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Clinical Aspects of Cyclosporine Therapy: A Summation

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In Describing the Australian trials, Sheil complimented those in the Sandoz Corporation for their professionalism and integrity, a remark that is germane to the Houston meeting. The program was developed not as a triumphant forum but in order to assess the problems as well as the prospects that transplantation will face in the new era which will be started this summer with the general availability of cyclosporine. A good look has been taken at this new pharmacologic emperor without its clothes, and cyclosporine has withstood the scrutiny quite well.

The reason for the excitement can be stated simply. With cyclosporine, it has been possible to transplant some of the solid organs with a success not previously possible and to carry out other kinds of solid organ transplantation that were previously beyond our grasp. Such successes provided half of the clinical story of this meeting. The other half concerned the price for these increased expectations.

The most extensive experience has been with the kidney, and certainly the most meaningful data have come from cadaveric transplantation. One-year graft survival after familial transplantation in good centers has been so high (greater than 70%) for almost two decades that statistically significant further increases with a new form of immunosuppression would be difficult to achieve. Thus, the superior results from Kyoto, Japan, with greater than 90% 1-year graft survival after parent-to-offspring transplantation under cyclosporine-steroid therapy were not considered better than those obtainable with conventional treatment in this group's historical experience. The same reservation applied to about 45% of the cases in the Minnesota randomized trial, in which the 1-year graft survival after consanguineous transplantation was better than 85% with both cyclosporine-steroid therapy and with the combined use of azathioprine, prednisone, and ALG.

Cadaveric renal transplantation under cyclosporine-steroid therapy (with a variable steroid component) versus conventional therapy were compared in multicenter trials in Europe and in Canada. Both studies showed a 20% 1-year advantage in the cyclosporine group. Adverse factors for the cyclosporine limb in the Canadian trials were said to be machine perfusion of the renal grafts for more than 24 hr or an ischemia time of more than 45 min during the construction of vascular anastomoses. It was interesting that one of the participating teams, from the Mount Sinai Hospital, Toronto, presented what amounted to a minority Canadian report. Their preexisting policy had been to treat cadaveric kidney recipients with azathioprine, prednisone, and Minnesota ALG. With this triple-drug therapy, they achieved better than 90% graft survival, compared to 74% with the proscribed cyclosporine-steroid combination; the results barely missed statistical significance. In a subset of the European trial reported from Birmingham, England, the 1-year graft survival was almost identical (70%) in the experimental and conventional groups, but the enormous advantage in the

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cyclosporine arm was that about half of the successfully treated recipients were not being given steroids. In a Helsinki report, the 1-year control and test groups both had 80% graft survival.

The importance of giving weight to the quality of life by avoiding excessive steroid treatment was most strongly emphasized in the descriptions of the randomized Australian trials in which cyclosporine alone was compared to conventional azathioprine-prednisone treatment. Although the life survival curves of the grafts were about the same, with 70% 1-year cadaveric kidney function at 2 years, the quality of life was better in the experimental series.

In the United States, randomized trials of cadaveric transplantation in single centers were conducted by the Pittsburgh, Boston, Houston, and Minnesota teams. Because of the wide divergence of results between the experimental and conventional azathioprine-prednisone groups, the trials in Pittsburgh and Houston had to be stopped. The trials have continued at the University of Minnesota for the simple reason that there has been no difference at that institution with cyclosporine-steroid therapy versus treatment with azathioprine, prednisone, and ALG. The cadaveric graft survival has been in the 80% range, with a 1-year patient mortality of about 10% in both conventional and test groups.

Throughout their investigations of cyclosporine and in the period preceding their use of this new drug, the Houston team has made a particular effort to stratify all of their recipients on the basis of preexisting immune reactivity. By so doing, they have been able to classify their recipients over the last several years into high, intermediate, and low immunologic responders. The value of cyclosporine-steroid therapy was particularly striking in the high-responder group; in the low-responder group, the results were already so good with conventional therapy that cyclosporine was more a convenience than an overriding advantage. In discussing the Minnesota experience at one of the forum meetings, Kahan speculated that high responders may have been culled out by preoperative preparation with at least 10 transfusions; the consequence would be to convert many high responders to a nontransplantable state because of stimulation of preformed antibodies. The transfusions plus the obligatory splenectomy in the Minnesota study could have edged those patients who made it through the full preoperative preparation into the nonresponsive group. No one could really argue with this carefully thought-out “strategy” of transplantation, but what was questioned was if this kind of pretransplant preparation was really going to be necessary or desirable in the future. The ability to treat patients efficiently and effectively without extensive preparation (including a major operation) before transplantation may be especially important in patients who are at high risk because of advanced age or other adverse factors. Groth of Stockholm reported an outstanding series of cadaveric transplantations under cyclosporine-steroid therapy in a group of patients who were 55 to more than 70 years old. The results were twice as good as in historical controls.

