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Cyclosporin

An Updated Review of the Pharmacokinetic Properties, Clinical Efficacy and Tolerability of a Microemulsion-Based Formulation (Neoral®)[1] in Organ Transplantation

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Data Selection

Sources: Medical literature published in any language since November 1995 on cyclosporin microemulsion, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'cyclosporin microemulsion' or 'cyclosporin modified' or 'microemulsion-based formulation' or 'cyclosporin A and microemulsion'. EMBASE search terms were 'cyclosporin microemulsion' or 'microemulsion-based formulation' or 'cyclosporin A and microemulsion'. AdisBase search terms were 'cyclosporin microemulsion' or 'cyclosporin-modified' or 'microemulsion-based formulation'. Searches were last updated 7 Sep 2001.

Selection: Studies in patients undergoing solid organ transplantation who received cyclosporin microemulsion. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Cyclosporin, pharmacodynamics, pharmacokinetics, therapeutic use, pharmacoeconomics, tolerability, dosage and administration, transplant rejection, review.

Contents

Summary

Abstract

Cyclosporin is a lipophilic cyclic polypeptide immunosuppressant that interferes with the activity of T cells chiefly via calcineurin inhibition. The original oil-based oral formulation of this drug (Sandimmun®)[1] was characterised by high intra- and interpatient pharmacokinetic variability, with poor bioavailability in many patients; a novel microemulsion formulation (Neoral®)[1] was therefore developed to circumvent these problems. Studies show increases, attributable chiefly to improved absorption in patients who absorb the drug only poorly from the original formulation, in mean systemic exposure to cyclosporin with the microemulsion, with no clinically significant differences in tolerability or drug interaction profiles.

Cyclosporin microemulsion is at least as effective as the oil-based formulation in renal, liver and heart transplant recipients, with trends towards decreased incidence of acute rejection with the microemulsion formulation in some (statistically significant in a few) trials. Cyclosporin microemulsion and tacrolimus appear to have similar efficacy in preventing acute rejection episodes in most renal, pancreas-kidney, liver and heart transplant recipients. However, there are indications of superior efficacy for tacrolimus in some trials, particularly in the prevention of severe acute rejection and in Black transplant recipients. Current 12-month data also indicate equivalent efficacy of sirolimus in renal transplantation.

Conversion from the oil-based to microemulsion formulation in stable renal, liver and heart transplant recipients is achievable with no change in acute rejection rates. The addition of an anti–interleukin-2 receptor monoclonal antibody and/or mycophenolate mofetil to cyclosporin microemulsion plus corticosteroids decreases rates of acute rejection; corticosteroid withdrawal without increased acute rejection rates was also achieved on the addition of these agents in some trials.

Pharmacoeconomic analyses have shown savings in direct healthcare costs in kidney or liver transplantation when cyclosporin microemulsion is used in preference to the oil-based formulation, although studies incorporating indirect costs or expressing costs in terms of therapeutic outcomes are currently unavailable.

Conclusions: The introduction of cyclosporin microemulsion has consolidated the place of the drug as a mainstay of therapy in all types of solid organ transplantation; research into optimisation of outcomes through more effective therapeutic monitoring in patients receiving this formulation is ongoing. Several novel immunosuppressants have been introduced in recent years: further clinical and pharmacoeconomic research will be needed to clarify the relative positioning of these agents, particularly with respect to specific patient groups. Other new drugs (basiliximab/daclizumab and mycophenolate mofetil) offer particular advantages when used in combination with cyclosporin.

Overview of Pharmacodynamic Properties

Cyclosporin inhibits the activation of the calcium/calmodulin-activated phosphatase calcineurin via complex formation with cyclophilin, and thereby prevents the translocation of the transcription factor nuclear factor of activated T cells (NF-AT). The drug also inhibits activation of the transcription factor NF-κB, and T cell activation is suppressed by inhibition of interleukin-2 gene expression. *In vitro* study of porcine aortic endothelial cells has shown complete suppression by cyclosporin of tumour necrosis factor-α–mediated induction of class II major histocompatibility complex expression.

Cyclosporin also has hypertensive effects; potential underlying mechanisms include effects on the sympathetic nervous system, upregulation of angiotensin

II receptors in vascular smooth muscle cells, increased plasma levels of endothelin-1, and effects on whole blood viscosity and plasma fibrinogen levels.

Pharmacokinetic Properties and Monitoring of Therapy

The original oil-based oral formulation of cyclosporin is characterised by widely varying bioavailability. The microemulsion, however, has self-emulsifying properties that enhance bioavailability and reduce pharmacokinetic variability between and within patients.

Assay Methods, Pharmacokinetic Monitoring and Clinical Outcomes. Measurement of cyclosporin concentrations in whole blood by immunoassay is currently used most commonly for monitoring therapy in patients receiving the drug for immunosuppression. Trough cyclosporin concentrations have been most frequently used to direct dosage adjustment, although they have little predictive value with respect to actual systemic exposure in patients receiving the original oil-based formulation.

