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The use of cyclosporin in organ transplants

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Cyclosporin is a metabolite isolated from culture broths of the fungus *Tolypocladium inflatum* Gams which was shown to be immunosuppressive by Borel *et al.* in rats, mice and guinea-pigs.[1,2] Cyclosporin may directly block the release of interleukin I from activated T helper cells and indirectly block the release of interleukin II from macrophages, thus suppressing both cellular and humoral immunity. The drug is most effective if given at the time of immunization or antigenic challenge, but the suppressive effect is reversible. These effects are not accompanied by bone marrow depression, and do not lower resistance to bacterial and fungal infections. There is some doubt about the effect of cyclosporin on viral infections.

When cyclosporin was first used in patients by Calne *et al.*[3] in 1978, it was hoped that no other drug would be routinely required. However, most of their experience has been with delayed administration of the drug because of the fear of nephrotoxicity and hepatotoxicity. Azathioprine and prednisone were used initially until renal and hepatic functions were adequate. Then cyclosporin was begun, and the steroid dose was slowly reduced and withdrawn.[4] The supervention of acute rejection during treatment with azathioprine and prednisone was troublesome.

In late 1979, cyclosporin became available for preliminary testing in the USA. The authors' initial experience in cadaver renal transplantation[5] led them to believe that the combination of cyclosporin and steroids is a more effective and safe immunosuppressive treatment than cyclosporin alone. From then until the end of 1984, approximately 500 cadaver renal,[6] 300 hepatic,[7] 100 cardiac and 10 pancreatic transplants were carried out at the University Health Centre of Pittsburgh under cyclosporin–steroid treatment. The authors' experience is briefly summarized here as an example of the use of cyclosporin.

Basic treatment

Cyclosporin: if there are several hours in which to prepare a patient for organ transplantation, cyclosporin, 17.5 mg/kg body weight, is administered orally as an initial loading dose. After this, cyclosporin is generally not given until the operation is completed. If there is not enough time for digestion of the drug before surgery, cyclosporin, 2 mg/kg body weight, is administered intravenously over 2–3 hours after the revascularization of the graft. The dose is repeated every 8 hours,

provided the patient is haemodynamically stable and producing an adequate amount of urine.

After surgery, kidney recipients can usually resume oral intake within 12–24 hours. They receive oral cyclosporin, 17.5 mg/kg body weight/day in two divided doses, and the trough level of cyclosporin is monitored carefully. Liver recipients can usually resume oral intake a few days after the transplant operation. Although they receive oral cyclosporin, 17.5 mg/kg body weight/day in two divided doses, as soon as can be tolerated, intestinal absorption of the drug is usually poor for a few weeks. Therefore, during this early postoperative period, cyclosporin is administered intravenously as well as orally (double route therapy) in order to maintain adequate levels of the drug. An adequate blood level is achieved when the trough level of cyclosporin is 800–1000 ng/ml of whole blood measured by radioimmunoassay, or 150–300 ng/ml measured by high performance liquid chromatography. When an adequate blood level of the drug is achieved by administering double route therapy, the intravenous dose of cyclosporin is gradually reduced and then discontinued. Commonly, the oral dose required to maintain an adequate drug level is greater than 17.5 mg/kg body weight/day (Figure 1).

The mean maintenance dose of oral cyclosporin 1 month after liver transplantation is 12.5 ± 4.3 mg/day for adults and 17.1 ± 3.9 mg/day for small children (Figure 2).

Corticosteroid treatment with methylprednisolone, 1 g i.v., begins immediately before revascularization of the graft. After surgery, a 5-day burst of prednisone or methylprednisolone is started at 200 mg/day. This dose is reduced daily by 40 mg to an initial maintenance dose of 20 mg/day for adults (Figure 1). In children, intravenous methylprednisolone, 250 or 500 mg, is given before revascularization. After the operation, a 5-day burst of prednisone or methylprednisolone is begun at

