Cyclosporin and Tacrolimus in Clinical Transplantation
A Comparative Review
Ashok B. Jain and John J. Fung
Pittsburgh Transplantation Institute, Pittsburgh, Pennsylvania, USA
Major advances have been made in the field of organ transplantation in the last 2 decades. In the early 1980s, cyclosporin made a significant impact in improving graft and patient survival following transplantation. However, acute and chronic rejection still remained a principal concern.

The introduction of tacrolimus has seen a significant reduction in the incidence and severity of rejections for heart, lung and liver transplantation. Its ability to control steroid-resistant rejection occurring on cyclosporin-based immunosuppression has been remarkable for kidney, liver, heart, lung and pancreatic transplantation. It also has shown the ability to control chronic rejection in liver transplant recipients in up to 70% of cases. The need for concomitant use of corticosteroids has been significantly lower with tacrolimus. The ability of tacrolimus to be absorbed independently of bile has significantly reduced the need for prolonged intravenous administration in liver transplant recipients and has contributed to the success of small bowel transplantation.

Both drugs are nephrotoxic and neurotoxic, effects which are reversible in most instances. Both drugs have a diabetogenic effect to an almost equal extent. Hypertension is more common with cyclosporin, while hyperkalaemia is more common with tacrolimus. Higher levels of cholesterol and low density lipoprotein have been observed with cyclosporin compared with tacrolimus. The hirsutism and gingival hyperplasia that occur with cyclosporin are not observed with tacrolimus.

Following the success of kidney transplantation from an identical twin without using immunosuppression in 1954, the field of organ transplantation has expanded exponentially as gauged by the various organs which can be transplanted and the total number of transplantations performed each year. The major limiting factor currently is supply of donor organs. The increased transplant success can be attributed to:

- technical advances
- better organ preservation solutions
- our increased understanding of the immunology of graft rejection
- the development of new immunosuppressive agents.

Initial allogeneic transplantations were done using antimetabolite agents such as mercaptopurine, which was shown to inhibit skin graft rejection in rats, and later to delay rejection in canine renal transplantation. A derivative of mercaptopu-
Cyclosporin and Tacrolimus in Clinical Transplantation

Cyclosporin and azathioprine, was found to prolong human kidney homografts. Corticosteroids have been shown to prolong skin graft survival in rabbits. In 1963, Starzl et al. and Murray et al. effectively used a combination of corticosteroids and azathioprine to achieve success in allogeneic kidney transplantation in humans. The results of their combination of immunotherapeutic agents enabled the progress of kidney, liver and heart transplantation in humans during the 1960s and 1970s.

The introduction of cyclosporin in the early 1980s resulted in a rapid and major expansion in the field of transplantation. However, a small percentage of patients continued to lose grafts due to acute or chronic rejection. In the late 1980s and early 1990s, tacrolimus therapy has reduced acute and chronic rejection. This has enabled successful intestinal transplantation with the use of tacrolimus.

1. Properties of Cyclosporin and Tacrolimus

1.1 Physical Properties

Cyclosporin is produced as a metabolite by the fungus species Tolypocladium inflatum, and tacrolimus is derived from the soil fungus species Streptomyces tsukubaensis. The molecular mass of cyclosporin is 1202Da and that of tacrolimus is 822Da. Both drugs are virtually insoluble in water and hexane, but are soluble in methanol, ethanol, acetone, ethyl acetate, chloroform and dimethyl ether.

1.2 Chemical Structures

The chemical structures of these 2 compounds are completely different. Cyclosporin is a neutral lipophilic cyclic polypeptide consisting of 11 amino acids, while tacrolimus is a macrolide lactone with a hemiacetal-masked αβ-dicetamide incorporated in a 23-member ring (fig. 1).

1.3 Mechanisms of Action

It is interesting that although cyclosporin and tacrolimus are structurally dissimilar, they appear to have similar mechanisms of action. They both inhibit T cell receptor-stimulated transcription of lymphokine genes. Cyclosporin and tacrolimus bind to different intracellular protein families: cyclophilins and tacrolimus-binding proteins (FKBPs), respectively. Both compounds bind to their respective intracellular immunophilins to form a drug-binding protein complex which specifically and

![Fig. 1. Structures of tacrolimus and cyclosporin.](https://via.placeholder.com/150)
competitively binds to and inhibits the phosphatase activity of calcineurin, which is important in signal transduction. Both immunosuppressants block the transcription of early-phase T cell activation genes, including the c-myc proto-oncogene and the genes encoding interleukin (IL)-2, IL-3, IL-4, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumour necrosis factor-α (TNFα) and interferon-γ (IFNγ). They inhibit the proliferative response of T lymphocytes to specific antigens, resulting in their immunosuppressive properties (fig. 2).

2. Measurement of Drug Concentration

2.1 Matrix

The concentrations of cyclosporin and tacrolimus can be measured in serum, plasma and whole blood. Although the concentrations in serum and plasma are the same, the concentration of cyclosporin in whole blood is twice the plasma concentration, and that of tacrolimus is more than 10 to 50 times higher than the plasma concentration due to extensive binding of these drugs to erythrocytes.

2.2 Cyclosporin

Cyclosporin can be measured by various methods. Radioimmunoassay with polyclonal antibodies measures the parent compound with its metabolites, and the resulting concentration is about 3 times higher than what is measured by high performance liquid chromatography (HPLC), which measures the parent compound only. Radioimmunoassay with monoclonal antibodies measures the parent compound only and the results are comparable with those of the HPLC method.

A more rapid method developed by Abbott Laboratories uses a fluorescence polarisation immunoassay method (Abbott TDx), and both polyclonal and monoclonal assays are available. However, concentrations with these assays tend to be higher than those measured by HPLC. In liver transplant recipients, when there is hepatic dysfunction, the ratio of metabolites to parent compound is increased and concentrations obtained by polyclonal methodology are more than 3 to 7 times higher than those of the parent compound. It is clear that the parent compound is active for immunosuppressive activity. Cyclosporin metabolites in experimental models are less immunosuppressive, and may be toxic.

