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Cyclosporine and Pancreas Transplantation

D.W.R. Gray, F.R.C.S., and P.J. Morris, Ph.D., F.R.C.S.

The Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom

A variety of experiments have thus far shown cyclosporine to be not nearly as successful in preventing rejection of pancreas allografts (islets, fetal, vascularized segmental) in experimental animals as it is with other tissues. Clinical experience has also been relatively disappointing, although surgeons at most centers have the impression that it is marginally better than azathioprine and steroids. The role of cyclosporine in pancreas transplantation, and indeed the place of pancreas transplantation, remains uncertain at this time.

Cyclosporine has proven to be a potent immunosuppressive agent in most experimental models of tissue transplantation as well as in clinical transplantation of kidneys, bone marrow, heart, and liver [1, 2]. Cyclosporine is of particular interest in pancreatic transplantation not only because of its potentially more potent immunosuppresive action but also because of the possibility of using it as a single agent, thus reducing the need to use steroids with their undoubted diabetogenic activity.

In this article we will review the use of cyclosporine in transplantation of the whole pancreas as a vascularized graft both in experimental models and clinically, as well as its effect on the transplantation of isolated adult pancreatic islets and fetal pancreas in experimental models.

It is perhaps worth noting that cyclosporine is a cyclic structure composed of 11 hydrophobic amino acids; thus, the drug is only soluble in lipids or lipid solvents which not only has given rise to problems in administration, but also causes a variation in absorption when gut function is impaired. This is particularly relevant in experimental models of diabetes in which the diabetes has been induced by total pancreatectomy with the subsequent loss of pancreatic exocrine secretions.

Reprint requests: D.W.R. Gray, The Nuffield Department of Surgery, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom.

Experimental Pancreatic Transplantation

Vascularized Segmental or Whole Pancreas

Cyclosporine has been demonstrated to prolong the survival of vascularized whole organ pancreatic allografts in rats with streptozotocin-induced diabetes. Rats given short courses of cyclosporine, 10 mg/kg per day for 15 days, following transplantation of duct-ligated segmental allografts across a major histocompatibility barrier showed only a modest prolongation of survival (longest survival 26 days compared to the survival of untreated animals of 7–9 days). Raising the dosage to 20 mg/kg per day increased the average survival slightly with the longest survival being 28 days, while 40 mg/kg was found to be toxic, all animals dying while receiving cyclosporine [3].

Better results were obtained by Rynasiewicz and colleagues [4] using continuing administration of cyclosporine. Vascularized segmental allografts transplanted across minor histocompatibility barriers were not rejected in 57% of cases using oral cyclosporine at a daily dose of 10 mg/kg. Higher doses prevented rejection completely, but resulted in death from infective complications in 50% of cases. These researchers were also able to achieve successful transplantation across a major histocompatibility barrier at a dose of 10 mg/kg per day given by intraperitoneal injection, no grafts rejecting at 36 days, at which time the study was ended. Oral doses of 20 mg/kg per day tapering to 10 mg/kg per day were also effective but toxicity was seen at this dosage. A daily dosage of 15 mg/kg orally seemed to suppress rejection without being toxic, although

Table 1. Effect of cyclosporine on the survival of segmental pancreatic allografts in dogs.

Treatment	No.	Days of normoglycemia
Total pancreatectomy	10	$<1 \times 10$
Segmental autograft	10	$>180 \times 10$
Segmental allograft, no immunosuppression	5	8, 9, 9, 9, 10
Segmental allograft, cyclosporine 25 mg/kg per day indefinitely	10	7[a], 8[a], 13, 15, 17, 17, 18, 18, 22, 40
Segmental allograft, cyclosporine 40 mg/kg per day for 120 days, then reduced to 5 mg/kg per day	8	6[a], 8, 9, 120[b], 195[c], 205[c], 220, >250

[a]Died of intussusception.
[b]Normoglycemic when killed.
[c]First day of rejection successfully reversed with methyl prednisolone and increased doses of cyclosporine.
(from DuToit et al., Transplantation *33*:432, 1982, permission granted from author.)

only small numbers of animals were transplanted at this dosage. Thus, the immunosuppressive effects of cyclosporine were relatively modest in models of vascularized segmental pancreatic allografts in the rat using doses that are strongly immunosuppressive for renal and cardiac allografts even when given for only 7 or 14 days.