The introduction of the microemulsion has led to new research into the therapeutic monitoring of cyclosporin therapy, with increasing emphasis on the importance of the 4-hour absorption phase that follows oral administration. Correlation has been shown between areas under curves of cyclosporin concentrations in whole blood versus time (AUCs) taken over 4 hours (abbreviated AUC) and a full 12-hour administration interval in patients undergoing renal transplantation. Other data suggest utility of 2-point sampling (at 2 and 6 hours), and a strong correlation has been shown between freedom from liver graft rejection during the first month after surgery and 6-hour AUCs (AUC_6) or peak drug concentrations in blood (C_{max}) in patients receiving cyclosporin microemulsion. Close correlations have been reported between drug concentrations measured in blood 2 hours post-dose and 4- or 6-hour AUCs, and there is evidence of improved overall clinical outcome with 2-hour over trough concentration monitoring.

General Pharmacokinetic Properties of Cyclosporin. Cyclosporin undergoes extensive extravascular distribution, with a volume of distribution at steady state of 3 to 5 L/kg after intravenous administration. The drug is 90 to 98% bound to plasma proteins, crosses the placenta, and is distributed into human milk.

Blood concentrations of cyclosporin generally decline in a biphasic manner. The initial elimination half-life is reported to average 1.2 hours, whereas the average terminal elimination half-life is reported to be 8.4 to 27 hours. The drug is metabolised extensively to at least 30 metabolites, chiefly by the hepatic cytochrome P450 3A enzyme system. Elimination is primarily biliary; around 6% of each dose is excreted in the urine, with 0.1% eliminated in the urine as unchanged drug. Clearance is not affected to any significant extent by haemodialysis or renal failure.

Pharmacokinetic Properties of Cyclosporin Microemulsion. In general, significant increases in mean systemic exposure of patients to cyclosporin, with attendant reductions in time to C_{max} (t_{max}), are seen when the microemulsion is used in place of the original oil-based formulation. These overall increases are attributable predominantly to improved absorption in patients who absorb cyclosporin only poorly from the oil-based formulation, with little or no change in good absorbers.

In renal transplantation, increases in AUC of up to 64% have been reported in randomised comparisons and in studies in which patients were converted from the older formulation to the microemulsion, with marked increases in drug exposure in patients previously classified as poor absorbers. Comparisons of variance data in several studies indicate significant reductions in intra- and interpatient

pharmacokinetic variability relative to the oil-based formulation in patients receiving the microemulsion. Substantially increased AUCs (median 71% increase in one 6-month study in 25 patients) relative to the oil-based formulation have been reported with the microemulsion in children undergoing renal transplantation.

Significant increases in AUC and C_{max}, and decreases in t_{max}, with cyclosporin microemulsion relative to the oil-based formulation have also been reported in patients undergoing liver transplantation. In one study, no clinically relevant effect of food intake was reported in microemulsion recipients. Most notably, the Canadian NOF-11 trial in 32 children showed exposure to cyclosporin (mean 8-hour AUC) to be increased by over 200% relative to the oil-based formulation in the early post-transplant period in patients treated with the microemulsion.

In general, systemic exposure to cyclosporin given as microemulsion appears greater than with the oil-based formulation when T tubes are open during the first few days after liver transplantation, although data are available to indicate that absorption of cyclosporin from the microemulsion is not fully independent of bile flow.

Enhancement of absorption of cyclosporin from the microemulsion relative to the oil-based formulation has also been reported in patients receiving heart and/or lung allografts. Increases were particularly marked in patients receiving lung transplants, with an increase in mean AUC_6 of just over 70% relative to the oil-based formulation after 12 months in a comparative study in 50 recipients of new allografts.

Relative to adults, absorption of and systemic exposure to cyclosporin are substantially reduced in children undergoing bone marrow transplantation who receive the microemulsion. AUCs were increased significantly by GI inflammation in one study. Increased systemic exposure to cyclosporin with the microemulsion has also been reported in renal transplant recipients with diabetes mellitus.

The pharmacokinetic characteristics of cyclosporin are not altered to any clinically significant extent by advanced age.

Effect of Formulation on Cyclosporin Dosage. Cyclosporin dosage reductions were required to maintain required drug concentrations in whole blood after conversion from the oil-based formulation to microemulsion in 12.3 to 87.2% of patients in case series of stable renal transplant recipients. Overall reductions in mean dosage (after initial conversion on a 1 **:** 1 basis) ranged from 4.7 to 14.7% over 8 weeks to 12 months in studies in a total of 1381 patients, and were predominantly statistically significant. Dosage reductions with the microemulsion relative to the original formulation have also been shown in randomised comparative studies, although statistical significance was not attained consistently. Reduced dosage requirements with the microemulsion have also been reported in liver and heart/lung transplant recipients.

Drug Interactions. A wide variety of agents increase (e.g. erythromycin, ketoconazole) or decrease (e.g. phenytoin, phenobarbital) plasma or whole blood concentrations of cyclosporin by competitive hepatic enzyme inhibition or induction, or by other mechanisms (e.g. absorption or binding to P-glycoprotein). Some drugs (e.g. aminoglycosides) are also associated with enhancement of nephrotoxicity of cyclosporin when coadministration takes place.

