

## Review Article

# Organ allotransplantation since the advent of cyclosporin

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### Summary

Successful long-term organ transplantation has been made possible by the use of conventional immunosuppression. In contrast with transplantation of other organs, transplantation of the kidney has become an accepted successful form of therapy, 80% of patients being fully rehabilitated. However, complications of therapy are frequent and severe and include bone necrosis, cataract formation, infections and stunted growth in children.

The discovery of the immunosuppressive properties of cyclosporin A (CYA) by Borel in 1976 offered new hope to recipients of hepatic, cardiac, pancreatic and heart-lung transplants, since rejection frequently resulted in death. Although the use of CYA has led to significant accomplishments, subsequent studies have documented deleterious side-effects including nephrotoxicity, hepatotoxicity, hirsutism, gingival hyperplasia, tremors and tumours. Yet despite the side-effects, CYA has proved to be a promising immunosuppressive agent for use in human organ transplantation and is at present being evaluated in transplant centres throughout the world.

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The legendary transplantation of a dead Ethiopian Moor's leg to replace the cancerous leg of a white man by Cosmas and St Damian was the inspiration for several Renaissance paintings.<sup>1</sup> The primitive skull trephination seen in Bronze Age skulls is possibly the oldest evidence of grafting. An interesting account of early skin allografting is illustrated by the story that Winston Churchill donated a small piece of skin to a wounded fellow officer in 1898.

The first human allograft kidney transplant was carried out in Kiev in 1933 by the Russian surgeon Yurig Voronoy (1895 - 1961); the case report was published in the West in 1936.<sup>2</sup> The sharing of the Nobel Prize for Medicine and Physiology in 1960 by Burnet and Medawar contributed to a better understanding of the immunology of transplantation.<sup>2</sup> The modern era of organ transplantation was ushered in during 1960 by the development of tissue typing, of regular pretransplantation haemodialysis and the introduction of immunosuppressive agents.

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In 1960 Calne, working at the Buckston Browne Farm, UK, reported the successful prolongation of canine renal allografts with the antimetabolite drug, 6-mercaptopurine. Later, azathioprine (AZA), a derivative of 6-mercaptopurine, prepared by Drs Elion and Hitchings of Burroughs Wellcome, New York, was used for clinical transplantation in Boston. The combination of steroids and AZA used today in most immunosuppressive protocols worldwide was described by Starzl *et al.*<sup>3</sup> in 1963. In 1967 Starzl *et al.*<sup>4</sup> reported the first clinical use of antilymphocyte serum after successful experimental studies in rats which showed prolongation of skin allografts.

The immunosuppressive properties of cyclosporin A (CYA), a metabolite isolated from the culture broths of the fungal species *Tolypocladium inflatum* Gams, previously known as *Trichoderma polysporum* Rifai, was reported by Borel<sup>5</sup> and his co-workers in 1983. CYA was introduced into the clinical arena in 1978 by Calne *et al.*<sup>6</sup> who subsequently showed the effectiveness of the drug in renal, liver and pancreatic transplantation in man.

The current status of renal, cardiac, lung, liver, pancreatic and bone marrow transplantation and the impact the introduction of CYA as an immunosuppressive agent has made on transplantation practice are reviewed.

### Immunosuppression of organ allograft recipients

Until recently prolongation of organ allograft survival in man has been possible with the administration of conventional immunosuppressive agents (AZA and steroids), antilymphocyte globulin (ALG) and irradiation. Although total body irradiation was one of the first forms of immunosuppression used in human renal allograft recipients, its application today is of historical interest only because of the danger of bone marrow suppression. In recent years there has been considerable interest in the use of total lymphoid irradiation (TLI), a form of irradiation practised for many years in the treatment of Hodgkin's disease. TLI has proved to be immunosuppressive in mice,<sup>7</sup> dogs,<sup>7</sup> primates<sup>8</sup> and man,<sup>9</sup> and its potential application to clinical transplantation has been reviewed by Myburgh *et al.*<sup>10</sup> The most effective ALG has been raised in rabbits but one of the disadvantages of its use is the difficulty of assessing its potency *in vitro*. In most studies the preparation was administered intravenously in high doses for at least 14 days, starting on the day of transplantation. ALG has also proved effective in the treatment of acute rejection episodes.<sup>11</sup>