In dogs given whole organ, duct-occluded pancreas allografts following total pancreatectomy, McMaster and colleagues found that rejection was delayed by continuous oral cyclosporine administration [5]. Untreated dogs remained normoglycemic for a mean of 13 days, while dogs receiving 25 mg/kg per day cyclosporine were normoglycemic for a mean of 85 days. All grafts eventually failed although this may not have been due to rejection. However, DuToit and colleagues in Oxford [6], using duct-injected segmental pancreatic allografts, found a less impressive prolongation of survival at a dose of 25 mg/kg (untreated mean 9 days, treated mean 17.5 days, range 7–40). A dose of 40 mg/kg per day prolonged survival to a mean of 126 days (range 6–>250). Long-surviving animals had their dosage reduced, but all rejected their grafts when the dose reached 5 mg/kg per day (Table 1). Interestingly, increasing the dose of cyclosporine again resulted in return to normoglycemia in 2 of 3 dogs. Similarly, Garvey and colleagues [7] showed that oral cyclosporine (25 mg/kg per day) in divided doses prolonged the median survival of segmental grafts from 9 to 17 days. However, they were able to show that cyclosporine was poorly absorbed in these pancreatectomized recipients of allografts in comparison to normal dogs. They attribute their own results and the Oxford results to poor absorption of the drug.

Table 2. Transplantation of isolated pancreatic islet allografts in rats treated with cyclosporine.

Histocompatibility barrier	Daily dose of cyclosporine (mg/kg)	Treatment duration (days)	Mean survival (days) (range)	Reference
Major	20	14	6.6 (1–13)	[3]
Major	40	14	10.3 (2–22)	[3]
Minor	20	Continuous	41 (13–56)	[10]
Major	50	14	24.8 (6–60)	[11]
Major	20	7	12.5 (8–18)	[12]

In baboons, cyclosporine was relatively ineffective in prolonging survival of vascularized segmental pancreas allografts [8]. Normoglycemia in untreated allograft recipients was maintained for a mean of 9.2 days. Continuous oral cyclosporine at a dose of 25 mg/kg per day prolonged the duration of normoglycemia to a mean of 15.1 days (range 6–50). These results were not substantially improved even by raising the dose to 85 mg/kg.

Dispersed Pancreatic Preparations and Isolated Islets

In the rat, isolated islet allografts have proven particularly sensitive to the rejection process. Transplantation of islets intraportally typically results in rejection in 4 to 6 days whether transplantation is across a major or minor histocompatibility barrier [9]. Several studies have looked at the effect of cyclosporine on islet allografts (Table 2). The survival of intraportal islet allografts transplanted across a major histocompatibility barrier was found to be unchanged with doses of cyclosporine up to 20 mg/kg per day given for 14 days (mean survival 6.6 days) and even a dose of 40 mg/kg per day only produced a mean survival of 10.3 days, with several rats dying of toxic effects [3].

Rynasiewicz and colleagues [10] also found that doses up to 50 mg/kg per day failed to prolong islet survival across a major histocompatibility barrier. However, the same workers found that cyclosporine was effective for islet allografts across a minor histocompatibility barrier, when graft survival was prolonged from a mean of 4 days in untreated animals to 41 days in rats treated with 20 mg/kg per day cyclosporine. It should be noted that cyclosporine treatment was continued in this study for the duration of normoglycemia, and at this dose most of the rats died of infection, presumably from over-immunosuppression.