A summary statement avoiding excessive enthusiasm as well as undue pessimism would have to note that the results with cyclosporine-steroid therapy have never been inferior to those achieved by any of the investigating groups using their own version of conventional therapy for controls and that they usually have been superior. This in itself says a lot about the quality of the immunosuppression provided by cyclosporine-steroid therapy, since its effective use has required a major intellectual adjustment by those accustomed to the use of azathioprine and prednisone (with or without ALG). Nephrotoxicity has been the most serious side effect of cyclosporine, meaning that a reduction in cyclosporine dosage is frequently the most appropriate response to a secondary decline in renal function, rather than the reflex increase in steroid doses that has been so often called for in the past.

The role of plasma or blood cyclosporine analysis in reaching a final dose under such circumstances is by no means clear. All groups are trying to use pharmacologic monitoring, but Ferguson, in a study of 70 consecutive Minnesota cases, found no correlation whatever between blood cyclosporine levels and nephrotoxicity. The Houston and London, Ontario, groups were in sharp disagreement. Yet all observers conceded that the blood-level determinations have permitted identification of specific situations in which the trough levels of cyclosporine were either much too high or surprisingly low. It is hard to believe that blood or plasma analysis will not have some value, at least in isolated cases. At the same time, it is equally clear that good clinical management can be carried out without this luxury.

It has always been comforting for clinicians to turn to the pathologist for final arbitration of disputes about the pathogenesis of complications. These roles have almost been reversed in trying to clearly distinguish cyclosporine nephrotoxicity and homograft rejection. Efforts were reported by the Minnesota group to categorize the histologic findings in subnormally functioning kidney grafts according to the clinical response to steroid therapy. Absolutely reliable guidelines for adjustment of therapy have not been delineated by this approach. K. A. Porter of London looked at a number of renal graft biopsies from our early cyclosporine experience. Rejection was common, but its features differed from those seen with conventional immunosuppression only in a somewhat greater proportion of the eosinophils in the infiltrating cells. In kidneys examined from both heart and hepatic recipients, Porter could not find specific lesions of drug nephrotoxicity. Discussion of this problem is certain to enliven clinical and pathologic conferences for years to come.

Since the beginning of clinical trials in renal transplantation, the unquestioned nephrotoxicity has explained higher average levels of serum creatinine in cyclosporine-treated kidney recipients than in successfully treated controls. Even if the creatinine is high early after transplantation (as high as the 3–4 mg/dl range), there is no urgency to reduce the cyclosporine dose if the patient feels well and if the abnormal creatinine is not rising. Our own policy has been to try to invest about 2 months of maximum cyclosporine dosage during the induction of graft acceptance. A premature pullback of dosage can lead to rejection. The coexistence of nephrotoxicity and rejection suggested by us some time ago has been supported strongly by the Houston, Stockholm, and Minnesota clinicians with evidence presented at this meeting. Personally, I believe that the extensive and beautiful Minnesota pathology studies could be interpreted as an expression of this dual problem. Anyone using cyclosporine at this time should carefully read the therapeutic strategies that have been developed by the various groups including ours to accommodate both possibilities of rejection and nephrotoxicity.

The other side effects of cyclosporine were mentioned frequently throughout the meeting. The hypertension and hyperkalemia that have been subjects of separate papers are certainly manifestations of the drug’s nephrotoxicity. Hepatotoxicity, hirsutism, tremors (and even possibly seizures), and gingival hyperplasia have been reduced or relieved by dose reduction. When life-threatening infections have appeared in any large numbers under cyclosporine and steroids, the usual conclusion has been that overimmunosuppression with one or the other of the two agents has been responsible. In earlier reports from the University of Minnesota, it appeared that infections with bacteria, fungi, protozoa, and viruses were all markedly less under cyclosporine-steroid therapy than under conventional immunosuppression, but Najarian reported that this advantage in Minneapolis had been narrowed if not lost in their later experience, with the striking exception of the cytomegalovirus syndromes. The bewildering cross section of infections and how the patterns differed with different kinds of transplantations in Pittsburgh were described by Ho.

A striking observation in almost all of the renal trials has been the remarkably good results in cadaveric renal retransplantation, even including patients with widely reacting T-warm antibodies or with a history of aggressive rejection of multiple previous organs. In the past, the justification for trying too hard to retain kidney grafts (with a resulting high mortality) has been the clouded future of recipients who rejected kidneys and then faced cadaveric retransplantation. That justification does not seem to exist anymore using cyclosporine-steroid therapy. As that new fact of life becomes broadly appreciated, the 1-year patient mortality after primary transplantation is apt to reach the 5% or lower level that will represent an irreducible minimum imposed by disease of other organ systems.

It would be easy to spend this entire summary talking about renal transplantation—and with some justification because of the broad applicability of the lessons being learned. The ripple effect certainly has been felt with liver transplantation, which (under cyclosporine) has become about twice as safe as in the past. The great improvement made possible with cyclosporine has increased the frequency and boldness with which liver replacement has been carried out, and now the prospect of escalating this advantage into other improvements (including technical) is a very bright one. Since the liver is the major site of metabolism of cyclosporine, all kinds of problems could easily be visualized about dose control. The major prediction in liver recipients could be of astronomical overdosage, but in fact the opposite has occurred, in that unreliable absorption of the drug has been the most consistent problem with consequent underdosage. Our liver recipients are now receiving double-route cyclosporine therapy, beginning with intravenous doses and continuing this intravenously for at least 2 weeks, long after the resumption of an oral diet and oral cyclosporine. The changeover from the double-route administration to an oral dose alone can be greatly aided by the systematic measurement of blood cyclosporine levels. The several groups who discussed their experience with liver transplantation under cyclosporine did not carry out randomized trials, and it is unlikely that this will ever be done.