A combination of AZA and steroids has proved successful in ensuring long-term immunosuppression of organ allografts in man.<sup>11</sup> AZA, an antimetabolite which is cycle specific, is effective against proliferating cells and is administered after transplantation. Although AZA inhibits RNA and DNA synthesis, antibody production and graft rejection, it is relatively ineffective on its own and is usually combined with steroids. Bone marrow suppression is the main toxic complication and manifests as leucopenia, thrombocytopenia or anaemia.<sup>11</sup>

## Immunosuppression with CYA

After the demonstration of the unique properties of CYA as an immunosuppressant by Borel,<sup>5</sup> Calne and White<sup>12</sup> and Calne<sup>13</sup> were the first to demonstrate CYA's ability to prolong organ allograft survival in laboratory animals. Since this important discovery, CYA has been found to be markedly effective as an immunosuppressant in a variety of animal species with significant suppression of rejection of heart allografts and xenografts in rats, primates and pigs; kidney allografts in rats, dogs and rabbits; pancreatic allografts in rats, primates and dogs; and skin allografts in mice and dogs.<sup>14-23</sup> CYA was shown to inhibit humoral immunity to T-cell-dependent antigens and also to suppress cell-mediated immunity. CYA is primarily lymphocyte specific and acts at an early stage of its activation.<sup>24</sup> It has been postulated that CYA affects the function of T lymphocytes and that many of its *in vivo* effects stem from this modification of T-cell function. Two different models, the subset and signalling models, have been proposed by Lafferty *et al.*<sup>24</sup> to account for the biological activity of CYA. Recent studies suggest that CYA prevents the production of lymphokines such as interleukin 2 from helper T lymphocytes after exposure to antigen, thus preventing the generation of specific cytotoxic T lymphocytes.<sup>25-30</sup>

Cyclosporins A, B, C and D were initially isolated from the culture broth of *T. inflatum* Gams. CYA used in clinical transplantation, a cyclic undecapeptide, has a molecular weight of 1202 daltons, contains 11 amino acids, is neutral and hydrophobic, and is almost completely eliminated by hepatic metabolism and broken down to at least 17 metabolites. Absorption of CYA from the gastro-intestinal tract is slow and incomplete with peak blood concentrations occurring between 2 and 4 hours after oral administration. About 90% of the dose binds to blood proteins, with red blood cells taking up 50%, leucocytes 15%, and lipoproteins 25%, leaving 10% free in plasma fluid.<sup>31,32</sup>

CYA can be measured in both plasma and whole blood samples by radio-immunoassay or high-performance liquid chromatography.<sup>33</sup> The clinical use of CYA is difficult because of the narrow therapeutic window between inadequate immunosuppression at low doses and the adverse effects of hepatotoxicity, nephrotoxicity, and septic complications resulting from overadministration. The therapeutic efficacy and safety are not clearly related to the dosage administered and a definite therapeutic range for CYA has not been determined. Nephrotoxicity can occur at any concentration, but is less frequent at concentrations below 300 µg/ml.<sup>33</sup> In renal allograft recipients, a slowly rising creatinine level and a high blood CYA concentration usually suggest nephrotoxicity.<sup>32</sup> A rapidly rising creatinine level and low blood CYA concentration suggest rejection and the individual sensitivity of patients to CYA is a major problem in clinical use.<sup>32</sup>

Drug interactions with CYA are poorly documented, but ketoconazole, an antifungal agent, has been reported to raise the blood level of CYA and may precipitate nephrotoxic reactions.<sup>32</sup>

The dosage of CYA for organ allograft recipients must be individualized; the majority of patients tolerate a maintenance dose of 2 - 5 mg/kg/d intravenously or 5 - 10 mg/kg/d orally.<sup>32</sup> Adjustments to the oral maintenance dose are frequently indicated and depend on the blood CYA level, creatinine concentration, and signs of adverse side-effects. Patients intolerant to CYA may be switched from CYA to a combination of AZA and prednisone.<sup>34-36</sup>