Recent data indicate possible enhancement by cyclosporin of the potential of HMG-CoA reductase inhibitors to induce rhabdomyolysis. Mycophenolate mofetil may increase systemic exposure to cyclosporin, but the proton pump

inhibitor pantoprazole has no apparent pharmacokinetic effect when coadministered with the drug.

Therapeutic Efficacy

Comparisons with Cyclosporin Oil-Based Formulation (Sandimmun®). The overall ranges of incidence of biopsy-confirmed acute rejection episodes in the various trials in adult *de novo* transplant recipients receiving cyclosporin microemulsion or the original oil-based cyclosporin formulation at trough blood concentration-controlled dosages were 25 to 44.2% versus 22 to 60.5% at 3 to 24 months for renal transplantation, 45.9 to 62.7% versus 49.2 to 59.1% at 4 to 24 months for liver transplantation, and (in a single study) 86.2 versus 84.9% at 6 months for heart transplantation. Azathioprine and corticosteroids were given concomitantly in most trials. A trend for improved efficacy in this respect, and for the incidence of more than one acute rejection episode, with the microemulsion formulation was seen in most renal transplantation trials, with a statistically significant difference at 3 months in one for both parameters. There were no significant differences in the end-point incidence of acute rejection between the formulations in adult recipients of liver transplants, but the microemulsion formulation appeared significantly superior in a small trial in children (35 *vs* 80%; $p = 0.01$) at 12 months.

The incidence of severe (corticosteroid-resistant in most studies) acute rejection tended to be lower in adult patients receiving the microemulsion formulation than in those receiving the oil-based formulation (0 to 18.5% *vs* 10.8 to 20.0% at 4 to 24 months) in liver transplantation but not in heart transplantation (46.3 *vs* 45.8% at 2 years). The difference between the formulations was more apparent in children receiving liver transplants in this respect (6 *vs* 53% at 12 months; $p = 0.004$).

There was a trend for fewer recipients of the microemulsion than the oil-based formulation to require antilymphocyte antibody treatment for acute rejection over the first 3 months after renal transplantation. This difference was more marked in heart transplant recipients (6.9 *vs* 17.7%; $p = 0.002$ at 24 months).

Graft survival rates for the microemulsion and oil-based formulations were 91 to 96% versus 89 to 98% at 3 to 24 months in renal transplant recipients and 90 to 94.1% versus 86 to 93.8% at 4 to 24 months in liver transplant recipients. Patient survival rates for the microemulsion and oil-based formulations were 98 to 100% versus 99 to 100% in renal transplant recipients and 84.2 to 100% versus 85.9 to 94% in liver transplant recipients. Graft/patient survival rates were 88.3 versus 85.4% at 2 years in heart transplant recipients.

Comparisons with Other Modified Formulations. There are preliminary indications of clinical equivalence between cyclosporin Neoral® and cyclosporins SangCya®, Consupren® and Neoplanta® in *de novo* renal transplant recipients. Equivalence has also been demonstrated between Neoral® and Consupren® or SangCya® in two small studies in patients with stable existing transplants who were transferred from therapy with the original oil-based formulation of cyclosporin. Available comparisons, however, are predominantly nonblind and are based on small numbers of patients only.

Comparisons with Tacrolimus. The incidence of acute rejection in *de novo* cyclosporin microemulsion (initially 8 to 15 mg/kg/day) and tacrolimus (initially 0.1 to 0.2 mg/kg/day; both dosages concentration-controlled) recipients was 10 to 39% versus 9 to 40% at 3 to 24 months in renal transplantation, 11 versus 11% at 3 months in simultaneous pancreas-kidney transplantation, 23 to 82.5% versus 17 to 66% at 1 to 30 months in liver transplantation ($p < 0.01$ favouring tacrolimus

in one of seven trials) and 30 versus 24% at 12 months in heart transplantation (in one trial).

The incidence of severe acute rejection in cyclosporin microemulsion and tacrolimus recipients was 0 to 14% versus 0 to 7% at 3 to 24 months in most trials of renal transplantation, 6 to 25% versus 0 to 19% at 1 to 30 months in liver transplantation ($p < 0.01$ favouring tacrolimus in one of seven trials) and 30 versus 21% at 12 months in heart transplantation. Tacrolimus 0.3 mg/kg/day was associated with significantly lower incidences of acute (20 *vs* 37%; $p < 0.001$) and severe acute rejection (9 *vs* 21%; $p < 0.001$) than cyclosporin microemulsion 8 to 10 mg/kg/day in the largest trial in renal transplant recipients, a nonblind comparative 6-month study in 577 patients in 50 European centres.

Graft survival rates in cyclosporin and tacrolimus recipients were 78 to 97% versus 83 to 100% at 3 to 24 months in renal transplantation ($p < 0.05$ favouring tacrolimus in one of nine trials) and 62 to 92% versus 68 to 95% at 1 to 30 months in liver transplantation ($p < 0.05$ favouring tacrolimus in one of seven trials). Patient survival rates in cyclosporin and tacrolimus recipients were 86 to 100% versus 90 to 100% at 3 to 24 months in renal transplantation, 67 to 98% versus 72 to 98% at 1 to 30 months in liver transplantation and 85 versus 85% at 12 months in heart transplantation.