2.3 Tacrolimus

Tacrolimus was initially measured by enzyme-linked immunosorbent assay (ELISA) in plasma,
sporin it is 2 to 4 hours and for tacrolimus it is 0.5 to 5 hours (fig. 3).148,50

3.6 Effect of bile

The presence of bile is necessary for the absorption of cyclosporin, and without it absorption is extremely poor. This has major therapeutic implications in liver transplant recipients, who often have a biliary reconstruction which drains bile externally.53,54 Tacrolimus absorption occurs independently of bile, and external drainage of bile does not affect its pharmacokinetic profile.52

However, the microemulsion form of cyclosporin (Neoral®) is absorbed in the absence of bile; higher peak concentrations and greater area under the concentration-time curve have been achieved without significant changes in trough concentration as compared with administration of similar doses of conventional formulations of cyclosporin.55,56

3.7 Effect of Hepatic Dysfunction

Since both cyclosporin and tacrolimus are metabolised by the liver, liver dysfunction prolongs the half-life and slows the clearance of both drugs.57,58 Higher plasma or blood concentrations with lower doses of drugs may thus occur (fig. 4).

Excretion of cyclosporin into bile is dependent on liver function.58,59 The accumulation of cyclosporin metabolites and the increase in parent compound in blood or plasma can give much higher concentrations when measured by polyclonal antibodies.36,50 An increased ratio between plasma concentrations and bioassay has been observed with tacrolimus,60 and an increase in tacrolimus metabolites with liver dysfunction has also been reported recently.61

3.8 Drug Interactions

Drugs that stimulate the cytochrome P450 enzyme system will lower the concentration of both cyclosporin and tacrolimus, while drugs that inhibit the cytochrome P450 system will raise the concentration of the drug, as shown in table II.63-70

4. Therapeutic Effects

4.1 Liver Transplantation

4.1.1 Cyclosporin
The introduction of cyclosporin for liver transplantation increased patient survival from 30 to 35% at 1 year on azathioprine/corticosteroids to 60 to 70%,71 and 5-year survival rates were also significantly better.72 85% of surviving adults could

Fig. 3. Kinetic profiles following intravenous and oral administration of cyclosporin and tacrolimus. (Left) Whole blood concentration by high performance liquid chromatography (note logarithmic scale) versus time after administration of a single dose of cyclosporin 3.2 mg/kg intravenously or 12.3 mg/kg orally (from Plochowski et al.,149 with permission). (Right) Plasma concentration versus time after administration of a single dose of tacrolimus 3 mg intravenously or 5 mg orally (from Vankutemans et al.,149 with permission).
Cyclosporin and Tacrolimus in Clinical Transplantation

and the plasma concentration measured was dependent on the temperature at which the plasma was separated from the whole blood. Concentrations at 37°C (body temperature) were almost twice those of plasma separated at 21°C (room temperature). The ELISA was also used to measure whole blood concentrations.[32-34] Zeeki et al.[35] developed a bioassay to measure the total immunosuppressive plasma concentrations of tacrolimus in liver transplant recipients, and have shown a clinical correlation.[35,36]

Recently, Abbott Laboratories has developed the IMx method for measurement of tacrolimus concentrations in whole blood samples.[37] The relative difference in blood and plasma concentrations is influenced by haematocrit, total drug concentration and temperature of blood separation.[24,33,38]

3. Pharmacokinetics

Table I summarises the pharmacokinetics of cyclosporin and tacrolimus.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Cyclosporin</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma versus whole blood concentration ratio</td>
<td>1:2</td>
<td>1:10 (range 1:11 to 1:50)</td>
</tr>
<tr>
<td>Primary site of metabolism</td>
<td>CYP</td>
<td>CYP</td>
</tr>
<tr>
<td>Volume of distribution based on plasma (L/kg)</td>
<td>3.5-11.1</td>
<td>5-65</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>5-12</td>
<td>5.5-18.6</td>
</tr>
<tr>
<td>Clearance (L/h/kg) blood</td>
<td>0.27</td>
<td>0.06 (range 0.02-0.06)</td>
</tr>
<tr>
<td>Clearance (L/h/kg) plasma</td>
<td>0.47</td>
<td>1.8 (range 0.42-6.16)</td>
</tr>
<tr>
<td>Absorption of oral dose (%)</td>
<td>5-69</td>
<td>5-67</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>2-4</td>
<td>0.5-5</td>
</tr>
<tr>
<td>Absorption depends on bile</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hepatic dysfunction affects metabolism</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Higher dosage in children (bodyweight basis)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect of dialysis on concentration</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: CYP = liver cytochrome P450; t_{max} = time to reach maximum concentration after administration.

3.1 Metabolism

Both drugs are metabolised by the cytochrome P450 III system, and the rate of metabolism depends on liver function and associated drugs which can interfere with cytochrome P450 metabolism. Several metabolites of cyclosporin have been identified.[39-45] Tacrolimus metabolites have been observed in the blood, bile and urine of recipients following liver transplantation.[46]

3.2 Volume of Distribution

Both drugs are extensively distributed, and have a large volume of distribution of 3.5 to 11.1 L/kg for cyclosporin and 17 (range 5 to 65) L/kg for tacrolimus, based on plasma concentration.[47-50]

3.3 Half-Life

The mean terminal disposition half-life of cyclosporin is between 5 and 12 hours, while that of tacrolimus is between 5.5 and 16.6 hours. However, the half-lives of both cyclosporin and tacrolimus are widely variable and are particularly prolonged in the presence of hepatic dysfunction.[48,50,52]

3.4 Clearance

The mean blood clearance for cyclosporin is 0.12 to 0.78 L/h/kg (2 to 13 ml/min/kg). The blood clearance of tacrolimus is 0.06 (range 0.03 to 0.09) L/h/kg and the plasma clearance is 0.42 to 6.18 L/h/kg (7 to 103 ml/min/kg).[51] Both drugs have low clearance in the presence of liver dysfunction.[50,52]

3.5 Oral Absorption

Oral absorption of both drugs is poor and incomplete, with wide variation. The mean absorption of cyclosporin is 30% of the oral dose (range of 5 to 89%), while that for tacrolimus is 25% (range of 5 to 67%). The time to reach peak concentration (t_{max}) also varies greatly for cyclo-
resume their normal activity. Children, however, required higher dosages of cyclosporin.[33-35]

### 4.1.2 Rescue Therapy with Tacrolimus

Clinical trials of tacrolimus began in March 1989[76,77] in liver transplant recipients who were experiencing acute or chronic rejection. Patients experiencing nephrotoxicity or severe hypertension while receiving cyclosporin were also included in the study. Significant improvements in biochemical and histological findings were noted, with a biochemical response rate as determined by liver function tests (bilirubin, ALT, AST) of up to 70%. Demetris et al.[78,79] reported a better histopathological response to tacrolimus in the early stages of chronic rejection, which was sustained in the long term.