CYA has been reported to have potential therapeutic application in other diseases with an immunological pathophysiology — juvenile-onset diabetes mellitus, psoriasis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, systemic lupus

erythematosus and auto-immune uveitis. It also has potential antimalarial and antischistosomal effects.<sup>5</sup>

The most troublesome side-effect of CYA administration is nephrotoxicity.<sup>37</sup> Differentiation between renal allograft rejection and CYA nephrotoxicity is a major dilemma in patient management. Hypertension, hyperkalaemia, and hyperuricaemia are frequently observed during CYA treatment. CYA-induced neurological effects include tremors, paraesthesiae, muscle weakness, sensitivity to extremes in temperature, and seizures. Hepatotoxicity is a serious adverse effect of CYA manifested by elevated bilirubin and liver enzyme levels.<sup>32</sup> These liver function changes are usually dose-dependent, and can be reversed by reducing the dosage. Other adverse reactions include hirsutism, nasal congestion, hyperplasia of the gums, and transient gastro-intestinal ileus. Although there is an increased incidence of malignancy in transplant recipients receiving immunosuppressive drugs the relationship between CYA and lymphoma is not clear.<sup>32,38</sup>

## Impact of CYA on clinical organ transplantation

### Renal transplantation

Calne<sup>12</sup> in 1978 first treated a cadaveric renal allograft recipient with CYA and demonstrated the potent anti-rejection properties of CYA. Of 38 patients with functioning grafts in White and Calne's<sup>17</sup> initial CYA study, 32 were fit for full-time or part-time employment, the degree of rehabilitation being inversely related to age. Nephrotoxicity was by far the most serious side-effect. Since Calne's original clinical study, other trials of CYA have shown potent immunosuppression without myelosuppression and without the high incidence of adverse effects.<sup>39-42</sup> In another study of 39 unmatched, diuresing, cadaveric renal allograft recipients treated with CYA alone the 1-year actuarial graft survival was 86%.<sup>17</sup> Subsequent studies by Starzl *et al.*<sup>39</sup> demonstrated that the addition of steroids warranted a reduction of CYA, thus diminishing the incidence and severity of nephrotoxicity while maintaining 80% 1-year actuarial graft survival.

The results of these uncontrolled trials have led to prospective randomized trials comparing CYA therapy and standard immunosuppressive drug regimens.<sup>43-45</sup> Splenectomized and transfused adult uraemic recipients of renal allografts, from cadaver or HLA-non-identical related donors, were randomized into one of two immunosuppressive regimens in the Minnesota study.<sup>43</sup> One group received CYA and low-dosage steroids, while the other group received AZA and a relatively high dose of prednisone plus ALG. At 1-year follow-up, 92% of the CYA and 95% of the AZA patients were alive, and 87% of the CYA and 80% of the AZA patients had functioning grafts. The difference between CYA- and AZA-treated recipients, overall or in subgroups, was statistically insignificant. The study's interim analysis shows that graft survival rates in patients treated with AZA are as good as those treated with CYA. Furthermore, the Minnesota study has reported on the advantages and disadvantages of CYA compared with AZA. Disadvantages included a longer duration of acute tubular necrosis, higher creatinine levels at all times after transplantation and difficulty in the management of hypertension and hyperkalaemia.<sup>43</sup> The advantages of CYA included fewer viral and bacterial infections, shorter hospitalization, and fewer rejection episodes than in AZA-treated patients. Kahan *et al.*<sup>46</sup> have confirmed that a combination of CYA and prednisone provides potent immunoprophylaxis without increasing patient mortality.

Apart from the troublesome side-effect of nephrotoxicity, a 1-year renal allograft survival of approximately 80% can be achieved by CYA immunosuppression.