In contrast, Vialettes and colleagues [11] found significant prolongation of graft survival at a very

high dose level of 50 mg/kg per day administered for 14 days to rats given intraportal islets across a major histocompatibility barrier (untreated: mean 5 days; treated: mean 24.8 days), with comparatively little toxicity. Similarly, Nash and Bell [12] also found significant prolongation of survival of intraportal islets across a major histocompatibility barrier; cyclosporine administered at a dose of 20 mg/kg per day for 7 days prolonged survival of intraportal islets across a major histocompatibility barrier from a mean of 2.3 days in untreated rats to 12.5 days in treated rats. All rats rejected their grafts shortly after the cyclosporine was stopped.

An interesting discovery was that simply placing the islets in a different site, namely, under the renal capsule, resulted in significantly prolonged survival (intraportal islets, 4–6 days, subcapsular islets, 6–13 days) [13]. Cyclosporine treatment of diabetic recipients with islets transplanted to this site had a modest effect, maintaining normoglycemia for a range of 9 to 14 days at a dose of 20 mg/kg per day and for 15 to 27 days at a dose of 40 mg/kg per day, although many rats died of toxic effects at this dose. The drug was discontinued after 14 days in these experiments [14].

The contrast between the effect of cyclosporine on renal allografts in rats in which a dose of 10 mg/kg per day for 14 days leads to indefinite survival in a high proportion of cases [15] and on islet allografts is striking and has led to suggestions that islets are more immunogenic than other tissues. In fact, the above studies show that cyclosporine can prolong islet allograft survival but rarely produces long-term survival. It has been shown that long-term survival of renal allografts after cyclosporine treatment in the rat is associated with development of an unresponsive state which may be non-specific or specific [16]. It seems likely that the difference in survival of islets and kidneys is related to the ease with which a specific unresponsive state is produced, this being easily achieved after renal transplantation, but rarely after islet transplantation.

An interesting experiment from our own laboratories [17] showed that if islets are first allowed to become vascularized under the kidney capsule of an intermediate diabetic host, before being transplanted along with the kidney as a vascularized composite graft, cyclosporine treatment (10 mg/kg per day for 14 days only) results in long-term survival of both kidney and islets across major histocompatibility barriers (Table 3). We have also shown that if an unresponsive state to a renal allograft is produced with cyclosporine, islets of the same strain as the renal allograft can be implanted successfully beneath the renal capsule or into the liver. Survival was prolonged to >100 days in 3 of 6 cases [18]. Not only is the site of implantation unimportant, but the effect is specific and is demonstrable in at least 2 strain combinations [19, 20]. Furthermore, it is possible to then remove the original renal allograft, leaving only the allografted islets, and the unresponsive state is still maintained (unpublished observations). Thus, islet allografts are capable of maintaining the unresponsive state after cyclosporine treatment in rats but are apparently not capable of initiating it.

Table 3. Transplantation of isolated pancreatic islets after several days of residence beneath the renal capsule of an intermediate syngeneic host as a vascularized allograft of kidney and islets into diabetic recipients treated with cyclosporine.

Strain	No.	Treatment	Survival (days)
LEW to DA	5	Nil	6, 7, 8, 8, 8
LEW to DA	6	Cyclosporine 5 mg/kg per day 14 days	11, >100 × 5
DA to LEW	5	Cyclosporine 10 mg/kg per day 14 days	>100 × 5

(from Reece-Smith et al., Transplantation *31*:442, 1981, permission granted from author.)

A satisfactory method for the isolation and transplantation of pure islets in larger animals has not been developed, but transplantation techniques using unpurified dispersed pancreatic preparations have proven successful in dogs [21]. In a study in our own laboratory using this technique in dogs made diabetic by total pancreatectomy, autotransplanted dogs survived normoglycemic for >60 days, while dogs given allografts never achieved normoglycemia. Dogs given allografts with cyclosporine treatment for 14 days never became normoglycemic although their survival time was prolonged by some days in comparison to dogs given allografts without treatment [22]. Thus, just as for experimental models of segmental pancreatic transplantation, cyclosporine has also proven relatively ineffective in preventing rejection in models of isolated islet transplantation.