The US Multicenter Tacrolimus Study Group and other centers confirmed these findings.[80-86] These studies showed that the use of tacrolimus led to marked improvement in liver function and performance status and a lower incidence of hypertension with reduced use of corticosteroids.[87,88] Similar results have been reported in pediatric populations.[89,90]

### 4.1.3 Primary Therapy with Tacrolimus

In 1990, Todo et al. first reported the use of tacrolimus in primary liver transplant recipients.[91] Later in the same year, a larger series of 110 patients was presented at the 13th International Congress of the Transplantation Society.[92] An increased incidence of freedom from rejection was clearly seen in primary liver transplant recipients.[93] Recently, a larger study of 1391 consecutive patients from a single institute has been published, showing improvement in patient and graft

---

### Table II. Drug interactions with cyclosporin and tacrolimus

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect on concentration of cyclosporin</th>
<th>Effect on concentration of tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Vorazemol</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Clofibratezol</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Danazol</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td>Phenoxybitaline</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Filtamicol (vitalin)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ticloplin</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*a Not reported in literature but would be predicted from known data.

Symbols: ↑ to ↑↑ indicate slightly to significantly increased; ↓ to ↓↓ indicate slightly or moderately decreased; ↔ indicates unchanged.
survival and reduced use of corticosteroids and antihypertensive medications.\textsuperscript{[94]}

Three separate randomized trials have been conducted to study the efficacy of tacrolimus versus cyclosporin in primary liver transplant recipients: (i) University of Pittsburgh (single centre: 154 patients);\textsuperscript{[95-97]} (ii) European Tacrolimus Multicentre (8 centres: 545 patients);\textsuperscript{[98]} (iii) US Multicenter Tacrolimus Liver Study Group (12 centres: 529 patients).\textsuperscript{[99]} All 3 studies have shown a significantly lower incidence of rejection under tacrolimus. In the Pittsburgh trial, a large percentage of patients were switched from cyclosporin to tacrolimus, mainly for persistent rejection. Patient and graft survivals were not different with intent-to-treat analysis, leading to 1-year patient and graft survivals of 91 and 91% with tacrolimus and 88 and 86% with cyclosporin, respectively; however, some of the grafts in patients receiving cyclosporin who experienced refractory rejection may have been lost if not rescued by tacrolimus.

There were some differences between the Pittsburgh trial and the 2 multicentre trials: (i) the starting dosages of tacrolimus used in the multicentre trials were higher than that usually used in Pittsburgh; (ii) at the initiation of the trials, daily monitoring of tacrolimus concentrations was not readily available at any of the 20 participating centres; (iii) patients randomised to cyclosporin invariably received higher dosages of concomitant corticosteroids, with or without simultaneous use of azathioprine and/or antilymphocyte preparations.\textsuperscript{[100]} In addition, the primary end-point in the Pittsburgh trial was freedom from rejection, while that for the multicentre trials was patient and graft survival.

One-year patient and graft survivals in the European trial were 82.9 and 77.5% for tacrolimus versus 77.5 and 72.6% for cyclosporin. The acute rejection–free rate was higher in the tacrolimus group: 56.6% versus 46.4% for cyclosporin (p = 0.004). The refractory rejection rate was 0.8% with tacrolimus versus 5.6% with cyclosporin (p = 0.005), and the chronic rejection rate was 1.5% with tacrolimus versus 5.3% with cyclosporin (p = 0.032), despite higher concomitant use of corticosteroids and/or azathioprine in the cyclosporin arm. The infection rate for patients receiving

![Diagram](https://via.placeholder.com/150)

**Fig. 5.** Protocol design of US multicentre trial of tacrolimus versus cyclosporin, showing concomitant higher use of corticosteroids, azathioprine and antilymphocyte globulin (ALG) at various centres using cyclosporin (from Starzl et al.,\textsuperscript{[100]} with permission).
Tacrolimus was lower (p = 0.005). Although more patients receiving tacrolimus experienced oliguria during the immediate post-transplant period, the serum creatinine concentrations of both groups at the time of discharge were not much different. There was no difference in the use of insulin or oral hypoglycaemic agents between the 2 groups. Tremors were most commonly reported in patients receiving tacrolimus, whereas there were no major differences in other neurological events.

In the US multicentre trials, actuarial 1-year patient survival, by intent-to-treat analysis, was 88% for both groups of patients, whereas graft survival was 82% for tacrolimus-treated and 79% for cyclosporin-treated patients. Overall, 22 cyclosporin-treated patients with refractory rejection were switched to tacrolimus, 19 of whom survived with their original grafts. Rates of acute rejection, steroid-resistant rejection and refractory rejection were 68, 19 and 3% with tacrolimus versus 76, 36 and 15% with cyclosporin (p < 0.002, < 0.001 and < 0.001, respectively). As illustrated in figure 5, patients in the cyclosporin arm received higher dosages of corticosteroids (at all 12 centres), azathiopine (at 11 centres) and antilymphocyte preparations (at 1 centre). In total, 14.1% of patients receiving tacrolimus were withdrawn from the study, mainly for neurotoxicity and nephrotoxicity, whereas 4.9% of cyclosporin-treated patients were withdrawn from the study (by the protocol design, conversion from tacrolimus to cyclosporin because of adverse events was allowed, but not cyclosporin to tacrolimus). Reanalysis of the US multicentre trial for undesirable endpoints (i) rejection, (ii) rejection, retransplantation or death; (iii) rejection, retransplantation, death or adverse event requiring withdrawal of the drug; or (iv) rejection, retransplantation, death or withdrawal of the drug for any reason) showed significantly better results with tacrolimus compared with cyclosporin (fig. 6). Lack of efficacy was observed in 12% of cyclosporin-treated patients versus 2.3% of tacrolimus-treated patients. At 1-year follow-up, no differences in the mean serum creatinine level or glomerular filtration rate were observed between the treatment groups.