Time	Cyclosporin regimen	Steroid regimen
Before transplantation	2 mg/kg body weight i.v. or 17.5 mg/kg body weight p.o.	
Day of transplantation	2 mg/kg body weight i.v. every 8 hours	Methylprednisolone, 1 g i.v.
Day 1	(the dose may be increased in the presence of uraemia or high trough levels)	Methylprednisolone, 50 mg i.v. every 6 hours
Day 2	(the dose may be increased in the presence of uraemia or high trough levels)	Methylprednisolone, 40 mg i.v. every 6 hours
Day 3	3 mg/kg body weight i.v. every 12 hours and 17.5 mg/kg body weight p.o. in 2 divided doses	Prednisone, 30 mg p.o. every 6 hours
Day 4	(i.v. dose decreased as the intestinal absorption increases and an adequate blood level is achieved)	Prednisone, 20 mg p.o. every 6 hours
Day 5		Prednisone, 20 mg p.o. every 12 hours
Day 6		Prednisone, 20 mg p.o. every 24 hours
Day 7		

1 Basic cyclosporin and low-dose steroid treatment.

Patients	Daily cyclosporin dose (mg/kg body weight)				
	1 month	3 months	6 months	9 months	12 months
Adults (>40 kg)	12.5 ± 4.3	10.8 ± 6.7	8.2 ± 3.6	7.6 ± 3.5	6.7 ± 2.2
School-aged children (21–40 kg)	12.7 ± 3.1	12.1 ± 5.6	10.5 ± 2.8	9.8 ± 3.6	8.9 ± 2.7
Pre-school-aged children (<20 kg)	17.1 ± 3.9	17.8 ± 5.6	14.7 ± 5.3	12.1 ± 3.8	11.1 ± 2.2

2 Daily oral cyclosporin dose in both adults and children to avoid nephrotoxicity at 1, 3, 6, 9 and 12 months after liver transplantation.

100 mg/day; this dose is reduced by 20 mg/day to an initial maintenance dose of 10 mg/day. A further reduction in steroid dose is made in small children and infants.

The maintenance dose of prednisone at 1 month is 15–20 mg/day for adults and 5–15 mg/day for children. Further reduction of prednisone dose depends on graft function.

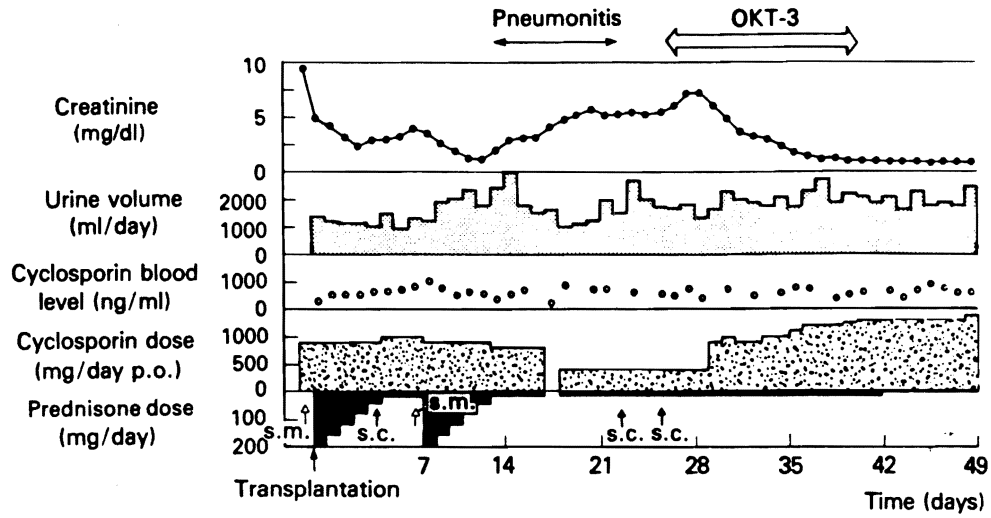
Treatment for rejection

If rejection occurs despite cyclosporin and low-dose steroid treatment, the course of action is the same as with conventional immunosuppressive treatment, that is, to administer large doses of intravenous hydrocortisone or methylprednisolone intermittently (pulse therapy), repeating the original 5-day burst of prednisone (recycle), and setting a higher maintenance dose of steroids. Although cyclosporin does not permit much dose manoeuvrability because of its toxicity, it is sometimes possible to increase the doses given orally or intravenously.