## Cardiac transplantation

Heart transplantation has evolved over the past decade to a therapeutic option for end-stage cardiac patients with otherwise untreatable disease. Although cardiac transplantation has achieved acceptable results with conventional immunotherapy, the mortality rate has been substantial. The initial years of heart transplantation were marked by widespread enthusiasm and disappointing results. Changes in cardiac transplantation since these early efforts have resulted in improved survival; this is attributed to better donor/recipient selection, earlier diagnosis of rejection and more effective treatment of rejection episodes. Cardiomyopathy and ischaemic heart disease have been the main indications for cardiac transplantation.<sup>47</sup> The chief criterion for patient selection is the presence of end-stage cardiac disease, irremediable by any other form of therapy associated with a life expectancy of only a few months. Contraindications include irreversibly elevated pulmonary vascular resistance, age over 55 years, insulin dependent diabetes, recent unresolved pulmonary infarction or underlying systemic disease that may be exacerbated by immunosuppression, and psychological disturbance.<sup>47</sup> Today cardiac allografts can be harvested some distance away and preserved at low temperature. Myocardial protection is achieved through initial cold cardioplegia, followed by simple topical cold preservation. Recipients are selected on the basis of ABO blood compatibility. A negative lymphocyte crossmatch is required, though HLA determination is not considered essential.

The technique of orthotopic cardiac transplantation as developed in the laboratory by Lower and Shumway in 1960 has remained standard practice in the Stanford series.<sup>47</sup> In the RSA, the Groote Schuur Hospital group has used the technique of heterotopic transplantation exclusively and the results compare favourably with other methods.<sup>48</sup>

Early and accurate diagnosis of impending graft rejection is essential to the achievement of long-term survival. Today the examination of a cardiac biopsy specimen has become the 'gold standard' for the diagnosis of rejection. Patients are treated for rejection when the biopsy specimen shows evidence of cellular infiltration associated with myocyte necrosis.<sup>49</sup>

Survival statistics of the Stanford cardiac transplantation group have improved steadily throughout the years. Between 1968 and 1973 the 1-year survival rate was 40%. By 1974, after implementing regular cardiac biopsy together with the administration of ALG, the 1-year survival rate increased to 60%, with a gradual decline to 40% at 5 years. The survival of cardiac allografts on CYA immunosuppression at both 1 and 2 years after transplantation has increased to 80% in the Stanford series. Of the 134 patients who survived at least 1 year, 86% have been rehabilitated at a satisfactory degree.<sup>47,50</sup>

Immunosuppression of cardiac allograft recipients with CYA has afforded distinct improvement in terms of survival, rehabilitation and hospitalization costs.<sup>47</sup> The introduction of CYA immunosuppression represents an important advance in clinical transplant immunology. Other centres have confirmed the efficacy of CYA immunosuppression in cardiac transplantation.<sup>49</sup> Recent studies indicate that patients treated with a combination of CYA and steroids may still reject the transplant with consistent frequency, which suggests that optimal survival may require the addition of antithymocyte globulin.<sup>49</sup> It is therefore clear that the choice of protocols and drug combination associated with CYA-based immunosuppressive regimens is still in a state of flux.

The advent of CYA has had a major impact in cardiac transplantation and the survival rate has been 82%, 70% and 52% at 1 year, 3 years and 5 years respectively.<sup>47</sup>

Encouraging success in experimental lung and heart-lung transplantation has been achieved with the use of CYA immunosuppression.<sup>51</sup>

Of 2 human CYA-treated single-lung allograft recipients, 1 patient died of multiple organ failure and the other from rejection of the lung. The optimal use of CYA in clinical lung transplantation remains to be defined. Six patients have undergone combined heart-lung transplantation since 1981; 5 have died and 1 recipient is alive more than 1 year after transplantation with markedly improved cardiopulmonary function.<sup>52</sup> At present lung transplantation cannot be considered a modality of clinical and therapeutic value.

## Liver transplantation

Transplantation of the liver in man was pioneered by Starzl, the first operation being performed in 1963.<sup>53</sup> Calne *et al.*<sup>54</sup> have confirmed the efficacy of liver transplantation. The longest surviving liver allograft recipient is now in her 14th post-operative year.

Two approaches to liver transplantation have been studied; they include orthotopic allotransplantation and auxiliary transplantation in which an additional liver is ectopically anastomosed in the abdomen.<sup>53</sup> Although technically more difficult, orthotopic transplantation has been more frequently performed and the current 1-year survival rate using CYA is about 75%.<sup>55</sup>