In both the European and the US multicentre studies, patients were switched from the tacrolimus to the cyclosporin arm, predominantly due to neurotoxicity, and from the cyclosporin to the
tacrolimus arm, predominantly to control rejection. However, in both studies, a higher incidence of neurotoxicity in the tacrolimus arm was noticeable, which may be because higher dosages of tacrolimus than in the Pittsburgh trial were used and monitoring of the drug concentration was not promptly available.[100] In another study from the Pittsburgh group,[101] a switch-over rate from tacrolimus to cyclosporin of approximately 2.5% of liver transplant recipients for neurotoxicity and other reasons has been reported. Over 75% of these patients were switched back to tacrolimus without recurrence of the events. It will be interesting to note in the future how many patients in both the US and European multicentre trials eventually will remain on tacrolimus or cyclosporin beyond 1 year. Significantly less need of retransplantation under tacrolimus compared with cyclosporin has been reported by Takaya et al.[102]

McDiarmid et al.[103] has also compared the efficacy of tacrolimus (30 patients) with that of cyclosporin (20 patients) for primary immunosuppression after paediatric liver transplantation. Patient and graft survival rates were almost identical, but freedom from rejection under tacrolimus was much higher. The need for antilymphocyte preparations and the cumulative dose of corticosteroids were lower in tacrolimus-treated children compared with cyclosporin-treated children.

A pharmacoeconomic analysis by Lake et al.[104] of the US multicentre trial has shown a significant economic advantage of tacrolimus over cyclosporin.

4.2 Kidney Transplantation

4.2.1 Cyclosporin

In the initial trial on cyclosporin by Calne et al. in 1979,[105,106] the nephrotoxicity of the drug was not realised during the early period of the trial and thus many patients received relatively high dosages of cyclosporin, contributing to significant toxicity of the drug. Subsequently, European and Canadian multicentre trials showed significantly improved 1-year patient and graft survival with the use of cyclosporin plus corticosteroids.[107,108] Sustained improvement in patient and graft survival at 3 years from a Canadian study and at 5 years from a European study has been reported.[109-111] Impaired, but stable, renal function without evidence of progressive nephrotoxicity in long term (3 to 5 years) studies with cyclosporin has also been reported in a large series from various centres.[112-114]

Much lower dosages of cyclosporin (8 to 12 mg/kg/day) in combination with azathioprine and low dosage corticosteroids have been used in clinical trials,[115,116] although reduction in cyclosporin dosage in the long term has been reported to lead to late acute rejection[117] and may contribute to chronic rejection.[118,119] A maintenance dosage of >4.0 mg/kg/day has been recommended.[120-122]

4.2.2 Rescue Therapy with Tacrolimus

Jordan et al.[123,124] have shown that up to 70% of patients on cyclosporin with acute rejection refractory to corticosteroids and antilymphocyte antibody can be rescued by tacrolimus. The dosage of corticosteroids could be lowered in these patients, with a consequent improvement in hypertension. In another centre, 95% of the 20 antilymphocyte antibody–treated rejections in renal allografts were salvaged with tacrolimus.[125]

4.2.3 Primary Therapy with Tacrolimus

Starzl et al.[126] reported the use of tacrolimus with low dosage corticosteroids in 36 high-risk renal transplant recipients. Patient survival was 94% and graft survival was 81% after 3 to 13 months follow-up. The Japanese multicentre phase II trial[127] has shown a 3-year patient survival of 100% and graft survival of 91.2% for living-related kidney transplantation with tacrolimus. They also reported a 3-year patient survival of 95.9% and graft survival of 79.4% for cadaveric renal transplantation with tacrolimus. Similar results have been observed in a phase III Japanese multicentre kidney transplant trial.[128]

Paediatric on bloc kidney transplantation (i.e. transplantation of both donor kidneys together with donor inferior vena cava and aorta into a single recipient) with cyclosporin has a greater rate of graft failure due to technical and immunological reasons.[129] However, improved results have been noted with tacrolimus.[130]
In 1991, Jensen et al.\textsuperscript{[131]} described 16 paediatric renal transplants under tacrolimus-based immunosuppression, with 100% patient survival and 94% graft survival during the follow-up period of 1 to 15 months. Subsequently, in 1994 Scantlebury et al.\textsuperscript{[132]} described a 4-year experience with 62 paediatric kidney transplants (63 grafts) under cyclosporin (32 children, 33 grafts) and tacrolimus (30 children and grafts). Although there was a slightly higher rate of rejection under tacrolimus-based immunosuppression compared with cyclosporin, more children were weaned off corticosteroids in the tacrolimus group.

Shapiro et al.\textsuperscript{[133]} reported the use of tacrolimus compared with cyclosporin in clinical kidney transplantation (436 grafts in 425 recipients). Patient and graft survival at 1 year was 94 and 77% for cyclosporin versus 90 and 74% for tacrolimus, respectively. However, the tacrolimus group of patients had lower numbers of living-related donors and higher percentages of previously failed grafts. Although the incidence of rejection episodes was the same in tacrolimus- and cyclosporin-treated recipients, the histological findings revealed a more severe degree of rejection with cyclosporin.\textsuperscript{[116]} 44% of patients receiving tacrolimus could be weaned off corticosteroids completely, whereas all the patients receiving cyclosporin were maintained on corticosteroids.\textsuperscript{[133]} A lower incidence of, and less severe, hypertension in the tacrolimus group was an important benefit, as well as the absence of gingival hyperplasia and hirsutism.

