 together, with or without small doses of steroids, the best results ever obtained with canine renal transplantation have been reported by Todo et al.[10,11]

Transplantation studies in cynomolgus monkeys and in baboons are underway as a last step in deciding if clinical trials are justified and if so, how to engage in these. It is our present expectation that CsA and low doses of FK 506 will be used together, with or without small doses of steroids. With this combination, the limiting factors of nephrotoxicity and refractory rejection that exist with the present day use of CsA could become a thing of the past. Whether these are realistic predictions or merely expressions of hope remains to be seen.

OTHER USES OF LIVER TRANSPLANTATION

Liver transplantation has profoundly affected the practice of hepatology. The indications for liver replacement are like a table of contents for a textbook of liver disease, in that any lethal, non-neoplastic disorder constitutes a potential reason for orthotopic liver transplantation. The great burst of both application and acceptance of this procedure is undoubtedly over, but perhaps exciting times are still ahead. In a recent inquiry by an Italian journalist, the question was posed "Do you think that in the next decade a 'puzzle man' with heart, liver, and pancreas taken from other human beings might be feasible?" The answer is that there are already numerous examples of puzzle men and women who have received a heart and kidney, a pancreas and kidney, a heart and lungs, a liver and kidney, and even a heart and liver. The increasing boldness with which transplantation is being developed makes it certain that other and more complicated combinations will be forthcoming in the near future.

Last week, an ancient operation developed more than a quarter of a century ago in dogs,[15] was pulled from the moth balls and used to treat a 3-year-old child who had lost all of her intestines from a perinatal midgut volvulous. After 3 years of parenteral hyperalimentation, the patient had developed hepatic failure. Now weighing 35 pounds, she was given a new stomach, small bowel, colon, liver, and pancreas in continuity from an 8-pound donor. This recipient has done well so far in a clinical trial that would have been inconceivable only a few years ago without the improved immunosuppression made possible by the CsA with which she is being treated, together with prednisone.

A threat of unknown seriousness for this child is graft-*v*-host (GvH) reaction in which the lymphoid tissue transferred by the multivisceral graft could prove to be a lethal instrument directed against the recipient. Serious GvH reactions have been seen in recipients given livers as reported by Burdick et al[16] at the Johns Hopkins Hospital and in our own institution, but this has been a rare complication of liver transplantation alone. It is to be expected that very effective immunosuppressive therapy given for the purpose of preventing classical rejection could also keep a GvH reaction at bay.

SUMMARY

Liver transplantation in the highly practical form that exists today has been made possible by multiple agent immunosuppres-

sion of which the most important component is CsA. Present day practices of immunosuppression are certain to be changed and probably in the near future in order to increase the effectiveness of therapy and to reduce the nephrotoxicity and other side-effects that until now have inhibited further applications. The introduction of new drugs such as FK 506, some of which are clearly synergistic with CsA, could ameliorate past problems with drug toxicity. With such improvements, and possibly even with more clever use of therapy that already is available, wider and more complex use of liver transplantation will be possible.

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