Antilymphocyte globulins (ALG) or monoclonal antibodies have been used occasionally for steroid refractory rejections.

Case 1 – RA was a 20-year-old female patient who received a cadaver renal transplant for the first time. The clinical course is summarized in Figure 3. She was given basic oral treatment. The renal graft functioned immediately. On day 7, an acute rejection episode was diagnosed. She received methylprednisolone, 1 g i.v., and a 5-day burst of oral prednisone. With this anti-rejection therapy, the acute rejection crisis was reversed. However, on day 14, she developed pneumonitis and was placed on a respirator for a few days. She recovered from pneumonitis after 1 week, but her renal function deteriorated during the infection because the immunosuppressive therapy was drastically reduced to overcome the life-threatening infection. During the fourth week, she received hydrocortisone, 1 g i.v., twice, with no improvement in renal function. On day 26, monoclonal antibodies (OKT-3) were given and continued for 2 weeks. With OKT-3 treatment and an increased dose of cyclosporin, the second rejection episode was completely reversed, without an increase in the basic steroid dose.

Case 2 – RM was a 5-year-old boy who received an orthotopic liver transplant for



3 Case 1: an example of acute renal graft rejection.
OKT-3 = monoclonal antibodies, s.c. = hydrocortisone sodium succinate
s.m. = methylprednisolone hemisuccinate.

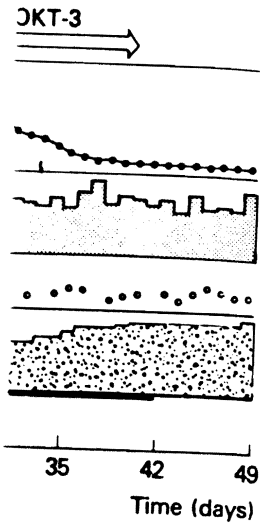
biliary atresia after a failed Kasai hepatic porto-enterostomy. Before the first and the second liver grafts he was prepared with basic intravenous treatment. His clinical course is summarized in Figure 4. The first liver graft was lost through hepatic artery thrombosis and the second graft was transplanted 15 days after the first. Acute rejection of the second graft occurred in the third week. It was treated with hydrocortisone, 1 g i.v., pulse therapy, followed by a 5-day burst of oral prednisone without success. Antithymocyte globulin (ATG) was then administered intravenously for 2 weeks, resulting in resolution of the rejection crisis. During the course of treatment, the patient's cyclosporin dose was adjusted on the basis of trough levels of the drug.

Side-effects of cyclosporin

Side-effects of cyclosporin include:

- nephrotoxicity
- hepatotoxicity
- acidosis
- hypertension
- convulsions
- lymphomas
- gum hyperplasia
- hirsutism
- tremor
- flushing
- paraesthesia.

These side-effects are generally related to the dose used and can be corrected by reducing the dose or discontinuing treatment.