In another randomised study by Shapiro et al.,\textsuperscript{[135]} the combination of tacrolimus and corticosteroids (double drug) was compared with tacrolimus, corticosteroids and azathioprine (triple drug) in 395 patients. The study showed no significant difference in survival, with overall patient survivals of 96 and 93% with graft survival of 89 and 83% at 1- and 2-year intervals, respectively. There was a trend to decreased incidence of rejection and reduced use of corticosteroids in the triple drug-treated patients.

In another multicentre kidney transplant trial with tacrolimus in 92 recipients, patient and graft survival of 98 and 93.7%, respectively, at 1 year has been reported.\textsuperscript{[136]}

4.3 Heart Transplantation

In early 1980, the introduction of cyclosporin resulted in an improvement in cardiac transplantation survival to 80 and 77% at 1 and 2 years, respectively.\textsuperscript{[137,138]} Improvements in surgical technique, organ preservation and a reduction in corticosteroid use led to further improvements in graft and patient survival.\textsuperscript{[139,140]} However, many patients who survived at 2 years had impaired renal function with hypertension. Changes in clinical protocols include triple or quadruple drug therapy, consisting of cyclosporin, azathioprine and corticosteroids\textsuperscript{[141]} with or without induction by antilymphocyte antibodies.\textsuperscript{[142]} Quadruple therapy seems to have the ability to delay the first episode of rejection.

Steroid- and antilymphocyte antibody-resistant cardiac rejection during cyclosporin-based immunosuppression can be successfully rescued with tacrolimus in both children and adults.\textsuperscript{[143-145]} Tacrolimus therapy in primary heart transplantation has been reported, with patient survival of 92% at 1 year in the adult population and 82% in the paediatric population at 1 to 3 years. While these survivals are comparable to those with cyclosporin, freedom from rejection at 90 days was higher with tacrolimus (40% in adults and 60% in children), with a lower incidence of hypertension (54% with tacrolimus compared with 70% for cyclosporin) in adults.\textsuperscript{[143-146]} Improved quality of life under tacrolimus has been reported by Dew et al.\textsuperscript{[147]}

4.4 Lung Transplantation

The combination of cyclosporin, azathioprine and prednisone with the use of antilymphocyte globulin has led to 1-year patient survival of 65% in 1983\textsuperscript{[148]} and up to 70% in 1992.\textsuperscript{[149]} Using various immunosuppressive protocols, Griffith et al.\textsuperscript{[150]} reported a reduced incidence of rejection with tacrolimus without using antilymphocyte antibodies. When antilymphocyte antibodies were added to a cyclosporin regimen, the incidence of rejection...
tions was reduced from 3 per patient to 2 per patient.

In a prospectively conducted randomised trial using cyclosporin plus azathioprine versus tacrolimus at the University of Pittsburgh, significantly better graft survival was seen in the tacrolimus group (86%) compared with the cyclosporin group (69%).[151] 36% of patients in the cyclosporin arm were switched to tacrolimus to control steroid/muromonab CD3 (OKT3)-resistant rejection. In addition, the rejection-free rate in the tacrolimus arm was higher compared with the cyclosporin arm.

A longer follow-up (>2 years) with a larger patient population (cyclosporin 67, tacrolimus 66) of this trial[151] has been reported.[152] There was a trend towards increased survival with a lower rate of acute rejection in the tacrolimus group. Of the 67 cyclosporin-treated patients, 13 (19.4%) were switched to tacrolimus, mostly to control steroid-resistant rejection. More importantly, significantly fewer patients (p = 0.025) developed obliterative bronchiolitis, the histological manifestation of chronic rejection, under tacrolimus.

4.5 Pancreatic Transplantation

Simultaneous kidney and pancreatic transplantation or liver and pancreatic transplantation under cyclosporin have been performed successfully.[153] A triple-drug therapy regimen consisting of cyclosporin, azathioprine and corticosteroids is usually employed, and induction with antilymphocyte antibodies has also been reported to decrease rejection rates.[154]

In 1 series,[155] tacrolimus has been shown to reverse refractory acute rejection and prevent the further progression of chronic rejection in pancreatic transplantation with cyclosporin. The Tacrolimus Pancreatic Transplant Cooperative Study Group has shown that tacrolimus is effective for both primary and rescue therapy.[156] Surprisingly, no diabetogenic effect was observed in the 72 patients treated. Also, no pancreatic grafts were lost due to rejection at 4 months when tacrolimus was used as a primary therapy (n = 37).

4.6 Intestinal Transplantation

Only a small number of patients have received intestinal transplantation successfully with cyclosporin.[157-159] The application of tacrolimus in isolated small bowel transplantation, small bowel with liver alone or multivisceral transplantation has led to a 1-year graft survival of 67% and patient survival of 78%.[160,161] 90% of the survivors are on oral nutrition only.[162] The rate of rejection and cytomegalovirus infection has been higher compared with liver transplantation alone.[163] Absorption of tacrolimus from the transplanted bowel has not been much different from that in recipients of other organs with native bowels.[165]

5. Clinical Efficacy

5.1 Acute Rejection

Most reports on liver,[93,98-100] heart,[143,144,146] and lung[131,132] transplantation have shown decreased incidence and less severe rejection episodes under tacrolimus compared with cyclosporin-based immunosuppression (table III). The rejection rate in kidney transplant recipients has been the same in 1 series,[133] but the histopathological severity of rejection under tacrolimus was lower.[134] In another multicentre randomised study of kidney transplant recipients, the incidence of rejection under tacrolimus-based immunosuppression was significantly lower compared with cyclosporin-based immunosuppression.[136]

5.2 Chronic Rejection

A lower incidence of chronic rejection has been reported under tacrolimus-based immunosuppression in early trials of liver transplantation.[99,106] The incidence of chronic rejection resulting in graft loss or death in a larger study group of primary liver transplant recipients after 1 to 5 years follow-up has been approximately 1% (our unpublished observations). Similarly, a prospective randomised trial of lung transplantation has shown a significantly lower incidence of obliterator bronchiolitis (a histological manifestation of chronic rejection)
Table III. Clinical efficacy of cyclosporin and tacrolimus