Fetal Pancreas

Fetal pancreas has been implanted beneath the renal capsule in streptozotocin-induced diabetic rats, restoring normoglycemia. Allografts are rejected in 9 to 10 days after transplantation across a major histocompatibility barrier, and cyclosporine treatment, even at the toxic dosage of 40 mg/kg per day, did not prolong survival, grafts being rejected in 9 to 15 days [3].

Clinical Pancreatic Transplantation

No successful technique has been described for the isolation and transplantation of isolated pancreatic islets as allografts in humans. Earlier attempts at islet transplantation were really transplantation of dispersed pancreatic preparations, azathiaprine and prednisolone being used for immunosuppression. Thus, this discussion will be confined to whole and segmental pancreatic transplantation.

The standard immunosuppressive regimen of steroids and azathioprine was used for the first whole and segmental pancreas allografts in the pioneering centers, but the encouraging results of cyclosporine treatment in renal transplantation and the previously mentioned possible advantages of not using steroids led to early trials of cyclosporine in pancreas transplantation. The problems experienced with the use of cyclosporine in renal transplantation were still problems in pancreas transplantation. Cyclosporine nephrotoxicity was still the major side effect of the drug, since many patients had impaired renal function, had previously received a renal allograft, or underwent simultaneous renal and pancreas transplantation. The use of an anti-lymphocyte globulin with cyclosporine and steroids in one center led to an unacceptable incidence of hematological malignancies [23], but probably represents the severe over-immunosuppression produced by the synergistic effect of anti-lymphocyte globulin and cyclosporine. Poor absorption of cyclosporine has been noted after intraperitoneal implantation of the pancreas due to the resulting ileus, but the recent availability of the intravenous preparation has enabled this problem to be circumvented. Nevertheless, at this time it is not possible to say that cyclosporine has led to improved survival of vascularized pancreatic allografts. The techniques used for segmental and whole organ grafts vary from center to center, as do the technical complications arising from same, making comparisons difficult. Many grafts still fail for technical reasons, and even late failures may be unrelated to rejection [24].

The international pancreatic transplant registry figures suggest that survival of pancreatic allografts is a little better in patients treated with cyclosporine and steroids compared to azathiaprine and steroids (1-year graft survival rate of 24% with cyclosporine versus 14% with azathiaprine) [25]. However, this may represent the more recent use of cyclosporine in units with fewer technical problems after initial experience. The background noise is too high at present in pancreatic transplantation and too few are being performed for a trial of cyclosporine and conventional immunosuppression to be performed. Most centers have changed to cyclosporine with or without steroids, from azathioprine and steroids and the only comparisons that can be made are historical. The center with the greatest experience (Minneapolis) reported 8 of 21 technically successful grafts in patients treated with cyclosporine to be functioning at the time of report, graft survival ranging from 1 to 17 months, while 5 of 12 conventionally treated recipients had grafts functioning with durations of 7 to 46 months [26]. There were major changes in technique between the groups over the period of the study, so little can be made of this comparison except to say that the introduction of cyclosporine clearly has not made an enormous difference to graft survival, even excluding known technical failures. More recently, at the same center the number of functioning grafts following cyclosporine treatment has risen to 12 out of 26 grafts (although 6 are living related grafts) while the same 5 grafts are still functioning after conventional therapy (2 are living related grafts) so perhaps further improvement will be seen [27]. The other center (Lyon) with a large experience has also changed to cyclosporine recently. There is no definite difference between patients given cyclosporine and those given azathioprine and steroids. Overall graft survival rate at 12 months was 20% for both groups. Again there were a high number of technical failures and many patients died of conditions not directly related to the transplant, but related to their long-standing diabetes [28]. Although cyclosporine has been used in several other centers, the numbers of patients are too small in individual centers, and variations in technique too large among centers, to draw meaningful conclusions.