Indications for liver replacement include hepatic malignant tumours; biliary atresia; liver cirrhosis; hepatic-based inborn errors of metabolism in children; congenital, primary and secondary biliary cirrhosis; sclerosing cholangitis; and the Budd-Chiari syndrome. Liver replacement for primary liver tumours is only considered under exceptional circumstances because of the possibility of recurrent lesions.<sup>55</sup> Between November 1981 and July 1983 43 paediatric patients received 57 hepatic allografts. The overall survival rate is 63%. Some children have required a second liver transplantation and the overall patient survival rate in retransplanted patients is 38%. Infarction, rejection and vascular accidents are the major causes of graft failure. Thus the high peri-operative mortality after liver transplantation is related to technical errors, inadvertent use of damaged allografts and transplantation into moribund recipients.<sup>55</sup>

Until recently liver transplantation in humans was considered an experimental procedure. The encouraging survival data of CYA-treated liver allograft recipients suggest that patients with terminal nonmalignant liver disease should be considered for liver transplantation. White and Calne<sup>17</sup> have found that the rehabilitation of patients surviving beyond 6 months has been satisfactory: many have gone back to work, and 1 recipient runs 8 km every day to keep fit. One patient in Starzl *et al.*'s<sup>53</sup> series gave birth to 2 normal children after she had undergone hepatic transplantation.

Hepatic transplantation remains a formidable procedure despite the introduction of CYA and should be performed in transplantation centres by surgeons with extensive clinical and experimental experience.<sup>56</sup> In an operation with such a high mortality rate, improved results could be expected if potential liver replacement recipients were referred for surgery before they become moribund.<sup>56</sup>

## Pancreatic transplantation

Pancreatic transplantation has enormous potential in the management of patients with insulin-dependent diabetes. At present diabetes mellitus cannot be prevented nor is there any known way of preventing the development of complications. Despite careful dietary control or insulin therapy, vascular changes in small arteries progress relentlessly because insulin provided by injection once or twice daily cannot provide

metabolic homeostasis such as occurs with insulin secreted from a normal pancreas.

Several investigators have demonstrated that diabetes induced in animals either chemically or by surgical pancreatectomy can be permanently ameliorated by islet-cell or whole pancreas transplantation.<sup>14,16,19,23</sup> Successful isolation of the islets of Langerhans from the pancreas and the transplantation thereof has rendered diabetic animals consistently normoglycaemic with sequential cessation of polyuria, polyphagia and polydipsia and normal rate of weight gain.<sup>23</sup>

Ideally, pancreatic transplantation should be applied in man early in the course of diabetes to prevent secondary complications. The experimental nature of the operation and the uncertainty of success or failure together with the hazards of immunosuppressive treatment have resulted in pancreatic transplantation being performed only in uraemic diabetics who have received renal allografts and are committed to antirejection therapy.<sup>57</sup>

The two clinical approaches studied include infusion of isolated islets of Langerhans into the portal circulation or the spleen and transplantation of whole vascularized pancreas or pancreatic segments.<sup>57</sup> Both techniques are being extensively evaluated.<sup>57</sup>

The long-term goal of pancreatic transplantation in diabetics is to restore carbohydrate metabolism in order to prevent the development of secondary complications. To date insufficient numbers of diabetic patients with functioning pancreatic allografts have been followed up to determine whether or not this objective has been achieved. Pancreatic transplantation has restored a normal or near normal metabolic milieu with improvement of neuropathic lesions but has not reversed advanced renal or retinal changes in the short term. Normoglycaemia has been restored in some insulin-dependent diabetic recipients by a successfully transplanted pancreas making further insulin therapy unnecessary.<sup>17,58,59</sup> The introduction of CYA has provided a valuable alternative to conventional methods of immunosuppression and has proved suitable for suppression of pancreatic rejection. CYA, when used as a single immunosuppressive agent, has rendered a more physiological glucose tolerance test response after transplantation.<sup>58</sup>

Pancreatic allograft recipients, like heart and kidney recipients, require life-long immunosuppressive treatment to prevent rejection.

The current actuarial 1-year survival rate is 25% with a patient survival rate of 85%. One juvenile-onset diabetic has a successfully functioning pancreatic allograft 5 years after transplantation, there are no signs of rejection and the subject remains insulin-independent.<sup>57</sup>

## Bone marrow transplantation

Bone marrow transplantation has been used to treat patients with acute or chronic leukaemia, aplastic anaemia, lymphoma and immunological deficiency diseases.<sup>60</sup> The diseased marrow of the recipient is replaced with the marrow of an HLA-histocompatible donor, preferably a sibling. Marrow is removed from the donor through multiple aspirations under general or spinal anaesthesia. A volume of 500 - 800 ml is usually obtained, which is administered by intravenous infusion to the recipient. The transplanted marrow takes about 14 - 28 days to function and provides cells for the peripheral circulation.