Interim 6-month data from 425 of 606 liver transplant recipients taking part in a randomised, nonblind study in the UK and Ireland indicate a lower incidence of death, retransplantation or treatment failure for immunological reasons with tacrolimus than with cyclosporin microemulsion (17 *vs* 28%; $p = 0.01$).

Black recipients of renal transplants tended to do better on tacrolimus than on cyclosporin microemulsion (acute rejection 14 *vs* 38%, respectively; severe acute rejection 7 *vs* 14%, respectively). Similarly, Black recipients of heart transplants did significantly better on tacrolimus at 12 months (acute rejection episodes requiring treatment, $p = 0.01$; patient/graft survival, $p = 0.04$).

Comparisons with Sirolimus. The efficacy of cyclosporin microemulsion appears similar to that of sirolimus on the basis of results from two 12-month, randomised, nonblind studies in a total of 161 patients undergoing *de novo* renal transplantation. Graft and patient survival rates were similar between treatments in both trials; rates of biopsy-confirmed acute rejection were also not statistically significantly different, although there was a trend in favour of cyclosporin in one study (18 *vs* 27.5%).

Conversion to Cyclosporin Microemulsion. Conversion of stable renal, liver and heart transplantation patients from the oil-based cyclosporin formulation (Sandimmun®) to the microemulsion formulation, at an initial 1 **:** 1 dosage ratio, appears not to affect the rate of acute rejection.

Preliminary evidence suggests that conversion from tacrolimus to cyclosporin microemulsion because of adverse effects or lack of efficacy is comparatively successful in renal and liver transplant recipients.

Use of Other Agents with Cyclosporin Microemulsion-Based Immunosuppression. Incidences of presumed or biopsy-proven acute rejection were significantly decreased on the addition of mycophenolate mofetil 2 g/day to cyclosporin microemulsion plus corticosteroids in nonblind studies in 173 renal transplant recipients. The addition of mycophenolate mofetil 2 or 3 g/day to cyclosporin microemulsion (initial daily dosage 5 to 15 mg/kg/day) plus corticosteroid-based immunosuppression significantly reduced the incidence of biopsy-proven rejection or treatment failure over 1 year in a randomised, multicentre, double-blind, placebo-controlled study in 491 recipients of first or second renal allografts.

A significantly lower incidence of acute rejection was reported with the addition of mycophenolate mofetil to cyclosporin microemulsion and corticosteroids than with the addition of azathioprine in a nonblind study in 57 liver transplant recipients (21.4 *vs* 44.8%; $p < 0.05$).

In a double-blind study (n = 376), rates of acute and severe acute rejection at 6 months were significantly reduced in patients receiving concomitant basiliximab 20mg on days 0 and 4 of renal transplantation compared with those receiving cyclosporin microemulsion and corticosteroids alone. A similar study in 346 renal transplant recipients showed statistically significant reductions in 12-month incidences of first acute rejection, second rejection, biopsy-confirmed rejection, and rejection episodes requiring treatment with augmented immunosuppression (other than corticosteroids) with the addition of basiliximab to cyclosporin microemulsion plus corticosteroid-based immunosuppression. Significantly reduced incidence relative to placebo of biopsy-proven acute rejection has also been noted with addition of daclizumab to cyclosporin microemulsion and corticosteroid therapy.

Two multicentre placebo-controlled, double-blind trials in a total of 1295 patients undergoing renal transplantation showed statistically significant reductions relative to placebo or azathioprine in a composite end-point of acute rejection, graft loss and death when sirolimus 2 or 5 mg/day was added to immunosuppression with cyclosporin microemulsion and corticosteroids.

The addition of basiliximab and/or mycophenolate mofetil also allowed the elimination of corticosteroids from the immunosuppressive regimen without affecting the rate of acute rejection in a number of small studies in patients undergoing renal transplantation. However, a larger (n = 266), placebo-controlled, double-blind study has indicated an increase in risk of acute rejection (particularly among Black patients) upon withdrawal of corticosteroids from renal transplant recipients also receiving cyclosporin microemulsion and mycophenolate mofetil. Similar findings were reported in a further double-blind study in 500 renal transplant recipients, 447 whom received cyclosporin microemulsion in addition to mycophenolate mofetil, although the authors stated that the increase in frequency of serious rejection episodes when corticosteroids were withdrawn was acceptable. Results of corticosteroid withdrawal studies in liver allograft recipients receiving cyclosporin microemulsion or tacrolimus, either as monotherapy or in combination with mycophenolate mofetil, are inconclusive.

Pharmacoeconomic Considerations

Various cost analyses have been carried out from a healthcare provider's or third party payer's perspective to assess potential pharmacoeconomic advantages of the use of cyclosporin microemulsion in place of the older oil-based formulation.