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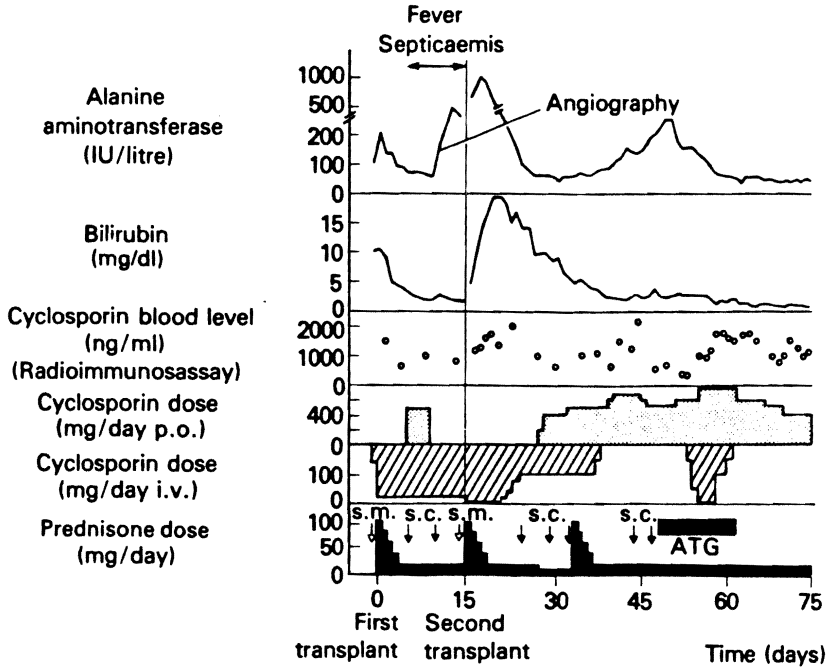
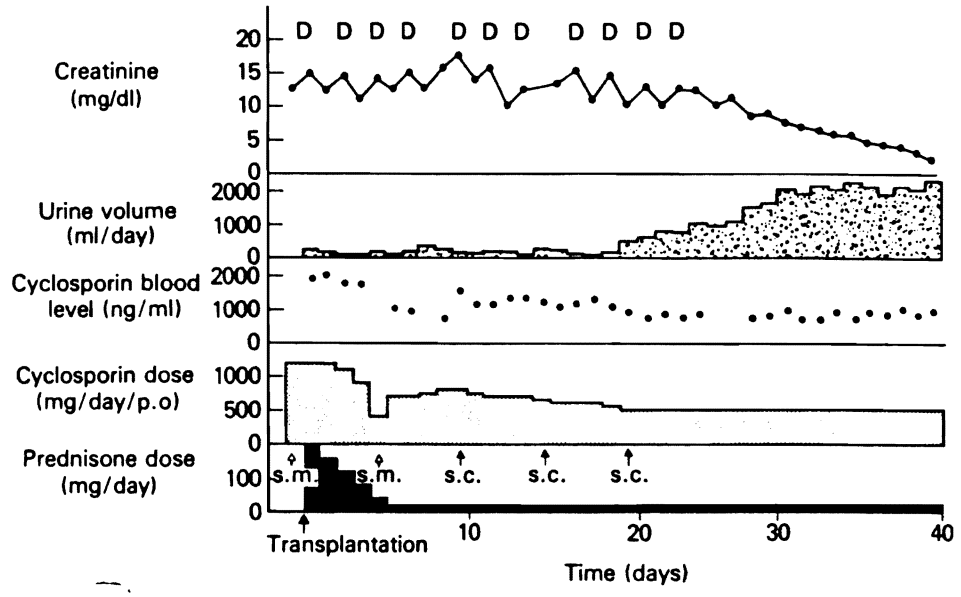


4 Case 2: an example of acute hepatic graft rejection. ATG=antithymocyte globulin, s.m. and s.c. – see legend for Figure 3.

Nephrotoxicity: acute nephrotoxicity of cyclosporin was recognized in the earliest clinical studies on kidney transplantation,[1,5] and was confirmed in liver transplantation,[8] bone marrow transplantation and cardiac transplantation. The toxicity can lead to oliguria or anuria and prolong the period of acute tubular necrosis (ATN). Calne *et al.*[4] recommended delaying the administration of the first dose of cyclosporin until post-transplant diuresis was established, conventional treatment (azathioprine and prednisone) being used before then. The authors have been starting cyclosporin treatment immediately before transplantation and continuing it, regardless of the immediate renal graft function; the dose is adjusted on the basis of the blood level of the drug. Although this practice may prolong the period of ATN, it is better for controlling acute rejection which may occur during the anuric phase of ATN.