Major life-threatening complications after bone marrow transplantation include infections, graft v. host disease (GVHD) or complications resulting from GVHD, graft rejection, and recurrent primary disease.<sup>61</sup> GVHD has been reported to occur in moderate to severe form in 40 - 50% of bone marrow transplant recipients. About 30% of these patients die.

Recent studies confirm the efficacy of CYA in HLA-identical

allogeneic bone marrow transplantation. The incidence of GVHD is similar to that with methotrexate but the mortality rate from this complication appears to be markedly reduced when CYA is used.<sup>62</sup>

Howes *et al.*<sup>63</sup> have reported an actuarial survival rate of 74%, 7 - 42 months after transplantation, in 35 aplastic anaemia patients using CYA for immunosuppression. Storb *et al.*<sup>62</sup> conducted a randomized trial comparing CYA with methotrexate in bone marrow transplant recipients for acute non-lymphoblastic leukaemia in first remission. The initial findings suggest a quicker haemopoietic recovery, slightly reduced evidence of GVHD, and moderately improved survival in CYA-treated recipients. The 1-year survival rate is 73% for CYA-treated patients and 59% for the control group. Other workers have confirmed that patients receiving CYA had a shorter hospital stay, faster engraftment and less severe GVHD than those given methotrexate. Further studies will establish the effect of CYA on GVHD, infection rate and leukaemic relapse rate.

## Prospects for the future

Significant developments in renal transplantation have been achieved in the past few years such as improved HLA DR matching, the implementation of radiation in transplantation in hypersensitized patients, donor-specific transfusions in related recipients, and improved immunosuppression with cyclosporin. Further improvements can be expected with better definition of the number and timing of pre-operative transfusions and pursuing the blood factors responsible for the favourable effect of blood transfusions on the recipient. An exciting new field is the recognition of lymphoid subpopulations in the blood and in the transplanted kidney which can be demonstrated by the presence of monoclonal antibodies.

Clinical heart transplantation is now in its 18th year at Stanford University and follow-up data for 1982 indicate that 92 of 241 patients are alive, some 12 years after cardiac transplantation. The prospect for 1-year survival is about 70%, and 90% of the heart recipients have improved dramatically by the time they leave hospital. The chances are that at least 50% of patients will survive 5 years or longer. It is to be hoped that further research will continue to stimulate new approaches and new ideas and perhaps offer some palliation to otherwise hopelessly ill patients.

Interest in the clinical application of pancreas transplantation for the treatment of diabetes mellitus has increased dramatically in recent years. The potential for application of pancreatic transplantation probably exceeds that of the liver and may approach that of the kidney. It is to be hoped that pancreatic transplantation will primarily be applied in nonuraemic diabetics before the development of end-stage complications. Further research is needed to identify those insulin-dependent diabetics who are at high risk of developing secondary complications.

The improvement in surgical technique, perfusion and preservation of the liver and the application of a multi-disciplinary approach to the many problems of liver transplantation have contributed to the improved results of liver transplantation world-wide. It is to be hoped that the introduction of cyclosporin has opened a new chapter in liver transplantation.

Bone marrow transplantation, once considered a desperate form of therapy in end-stage patients, has now become increasingly successful when used early in the course of aplastic anaemia or acute leukaemia. Results of human bone marrow transplantation from unrelated donors for the treatment of patients with acute leukaemia and aplastic anaemia are awaited with keen interest.

Remarkable accomplishments in transplantation of the kidney, heart, heart-lung, liver, pancreas and bone marrow have been achieved in a relatively short time and we have, it is hoped, entered an exciting new era for transplantation research.

## Conclusion

Cyclosporin has led to significant accomplishments in organ allotransplantation and the compound has made an indelible impact on immunology and research. Further refinement of monoclonal antibodies and their potential therapeutic application in the immunosuppressive armamentarium are eagerly awaited.

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