Details from a study reported as an abstract have suggested a monthly cost saving of $US52 per patient after conversion from the oil-based formulation to microemulsion in 181 French individuals with stable renal allografts. Costs accounted for and year of costing were not given, however, for this 6-month analysis, which appeared to have been carried out from a healthcare provider's perspective.

Prospectively gathered resource utilisation data from the MILTON study in 390 *de novo* liver transplant recipients showed savings (relative to treatment with the oil-based formulation) from a healthcare system perspective of 8 to 10% over the 4-month post-transplant period in patients receiving cyclosporin microemulsion. This was attributed partly to a more rapid discontinuation of intravenous cyclosporin therapy in patients receiving the microemulsion.

Examination of healthcare utilisation based on time in hospital and treatment of acute rejection indicated a cost saving of 2162 Canadian dollars per patient (year of costing and statistical significance not stated) relative to the oil-based formulation in a 3-month retrospective case-control study in 20 *de novo* liver transplant recipients. Three other analyses in patients undergoing liver transplantation have indicated reductions in direct healthcare costs when patients receive cyclosporin microemulsion rather than the original formulation.

Data from studies in patients receiving *de novo* kidney or liver transplants have suggested that the direct cost of using cyclosporin microemulsion is similar to or lower than that with tacrolimus. In one study, 6-month direct healthcare costs in 89 renal transplant recipients were £13 216 with cyclosporin microemulsion and £12 982 with tacrolimus (year of costing not stated). In 86 patients receiving liver transplants, the mean cost of cyclosporin microemulsion was 22% lower than that of tacrolimus (on the basis of dosages used over 1 year), although few details were available for this analysis (abstract published only).

Tolerability

The tolerability profile of cyclosporin is characterised by a number of potentially serious adverse effects that are related to exposure, including acute or chronic nephrotoxicity, hypertension and neurotoxicity. The main dose-limiting adverse effect of cyclosporin is nephrotoxicity, which usually presents as a reversible decrease in glomerular filtration rate. Nephrotoxicity is reported to affect 25 to 37% of kidney, heart or liver transplant recipients being treated with cyclosporin and may progress to permanent renal dysfunction in up to 15% of patients. Glomerular capillary thrombosis, progressing to graft failure in some patients, may also occur in transplant patients receiving cyclosporin.

In comparative trials conducted in recipients of renal transplants, hypertension was reported in fewer than 25% of patients treated with either cyclosporin microemulsion or the oil-based formulation. Hypertension was also reported in recipients of liver or heart transplants treated with either cyclosporin formulation.

Neurological symptoms, such as headaches, tremor, paraesthesia and convulsions, are also common adverse effects of cyclosporin in patients who have received transplants (1 source notes tremor in 12 to 21, 31 and 55% of patients receiving kidney, heart or liver transplants, respectively). Factors contributing to the development of convulsions in patients receiving cyclosporin therapy include hypomagnesaemia, hypertension, high-dose methylprednisolone therapy, nephrotoxicity and hypocholesterolaemia.

Numerous comparative double-blind or nonblind clinical trials have shown that the increased bioavailability of cyclosporin and greater systemic exposure achieved with the microemulsion formulation does not result in an increase in incidence or severity of adverse events compared with the original oil-based formulation in stable renal, liver or heart transplant recipients (provided that the dose of the microemulsion formulation is adjusted on the basis of target trough cyclosporin concentrations in whole blood).

Muscle weakness, oedema, epigastric pain, headache and hypertension were the most common events in stable renal transplant patients receiving treatment with cyclosporin microemulsion in a large comparative trial. About 40% of patients treated with either the cyclosporin microemulsion or the oil-based formulation experienced adverse events that were described as ‘serious’ in this study.

In patients who had received primary orthotopic liver transplants, the most common adverse events reported during therapy with cyclosporin microemulsion or the oil-based formulation were infections, cardiovascular effects, hyperten-

sion, nervous system effects and renal failure. Clinical diabetes mellitus, hirsutism and gum hyperplasia developed in small numbers of patients in each treatment group.

Overall, both formulations of cyclosporin were equally well tolerated in a randomised double-blind trial in 380 *de novo* heart transplant recipients. However, relative to the oil-based formulation, patients treated with the microemulsion had a lower (not statistically significant) incidence of candidiasis (5.9 *vs* 10.9%), cytomegalovirus infections (10.1 *vs* 15.1%) and *de novo* diabetes mellitus (3.9 *vs* 8.5%), whereas incidences of gingival hyperplasia and GI symptoms were higher in the microemulsion treatment group than in the comparator group (3.2 *vs* 2.6% and 81.9 *vs* 76.5%); these adverse events were transient and mild to moderate in severity.

The tolerability profile of cyclosporin microemulsion was broadly similar to that of tacrolimus (both drugs were given in combination with a corticosteroid and azathioprine) in cadaveric renal transplant recipients in a nonblind randomised study. In contrast, significant differences in the biochemical profiles of patients treated with either cyclosporin microemulsion or tacrolimus were reported in another study in renal transplant recipients. In a study in 577 renal transplant recipients, the incidences of new-onset diabetes mellitus after 6 months' treatment were 4.5% with tacrolimus group and 2% with cyclosporin microemulsion (statistical significance not stated). Mean serum creatinine levels were similar for both drugs from the end of month 1 to study completion.