<table>
<thead>
<tr>
<th>Efficacy criteria</th>
<th>Cyclosporin</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of acute rejection</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>lung</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>kidney</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Severity of rejection</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>lung</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>kidney</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Freedom from corticosteroids at 3 to 4 months post-transplant</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>liver</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>heart</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>lung</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>kidney</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ability to control acute rejection on optimum cyclosporin-based regimen</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to control established chronic rejection</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>liver</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>kidney</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>pancreas</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>heart/lung</td>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Symbols: + indicates mild; ++ indicates moderate; +++ indicates severe.

over time in tacrolimus-treated compared with cyclosporin-treated patients.\(^ {122} \)

The impact of tacrolimus on chronic rejection in kidney transplant recipients has not been clearly defined. However, Gjertson et al.\(^ {167} \) analysed United Network for Organ Sharing kidney transplant registry data from 1988 to 1994, consisting of 38,057 first cadaveric kidney transplants from 224 centres in the US. They predicted a significantly prolonged half-life of kidney allografts with tacrolimus (14 years) versus cyclosporin (8 to 9 years).

Currently, no such data on chronic rejection in heart transplantation are available.

5.3 Rescue Therapy

Tacrolimus has been shown to reverse acute rejections in liver,\(^ {77-85,16} \) kidney,\(^ {122-125} \) heart,\(^ {142-145} \) lung,\(^ {151,152} \) and pancreatic\(^ {155,156} \) transplant recipients. It appears to improve chronic rejection in liver transplant recipients\(^ {77,83} \) and halt the progression of rejection in pancreatic transplant recipients.\(^ {155,156} \) It cannot reverse the established chronic rejection in renal allografts, and no data are available on chronic rejection in heart and lung transplant recipients.

5.4 Corticosteroids and Antilymphocyte Antibodies

The need for concomitant use of corticosteroids and antilymphocyte antibodies has been significantly lower in all primary liver,\(^ {98,99,103} \) kidney,\(^ {132} \) heart,\(^ {143} \) and lung\(^ {150} \) transplant recipients receiving tacrolimus compared with cyclosporin. Also, the dosage of corticosteroids could be reduced after successful rescue therapy with tacrolimus, resulting in improvement of cushingoid facial appearance.\(^ {123,124} \) At the same time, it should be noted that although the majority of the centres used baseline corticosteroids routinely with cyclosporin, there are reports of good renal graft survival with cyclosporin monotherapy, with equal or lower incidence of infection.\(^ {171-174} \)

6. Therapeutic Dosage Adjustment

6.1 Intravenous and Oral

The oral dosage requirements are about 3 to 4 times higher than the intravenous dosages for both cyclosporin and tacrolimus, since oral absorption is incomplete.\(^ {50,175} \) Longer periods of intravenous therapy are necessary in cyclosporin-based therapy compared with tacrolimus-based therapy, due to poor absorption during the early postoperative period following liver transplantation\(^ {198,175} \). The European study has shown that oral use of tacrolimus in the immediate postoperative period eliminates the need for intravenous administration following liver transplantation.\(^ {176} \)

6.2 Children

Children metabolise both cyclosporin and tacrolimus faster than do adults, as in this population the
drug half-life is shorter and clearance is faster. Hence, on average they require twice the adult dosage based on bodyweight.\textsuperscript{103,175-180}

6.3 External Bile Drainage

The absorption of cyclosporin is dependent on availability of bile in the gut,\textsuperscript{53} but tacrolimus is absorbed independently of bile.\textsuperscript{52} Higher dosages of cyclosporin may be necessary to achieve therapeutic concentrations in individuals with external bile drainage, and intravenous administration may even be required. No such adjustment is necessary with tacrolimus. However, the microemulsion formulation of cyclosporin is reported to be absorbed independently of bile.\textsuperscript{56}

6.4 Liver Dysfunction

Liver dysfunction impairs the metabolism of both cyclosporin and tacrolimus.\textsuperscript{50,52} Hence, significant decreases in dosages are necessary for both cyclosporin and tacrolimus in the presence of hepatic dysfunction.\textsuperscript{50,181} With prolonged impairment in metabolism, careful drug monitoring is extremely important.

6.5 Transplanted Organ

The mean tacrolimus dosage in renal transplant recipients\textsuperscript{135,136} is higher compared with the mean dosage in liver transplant recipients.\textsuperscript{182} Kidney transplant recipients seem to tolerate a higher dosage with relatively less toxicity compared with liver and heart transplant recipients. Small bowel transplant recipients reject more frequently and need higher dosages of tacrolimus.\textsuperscript{163} Similar data are not well documented for cyclosporin.

6.6 Dialysis

Neither cyclosporin nor tacrolimus are dialysable, and hence no change in the dosage is necessary when patients are on haemodialysis.\textsuperscript{48}

6.7 Drug Monitoring

There is a wide variation in the absorption of cyclosporin and tacrolimus in both children and adults.\textsuperscript{175-179} The rate of metabolism varies with liver function and the presence or absence of certain drugs. In addition, there appears to be a correlation between concentrations of both drugs and the incidence of certain major adverse events, e.g., nephrotoxicity\textsuperscript{183,184} and neurotoxicity. In order to achieve the correct therapeutic dosage in transplant recipients, it is important to monitor the drug concentration, anticipating the above changes for both tacrolimus and cyclosporin.

Daily trough concentrations in the immediate postoperative period are useful, particularly to avoid nephro- and neurotoxicity.\textsuperscript{184} Backman et al.\textsuperscript{184} in 59 liver recipients, found increased toxicity with tacrolimus whole blood concentrations >25 μg/L and plasma concentrations >1.3 μg/L. Recipients with persistent plasma concentrations <0.2 μg/L were more prone to acute rejection. Consequently, tacrolimus plasma concentrations of 0.4 to 1.2 μg/L are recommended following liver transplantation. The corresponding whole blood trough concentrations would be approximately 8 to 24 μg/L.

For cyclosporin-treated patients a therapeutic range of whole blood trough concentrations of parent compound of 150 to 350 μg/L has been recommended,\textsuperscript{185} which would be approximately 400 to 1200 μg/L when measured by polyclonal assay.