The same lack of enthusiasm about randomized trials in cardiac transplantation was evident. The Stanford heart transplanters have achieved a 1 -year survival of 80%, with a 2-year actuarial survival in excess of 70%. The fact that other groups have been able to do almost as well in Pittsburgh, Cambridge, and Houston means that pressure to expand this type of clinical service is bound to increase. At Stanford, the more complex heart-lung transplantations, which were not previously possible either in experimental animals or humans, have been successful in 8/11 patients who have been followed for 2 months to 2 years. In Pittsburgh, the survival record with heart-lung transplantation has been 3/5. Shumway has speculated that isolated lung transplantations may be infinitely more difficult than composite thoracic organ transplantation, but the merits of that argument aside, Veith has accomplished single-lung transplantation in dogs using cyclosporine, although he has not yet succeeded in human patients.

With cyclosporine, it will be surprising if major advances cannot be made in pancreas transplantation. Sutherland pointed out that this has not been achieved at the University of Minnesota. The same conclusion was reached by Dubernard of Lyon, but Groth has had successes with half of his cadaveric segmental pancreas transplantations in Stockholm during the last year. The prospect of using the pancreatico-duodenal-jejunal composite grafts now that better immunosuppression is available was raised, and two successful cases with perfect results after 1 and 3 months were presented from Pittsburgh. Parenthetically, both of these recipients are carrying about 3 ft of donor small intestine. Several groups are poised to attempt intestinal transplantation in humans, a procedure that has been successfully carried out in mongrel dogs with survival of almost 2 years.

Most of what I have summarized has come from recent trials. In chronic survivors after various kinds of transplantation, the question keeps coming up of the possible desirability of early or late conversion from cyclosporine to maintenance therapy with azathioprine. This will be necessary in some patients, but at what frequency is debatable. In our renal graft recipients treated 3 years ago, the conversion rate was about 20%, and in this subgroup, 40% subsequently rejected their grafts, as Klintmalm has reported. Our switch rate has steadily declined; it is now about 5%. The opposite trend is identifiable in the data presented from Minnesota, and, of course, all patients at Oxford have been converted at 90 days.

In the recipients of hearts and livers, the predominant conversion has been in the other direction—from conventional azathioprine-prednisone therapy to cyclosporine. Typically, a patient whose survival with one of these organs years after transplantation depends on unacceptably high steroid doses has been switched to cyclosporine and the prednisone has been discontinued. We have carried out this change in half a dozen liver recipients. The hepatic function has not deteriorated in any case, and in most it has actually improved. The advantages and dangers of this switchover were discussed in one full session and cannot be adequately summarized here. It should be noted that there is a potential risk of mixing drugs, especially in the early postoperative period, as was exemplified by the frightening experience in Lyon, which resulted in a nearly 50% incidence of lymphoproliferative complications in a small series of patients given azathioprine, prednisone, ALG, and cyclosporine, in that general order.

Except for this experience, the incidence of de novo malignancies under cyclosporine-steroid therapy has been acceptable. It looks as if the incidence of lymphoproliferative complications is going to be less than 2%, but the implications of even that figure are relatively bland. Rosenthal reported that the simple discontinuance or reduction of immunosuppression (both cyclosporine and steroid doses) in patients with so-called lymphomas resulted in the involution and disappearance of the lesions. Most of the lymphomas seen under immunosuppression are probably associated with (or caused by) the Epstein-Barr virus.

Where cyclosporine will fit in the future of bone marrow transplantation is difficult to predict. The cross section of side effects of cyclosporine in bone marrow recipients has been very broad, and almost invariably some other potentially toxic drug was thought to have had an adverse interaction with the cyclosporine. The most common culprits were antibiotics, especially those used for their antifungal effect. It may be that cyclosporine will not influence practices in bone marrow transplantation to the extent that looks probable with solid organs, but it would be less than fair not to point out that the pioneering observations of Powles about the control of graft-versus-host reactions in humans made 4 years ago have been confirmed under a number of clinical circumstances.

So much material was presented at this conference and with such immediate clinical applicability that I find it impossible to do justice to the conference and to its participants in this summary. The conference came at a uniquely propitious moment, since cyclosporine will become available to all clinicians within the next few weeks or months. I believe that we of the transplantation community owe a unique debt to the fathers of cyclosporine, Jean Borel, David White, and Roy Calne, (who could not be here); to those highly responsible men and women in the Sandoz Corporation who have permitted and encouraged us to look at the blemishes as well as the perfections of cyclosporine; and to the masterful host of this conference, Barry Kahan, who, as I have remarked to others, is one of the great scientist-surgeons in the world today.

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