Case 3– RC was a 53-year-old male patient who received a second cadaver renal graft. He was moderately sensitized after losing the first graft from rejection. The second graft was stored in cold Collins solution for 36 hours and initial renal function was poor. A renal scan indicated ATN with excellent blood flow. Oral basic therapy was begun before transplantation and was continued through the period of ATN; the dose of cyclosporin was adjusted on the basis of the blood level of the drug (Figure 5). Because the patient was moderately sensitized, intravenous steroid pulse therapy was given at 5-day intervals during the anuric phase to prevent or treat rejection masked by ATN. Despite the continuous use of cyclosporin, diuresis began after 2 weeks and haemodialysis was discontinued after 3 weeks. The patient's serum creatinine level returned to normal 40 days after transplantation.



5 Case 3: the use of cyclosporin during acute tubular necrosis (ATN). D = dialysis, s.m. and s.c. – see legend for Figure 3.

Some renal toxicity was observed in the majority of liver recipients who were treated with cyclosporin and low-dose steroid treatment. However, less than a few percent of the last 300 recipients required haemodialysis following liver transplantation. Most of the patients had renal failure before transplantation or had been very unstable haemodynamically.

Renal toxicity: The cause of postoperative anuria or oliguria is generally pre-renal in liver transplantation. However, postoperative renal failure can be exacerbated by cyclosporin nephrotoxicity. When anuria or oliguria persists despite adequate volume replacement and cardiac support, a brief reduction in the dose of cyclosporin is recommended. Following dose reduction, the urine volume increases and renal function improves; the dose of cyclosporin can then be gradually increased to the basic treatment level. If the recipient requires haemodialysis, the cyclosporin dose is reduced to maintain the trough level of the drug in the lower ranges (500–800 ng/ml of whole blood measured by radioimmunoassay) until renal function recovers.

Mild renal impairment manifested by slightly elevated blood urea nitrogen levels and serum creatinine levels is commonly seen later in the post-transplant period. Often, the dose of cyclosporin is maintained at a relatively high level in the presence of mild rejection. Gradual reduction of the dose usually improves the renal function. Interstitial fibrosis of the kidney has been reported in cardiac transplant[9] and in renal transplant[10] after long-term use of cyclosporin. This fibrosis seems to be caused by a relatively high dose of cyclosporin administered during the 6 months following transplantation. The maintenance doses of oral cyclosporin required to avoid nephrotoxicity in liver transplant patients at 1, 3, 6, 9 and 12 months are given in Figure 2. Small children and infants can tolerate higher doses of cyclosporin than adults.

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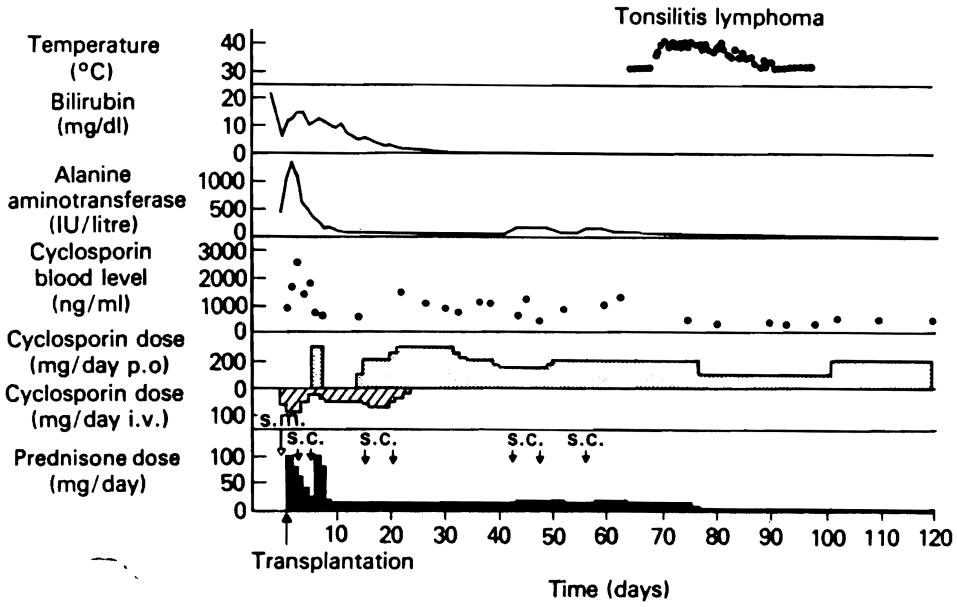
Hepatotoxicity of cyclosporin is an uncommon side-effect and is generally mild. It can manifest clinically both in hepatocellular injury form and in cholestatic form. The clinical differentiation of cyclosporin hepatotoxicity from viral hepatitis, mild bile duct obstruction, other drug toxicity and graft rejection in liver transplants is difficult, even with liver biopsy. When cyclosporin hepatotoxicity is suspected, it is worthwhile reducing the dose of cyclosporin briefly to observe the response, particularly in the presence of high trough levels of the drug. Only careful analyses of chemical, serological and histological studies can lead to a proper diagnosis. Fortunately, cyclosporin hepatotoxicity is much less troublesome in the management of patients than nephrotoxicity.