As pointed out in section 6.5, kidney and heart transplant recipients seem to need higher dosages and higher concentrations compared with liver transplant recipients.\textsuperscript{189} Small bowel transplant recipients also require higher dosages and blood/plasma concentrations.\textsuperscript{163-165}

7. Adverse Effects

7.1 Neurotoxicity

Both cyclosporin and tacrolimus exhibit a variety of neurological adverse effects. Most of these events are dosage-dependent, mild and reversible. Optimum usage of both drugs demands considerable experience and constant monitoring of the blood/plasma concentration.\textsuperscript{187,188} Both the randomised multicentre European and US liver transplantation trials have shown some patients being
switched from tacrolimus to cyclosporin in order to minimise neurotoxicity.\textsuperscript{[90,91]} However, the Pittsburgh randomised trials, with more extensive single centre experience, used a lower dosage of tacrolimus and daily monitoring of drug concentration and showed no requirement for such switching.\textsuperscript{[93-97]}

Neurotoxicity consists of tremors, paraesthesia, confusion, headache, photophobia, akinesia mutism, expressive aphasia, psychosis and seizure disorders.\textsuperscript{[188,189]} The incidence of these adverse effects tended to be higher in the tacrolimus group of patients than in the cyclosporin group in both the US and European\textsuperscript{[98,99]} randomised trials (table IV), where higher dosages of tacrolimus were used without daily drug concentration monitoring.

### 7.2 Nephrotoxicity

Both drugs are nephrotoxic; as with neurotoxicity, this is dosage-dependent and mostly reversible. The majority of studies have shown comparable nephrotoxicity in both the cyclosporin and tacrolimus groups of liver transplant patients.\textsuperscript{[98,99]} Reductions in glomerular filtration rate of 29% in the cyclosporin group and 35% in the tacrolimus group have been reported with long term use.\textsuperscript{[99]}

The mean serum creatinine levels at intervals after transplantation were similar in both groups of patients in the randomised studies of liver transplantation.\textsuperscript{[190-192]} A similar nephrotoxic effect of tacrolimus has been described by McCauley et al.\textsuperscript{[193]} in heart and lung transplant recipients as in liver transplantation.

Histopathological changes in renal allograft biopsies are also similar with cyclosporin and tacrolimus: vacuolation, tubular atrophy, interstitial fibrosis and hyalinosis have been observed in equal proportions.\textsuperscript{[194,195]}

### 7.3 Electrolyte Disturbances

#### 7.3.1 Hyperkalaemia

Over 40% of patients receiving tacrolimus require treatment to reduce hyperkalaemia, a higher incidence than reported with cyclosporin.\textsuperscript{[182,196]}

However, this is easily controlled with potassium-binding resins, dietary restriction and fluocortolone. Hyperkalaemia is thought to be associated with type IV renal tubular acidoses, where lower levels of the normal range of aldosterone and renin have been observed with hyperkalaemia in tacrolimus-treated patients.\textsuperscript{[196]} Also, renal insufficiency without acidosis is frequently observed.

#### 7.3.2 Hypomagnesaemia

Hypomagnesaemia with cyclosporin treatment has been reported.\textsuperscript{[197]} Similar observations with tacrolimus treatment have been made.\textsuperscript{[86]}

### 7.4 Hypertension

In liver, kidney and heart transplantation, hypertension is less severe and less frequent in the tacrolimus group than in the cyclosporin group.\textsuperscript{[133,146,190,198]} Also, improvement in hypertension has been reported when patients are switched from cyclosporin to tacrolimus following liver\textsuperscript{[199]} and heart\textsuperscript{[143]} transplantation. This may partially reflect the reduced use of corticosteroids in the tacrolimus group.

### 7.5 Metabolic Effects

#### 7.5.1 Diabetogenic Effects

12 to 18% of transplant recipients develop new onset insulin-dependent diabetes mellitus when receiving tacrolimus.\textsuperscript{[135,182,200,201]} In the US multi-
centre randomised studies of liver\textsuperscript{202} and kidney\textsuperscript{136} transplantation, the need for hypoglycaemic agents in tacrolimus- and cyclosporin-based immunosuppression was similar, although tacrolimus patients were receiving lower dosages of corticosteroids. It is conceivable that insulin-dependent diabetes mellitus is more readily induced in high-risk recipients receiving tacrolimus.\textsuperscript{203} Interestingly, diabetogenic effects in primary or rescue therapy with tacrolimus in pancreatic transplants have not been observed.\textsuperscript{156}

7.5.2 Hypercholesterolaemia

Higher cholesterol levels are seen with cyclosporin-based regimens,\textsuperscript{204} while lower levels of cholesterol have been reported with tacrolimus.\textsuperscript{146} Also, in a large randomised trial, low density lipoprotein levels were significantly higher in the cyclosporin group of patients 6 months after liver transplantation.\textsuperscript{203}

7.6 Infection

The incidence of bacterial infection was lower in liver transplant recipients receiving tacrolimus,\textsuperscript{203} and the rate of onset of infection was significantly lower in the tacrolimus group in the European liver transplantation trial.\textsuperscript{399} In a single-centre randomised study, reduced incidences of cytomegalovirus, deep fungal and intra-abdominal bacterial infections were observed with tacrolimus following liver transplantation.\textsuperscript{206} A reduced incidence of infection has also been reported with tacrolimus in a randomised study of lung transplant recipients.\textsuperscript{131}

7.7 Lymphoproliferative Disorders

Epstein-Barr virus (EBV) infection resulting in B cell proliferative disorder occurs at a similar frequency with cyclosporin and tacrolimus, <2% of the adult transplant population.\textsuperscript{207,208} Cox et al.\textsuperscript{209} reported an increased incidence of EBV infection and lymphoproliferative disorder (LPD) in children <5 years of age under tacrolimus compared with cyclosporin following liver transplantation (tacrolimus: n = 37, EBV 37.8%, LPD 18.9%; cyclosporin: n = 68, EBV 13.2%, LPD 2.9%). In the same study, children >5 years of age did not experience EBV infection or LPD under tacrolimus (n = 14), whereas 17.4% of children experienced EBV infection under cyclosporin (n = 23). However, 44 out of 51 children under tacrolimus were originally commenced on cyclosporin and subsequently converted to tacrolimus-based immunosuppression. More than 90% of the children in the study also received antilymphocyte antibody.