Despite the difficulty in interpreting the clinical data, it is hard to escape the feeling that the results of the use of cyclosporine in whole organ and segmental pancreatic transplantation are disappointing compared to the apparent improved survival of renal and cardiac allografts. It is possible that the reasons for the lack of improvement may be related to factors other than rejection. Many centers are using duct-injection techniques, and it is possible that many of the failures are, in fact, due to fibrosis consequent to this technique. It is possible too that, although cyclosporine produces a better basal immunosuppression, graft survival also depends on the early treatment of rejection episodes. At present the usual guide to rejection is the blood sugar and this is probably a very late indicator of rejection. A better indicator of rejection might therefore lead to earlier treatment of rejection and better graft survival.

It was originally hoped that cyclosporine might allow discontinuation of steroids in pancreas transplantation, and it was in fact suggested that introduction of cyclosporine had led to better glucose tolerance in a clinical study of patients with func-

tioning pancreatic allografts [29]. Most centers have found it necessary to use steroids to prevent, as well as to treat, rejection particularly when a renal allograft has been implanted with the pancreas. The case for steroids being harmful to islet function in the pancreatic allograft has not been proven. One study in dogs given duct-obliterated segmental pancreatic autografts has shown no deleterious effect of prednisone and azathioprine treatment compared to no treatment [30]. Furthermore, in contrast to the study cited above [29], it has even been suggested that cyclosporine may be harmful to islet function, for a recent study of patients with functioning pancreatic allografts on azathioprine and steroid immunosuppression showed significant deterioration in glucose tolerance after conversion to cyclosporine, this deterioration being reversible in one case on reverting to the original treatment [31].

It is also worth noting that experimental studies in the rat have suggested that cyclosporine may be more effective if used in conjunction with azathioprine for pancreas transplantation, although this has not been tested clinically [32].

In conclusion, therefore, cyclosporine is not nearly as successful in preventing rejection of pancreas allografts (islets, fetal, vascularized segmental) in experimental animals as it is with other tissues. Clinical experience has also been relatively disappointing, although most centers have the impression that it is marginally better than azathioprine and steroids. The role of cyclosporine in pancreas transplantation, and indeed the place of pancreas transplantation, remains uncertain at this time.

Résumé

La cyclosporine est un puissant agent immunosuppresseur, de structure cyclique, constitué de 11 acides aminés hydrophobes. C'est dans les hétérogreffes de rein ou de coeur qu'elle a fait la preuve de son efficacité remarquable. Dans les hétérogreffes de pancréas ou d'îlots chez l'animal, la cyclosporine est loin d'atteindre la même efficacité que pour les autres greffes tissulaires. Lors des transplantations de tissu pancréatique chez l'homme, l'association cyclosporine plus corticoïdes donne des résultats voisins de ceux obtenus avec l'association azathioprine plus corticoïdes. L'un des problèmes tient sans doute à la difficulté d'identifier les épisodes de rejet aigu dans les greffes pancréatiques, ce qui rend difficile pour le pancréas le type d'études qui ont été réalisées sur les greffes rénales et cardiaques. La place de la cyclosporine dans la transplantation pancréatique reste à préciser à ce jour.

Resumen

La ciclosporina es un agente inmunosupresor potente que consiste de once aminoácidos hidrofóbicos en una estructura cíclica. La eficacia de este agente inmunosupresor ha sido demostrado en aloinjertos renales y cardiacos en animales. Sin embargo, en investigaciones de aloinjertos de islotes pancreáticos en animales, resultados similares a los demostrados en otros tejidos no han sido confirmados. El uso de la ciclosporina y prednisona en transplante de tejido pancreático ha dado resultados similares a los obtenidos con el uso de la prednisona y azatioprina. La dificultad en la identificación temprana del rechazo agudo hace difícil comparar el uso de este agente en aloinjertos de islotes con los resultados en aloinjertos renales y cardiacos. La utilidad de la ciclosporina en el transplante pancreático no está todaviá debidamente definida.

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