Lymphomas and lymphoproliferative lesions: the incidence of post-transplant lymphoma is probably less with cyclosporin–prednisone treatment than with azathioprine–prednisone–ALG treatment.[11] Epstein-Barr virus infections are generally associated with the development of these lesions. Fever, malaise and lymphadenopathy are the usual clinical manifestations. Acute abdominal symptoms, such as perforation, obstruction, bleeding or diarrhoea, also develop when intestinal lymph nodes are affected.

When lymphoma is confirmed by pathological examination, or when it is suspected on the basis of clinical manifestations, drastic reduction or discontinuation of immunosuppressive drugs (both cyclosporin and prednisone) is mandatory to overcome the otherwise fatal lesions. The results of anti-neoplastic chemotherapy for this type of lymphoma are much worse than those caused by discontinuation of immunosuppressive treatment. Antiviral chemotherapy alone cannot cure this lesion. Early recognition of lymphoproliferative lesions is vital and the subsequent drastic reduction of immunosuppressive therapy is the treatment of choice. The grafts commonly suffer from rejection during this period of drastic reduction of immunosuppressive treatment, but most grafts recover from rejection when the immunosuppressive treatment is restored following the disappearance of the lymphomas.

Case 4– KH was a 2-year-old girl with biliary atresia who received an orthotopic liver transplant after a failed Kasai operation. She was initially given basic intravenous treatment, and then double route therapy. After 3 weeks, cyclosporin was administered by the oral route alone (Figure 6). The dose was well-adjusted by monitoring renal function and the blood levels of the drug. She had two episodes of acute rejection, 1 week and 6 weeks after transplantation. Both rejection crises were successfully reversed by intravenous steroid pulse therapy and increasing the dose of oral prednisone. Approximately 10 weeks after transplantion, the patient developed fever, malaise, loss of appetite and enlargement of the tonsillar glands causing partial airway obstruction. Despite intensive intravenous antibiotic treatment she remained febrile, and the signs of airway obstruction worsened. Tracheostomy and tonsillectomy were performed on an urgent basis.

Pathological examination of the enlarged tonsillar glands confirmed the diagnosis of lymphoma. The doses of both cyclosporin and prednisone were reduced to half their previous levels and antiviral chemotherapy (acylovir) was given for 10 days. The patient became afebrile and all the signs and symptoms of lymphoproliferative lesions subsided in 10 days. Three weeks later, the dose of cyclosporin was restored to the previous level. There was no rejection of the liver graft despite a drastic reduction in immunosuppressive therapy for 3 weeks.



6 Case 4: an example of lymphoma, successfully treated by drastic reduction of immunosuppression, s.m. and s.c. – see legend for Figure 3.

Conclusion

Cyclosporin is the most effective immunosuppressive agent available today, and is more effective and safe when used with low doses of corticosteroids. Some of its side-effects are troublesome and serious. Measurements of drug concentrations in the blood or serum can provide a useful guide to the proper use of cyclosporin. However, the drug level and the toxicity do not correlate in many instances, nor do the drug level and the immunosuppressive activity of the sera obtained from the individuals who are taking cyclosporin. A great deal of information is to be learned as experience with this drug extends rapidly.

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