The increased incidence of post-transplant LPD in children may be the result of a cumulative effect of immunosuppression. Factors such as: (a) the incidence of seronegativity for EBV in paediatric recipients and seropositivity in the donor; and (b) the rate of conversion from seronegative to seropositive at various time intervals after transplant and its correlation to development of post-transplant LPD need further prospective evaluation.

7.8 Cardiomyopathy

Recently, Atkinson et al.\textsuperscript{110} have described hypertrophic cardiomyopathy, seen on routine two-dimensional echocardiography, in 5 of 5 children on tacrolimus following liver and/or intestinal transplantation. The condition improved after lowering the dosage (n = 3) or conversion to cyclosporin (n = 2).

This reversible phenomenon of cardiomyopathy after tacrolimus has not been reported from other centres. The cause and effect of associated fluid overload from impaired renal function in the immediate postoperative period needs further evaluation.

We recently compared the cardiac findings at autopsy in liver transplantation recipients who received tacrolimus (n = 67) with patients who died of end-stage liver disease (n = 72) without liver transplantation or tacrolimus. The weight of the heart, left and right ventricular wall thickness and circumferences of all the valves were identical. >80% of patients in both groups of patients at autopsy had left ventricular hypertrophy.
7.9 Other Adverse Effects

Hirsutism and gum hyperplasia have been observed only with cyclosporin. When children are switched to tacrolimus from cyclosporin, this facial appearance improves. Alopecia was observed more frequently in patients receiving tacrolimus compared with cyclosporin in a US multicentre trial. Similarly, anaemia was reported with a higher frequency with tacrolimus.

8. Conclusions

The majority of transplant centres using cyclosporin use triple or quadruple drug regimens to minimise the adverse events of cyclosporin without increasing the rate of rejection. Unfortunately, the combination of tacrolimus and cyclosporin has not worked in clinical settings because of increased nephro- and neurotoxicity. Not many trials have been conducted using tacrolimus with triple or quadruple drug regimens, except for Shapiro et al. for kidney transplantation. The recently approved mycophenolate mofetil, which is more potent than azathioprine, in combination with an even lower dosage of tacrolimus, may provide a balanced outcome in the majority of the patients since the toxicity profiles of the 2 drugs are separate (except for gastrointestinal toxicity).

Neurotoxicity and nephrotoxicity are major concerns with both cyclosporin and tacrolimus. However, they are dosage-dependent and neurotoxicity is reversible in most instances. Hypertension is more common with cyclosporin, while hyperkalaemia is more common with tacrolimus. Both drugs are diabetogenic in almost equal proportions. Gingival hyperplasia and hirsutism, which is noticed with cyclosporin, is not observed with tacrolimus.

Currently, it is clear that children have a distinct benefit from tacrolimus since it is absorbed better, leads to a lower incidence of hypertension and does not cause hirsutism or gum hyperplasia. The ability to be weaned off corticosteroids at a faster rate may lead to better growth and development in paediatric transplant recipients.

In liver transplant recipients, tacrolimus offers better absorption in the absence of bile when there is an external biliary drainage. However, some patients may be prone to develop neurotoxicity more easily, particularly the elderly population. In lung transplantation, the reduced incidence of obliterative bronchiolitis on tacrolimus is particularly appealing. In heart transplantation, the incidence of hypertension is lower when the patient is on tacrolimus as opposed to cyclosporin. However, some patients seem to be more prone to nephrotoxicity. In pancreatic transplantation, tacrolimus has shown encouraging results, surprisingly with no diabetogenic effects.

The benefits of a significantly reduced incidence of rejection under tacrolimus in liver, heart, lung and pancreatic transplantation have not been observed in kidney transplant recipients. However, the long term advantage of tacrolimus in kidney transplant recipients, with a predicted prolonged half-life of 14 years versus 8 to 9 years under cyclosporin, may require further consideration.

In the end, the ability of rescue therapy with tacrolimus to control acute rejections occurring under cyclosporin in all forms of solid organ transplantation, and the ability of the drug to diminish the process of chronic rejection in liver, lung and pancreas transplantation, will remain a major factor in the field of clinical transplantation. However, some patients may not be able to tolerate tacrolimus for primary or rescue therapy; in these patients, cyclosporin will provide an alternative treatment in such situations.

Acknowledgements

We acknowledge Professor T.B. Starzl for his dedication in development of experimental and clinical trials.

References

1. An illustrated history of organ transplantation. The great adventure of the century. Ruei Malmsteen (France): Laboratories Sandox, 1992; 45


Cyclosporin and Tacrolimus in Clinical Transplantation


86. McDermott SV, Klatman MB, Bussul WR. FK506 conversion for intractable rejection of the liver allograft. Transplant Int 1993; 6 (6): 305-12


© Adis International Limited. All rights reserved.
98. European FK506 Multicentre Liver Study Group. Randomized trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet 1994; 343: 423-4
106. Calne RV, Rolles K, White DG, et al. Cyclosporine A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979; II: 1033-6
111. Calne RV. Cyclosporine in cadaveric renal transplantation: 5 year follow up of a multicentre trial. Lancet 1987; II: 266-7


156. Grossner RK, FK506 Pancreatic Transplant Cooperative Study Group. Multicenter analysis of first experience with FK506 for induction and rescue therapy after pancreatic (PD) transplantation (T3) (abstract). American Society of Transplant Surgeons' 21st Annual Scientific Meeting, 1995 May; Chicago (IL); 33, abstr. 1-2


188. Kusse S, Pung J, Alasmimi M, et al. Infection during a randomized trial comparing cyclosporine to FK506 immunosup-
Cyclosporin and Tacrolimus in Clinical Transplantation


Correspondence and reprints: Dr John J. Fang, Pittsburgh Transplantation Institute, 4C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, PA 15213, USA.