Thrombocytopenia and diarrhoea were reported significantly more frequently with sirolimus than with cyclosporin microemulsion in a randomised, nonblind comparison in 78 renal transplant recipients. Increased serum creatinine levels, hyperuricaemia, cytomegalovirus infection and tremor were more frequent with cyclosporin.

At present, there are no published well designed and controlled studies of the efficacy and tolerability of cyclosporin microemulsion in pregnant transplant recipients and their offspring. However, in a retrospective analysis, no notable malformation trends were evident among the 175 children (mean age 4.4 years) of renal transplant recipients who had been treated with cyclosporin during pregnancy.

Dosage and Administration

Cyclosporin microemulsion is available variously in different countries as 10, 25, 50 and 100mg soft gelatin capsules and as an oral solution containing 100 mg/ml. The oral solution may be made more palatable by diluting with orange or apple juice. Blood cyclosporin concentrations increase when cyclosporin microemulsion is taken with grapefruit/grapefruit juice, which should therefore be avoided by patients taking the drug.

Cyclosporin microemulsion is indicated for the prophylaxis of organ rejection in patients who have undergone allogeneic renal, liver or heart transplantation. Cyclosporin microemulsion should be taken twice daily (in two equal doses). An optimal dosage of the drug will produce trough whole blood concentrations sufficient to achieve immunosuppression while preventing high peak blood concentrations and drug-related toxicity. Importantly, because cyclosporin is more bioavailable from the oral microemulsion than from the oil-based oral formulation, the two formulations cannot be interchanged without careful monitoring of the patient by a physician.

Whole blood concentrations of cyclosporin should be measured frequently (three to four times weekly or daily in the early post-transplantation period) in

patients receiving treatment with cyclosporin microemulsion, as lower than recommended therapeutic concentrations may result in rejection of the transplanted organ and higher concentrations are likely to produce drug-related toxicity. Renal function, liver function and blood pressure should be monitored closely in patients receiving treatment with cyclosporin microemulsion. In addition, levels of serum lipids, potassium and magnesium should be checked regularly during treatment with the drug. In randomised controlled trials in transplant recipients, most patients received an initial dosage of 10 mg/kg/day. Dosages were adjusted thereafter to achieve target therapeutic trough concentrations in whole blood and then further titrated according to assessments of transplant rejection and tolerability.

Stable transplant recipients receiving the original oil-based formulation of cyclosporin may have their therapy changed to the microemulsion formulation with careful monitoring. In these patients, it is recommended that the initial dosage of cyclosporin microemulsion is the same as that of the previously administered cyclosporin formulation. Thereafter, the dose of cyclosporin microemulsion should be adjusted to obtain a whole blood trough cyclosporin concentration the same as that achieved previously with the original formulation.

1. The Immune System and Organ Transplantation

Over the 40 years since the immunosuppressive effects of corticosteroids in animals were first reported, solid organ transplantation has become a routine clinical procedure. Rapid advances in molecular immunology over the last 20 years in particular have given researchers a comprehensive understanding of the cellular and molecular mechanisms that underlie the immunological response to transplanted organs (reviewed by Denton et al.[1] and Perico and Remuzzi[2]).

It is now known that CD4 T cells play a central role in the immune response to allograft rejection, and drugs that prevent T cell activation or effector function are therefore potential immunosuppressants.[2] Rejection responses in the presence of allograft tissue are elicited after recognition of foreign antigens encoded within the major histocompatibility complex and presented to T cell receptors (fig. 1). The engagement of these receptors with alloantigens results in the recruitment and activation of a series of tyrosine kinases (including $p56^{lck}$, $p59^{Fyn}$ and ZAP-70), the phosphorylation and activation of phospholipase C, and increases in intracellular calcium levels. This leads to the activation of the serine-threonine phosphatase calcineurin and the subsequent transcription of genes encoding cytokines needed for the transition of the T cell from its resting to activated state.[3-5]

Receptor activation alone is not sufficient to sustain full activation of the CD4 T cell; costimulatory signals, delivered by cognate ligands on the antigen-presenting cell, are also required.[6] These signals synergise with T cell receptor activation through independent intracellular pathways. Under the influence of both signals, the CD4 T cell secretes optimum amounts of interleukin (IL)-2, a potent autocrine growth factor that induces T cell proliferation, clonal expansion and cytokine production (fig. 1). When the second signal is absent, the CD4 T cell becomes unresponsive to further antigenic stimulation, fails to secrete cytokines and may undergo apoptosis.[7,8] The best characterised costimulatory signal is that driven by the ligation of CD28 (a member of the immunoglobulin gene superfamily found on the surface of T cells) with a member of the B7 family of molecules on the antigen-presenting cell.[5,9]

CD4 T cells activated by alloantigens interact with effector cells of the rejection response by di-

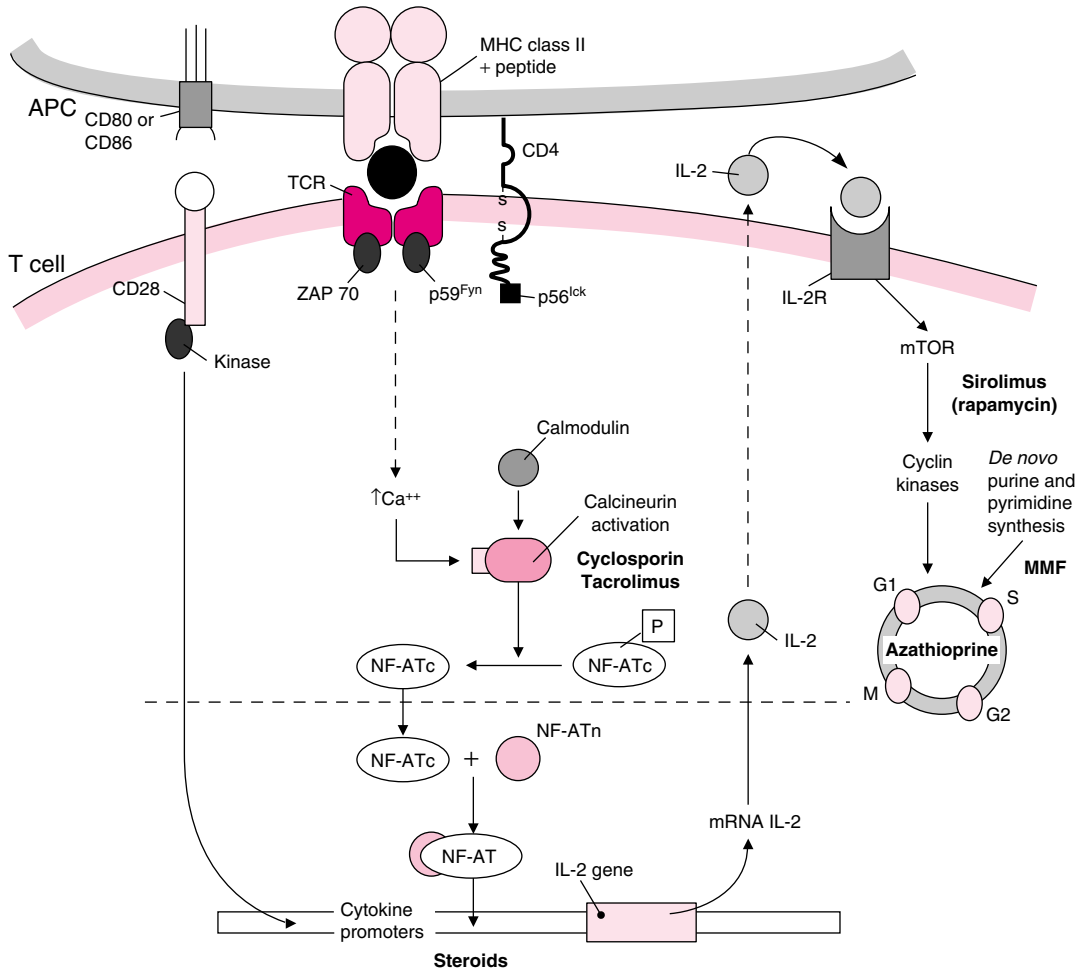

Fig. 1. T cell activation and immunosuppression. The foreign antigen, encoded within a major histocompatibility complex (MHC), is presented by the antigen presenting cell (APC). Recognition by the T cell receptor (TCR) results in the recruitment and activation of tyrosine kinases (including $p56^{lck}$, $p59^{Fyn}$ and ZAP-70), phosphorylation and activation of phospholipase C, and increased cellular calcium levels. Subsequent activation of the serine-threonine phosphatase calcineurin leads to the transcription of genes encoding cytokines needed for T cell activation. The principal sites of action of cyclosporin and a number of other immunosuppressants (in bold type) are shown. **CD** = cluster determinant; **IL** = interleukin; **IL-2R** = interleukin-2 receptor; **MMF** = mycophenolate mofetil; **mTOR** = 'target of sirolimus (rapamycin)' protein; **NF-AT** = nuclear factor of activated T cells; **NF-ATc** = cytoplasmic subunit of NF-AT; **NF-ATn** = nuclear subunit of NF-AT; **P** = phosphate.

rect cell to cell contact and by cytokine secretion. Alloantibody production, antigen-specific cell lysis and delayed hypersensitivity responses are promoted by increased activation and functioning of B cells, cytotoxic CD8 T cells and macrophages, respectively. These processes result in graft destruction.[1]

Cyclosporin (also known as cyclosporin A) is a lipophilic cyclic polypeptide that has been accepted for some years as first-line immunosuppressive therapy for patients undergoing solid organ transplantation. The oil-based formulation of the drug originally introduced (Sandimmun®) was characterised by poor and generally unpredictable

absorption and the need for intensive monitoring of blood cyclosporin concentrations and frequent dosage adjustments to obtain the desired therapeutic response after oral administration. In the mid-1990s, however, a novel microemulsion preconcentrate was introduced (Neoral®). This formulation combines cyclosporin with a surfactant, lipophilic and hydrophilic solvents and a hydrophilic cosolvent, and is designed to disperse rapidly in the gut lumen as a microemulsion with improved absorption characteristics (see reviews by Perico and Remuzzi,[2] Lee and Canafax[10] and Noble and Markham[11]).

The pharmacology, clinical efficacy and tolerability of cyclosporin were reviewed in *Drugs* in 1993,[12] and the microemulsion was first reviewed in the journal and compared with the original oral formulation 2 years later.[11] This article updates the 1995 review and focuses in particular on the pharmacokinetic characteristics of the microemulsion and their influence on the clinical use and efficacy of cyclosporin in patients receiving solid organ transplants.

2. Overview of Pharmacodynamic Properties

Cyclosporin inhibits the activation of the calcium/calmodulin-activated phosphatase calcineurin[13] (see section 1 and fig. 1) via complex formation with cyclophilin, a member of the immunophilin family (reviewed by Borger et al.[14]). This action prevents the translocation of the transcription factor nuclear factor of activated T cells (NF-AT; fig. 1).

Studies in T lymphocytes have shown that cyclosporin also inhibits activation of other transcription factors, including NF-κB,[15,16] which is required for the induction of various cytokine genes. IL-2 gene expression in particular is inhibited by cyclosporin (this leads to suppression of T cell activation);[17,18] expression of several cytokines involved in the inflammatory response (notably IL-6 and IL-8) is also reduced.[14,19,20] The effects of cyclosporin on non-lymphoid immune cells have not been well characterised, but data obtained *in vitro* indicate complete suppression by the drug of tumour necrosis factor-α–mediated induction of class II major histocompatibility complex expression in porcine aortic endothelial cells.[21]

Hypertensive effects of cyclosporin in some patients are linked to nephrotoxicity (see section 6.1 for further discussion of this issue). Potential underlying mechanisms identified in studies include effects on the sympathetic nervous system,[22-25] upregulation of angiotensin II receptors in vascular smooth muscle cells,[26] increased plasma levels of endothelin-1,[27,28] and effects on whole blood viscosity and plasma fibrinogen levels.[29] In addition, one group of authors has reported an apparent difference between the original and microemulsion formulations of cyclosporin in effect on intracellular calcium levels.[30] In patients who had undergone renal transplantation, erythrocyte calcium levels were raised ($p < 0.05$ *vs* levels in healthy volunteers) after 4 weeks' treatment with the original formulation; these levels normalised after conversion to the microemulsion.

3. Pharmacokinetic Properties and Monitoring of Therapy

As discussed earlier (section 1), cyclosporin was originally formulated as an oily solution, presented as a liquid or in soft gelatin capsules. This formulation is not ideal, however, as cyclosporin is a lipophilic drug and the absorption of the oil-based solution from the gut is highly bile-dependent (reviewed by Friman and Bäckmann[31]). Emulsification of the crude oil-in-water droplet mixture formed on contact with GI fluids by bile salts is necessary before cyclosporin can be absorbed, and it is this emulsification step that causes the extent of absorption of the drug from this formulation to vary according to the presence of food, bile flow and GI motility. Erratic absorption through the GI mucosa has been cited as the main reason for the variable bioavailability of cyclosporin when the drug is given as oily solution.[32] Indeed, the previous review in *Drugs*[11] reported the absolute oral bioavailability of this formulation of cyclosporin to vary between 1 and 89%, with a mean value of around 30%.[32,33]

Cyclosporin is absorbed in the upper part of the GI tract, with no apparent absorption from the colon in healthy volunteers.[34] The requirement for solubilisation in bile for absorption creates difficulties, especially in patients undergoing liver transplantation, because bile secretion is impaired after this procedure: in these patients, bile is usually diverted through a T-tube during the early post-transplant period, and this interrupts the enterohepatic circulation.[35] Patients with autonomic GI neuropathy secondary to diabetes mellitus and individuals with short bowel syndrome also show unpredictable and reduced absorption of cyclosporin.[31]

The microemulsion preconcentrate formulation of cyclosporin has self-emulsifying properties and creates micelles in the stomach that are absorbed in the small bowel with less need for the presence of bile. This enhances the bioavailability of the drug and reduces the variability in pharmacokinetic characteristics displayed by the original formulation. These properties would be expected to facilitate therapy, because cyclosporin has a narrow therapeutic index, and it is necessary to maintain concentrations of the drug in blood that are sufficient to ensure effective immunosuppression while avoiding high peak concentrations that might cause serious adverse effects. Thus, information on the bioavailability and absorption of cyclosporin from the microemulsion formulation, and its clinical implications, are of paramount interest and will form the focus of discussion in this part of the review. Other pharmacokinetic characteristics that apply to cyclosporin after its absorption into the circulation are well documented in other sources and the manufacturer's literature, and will be dealt with only briefly (section 3.3).

3.1 Cyclosporin Assay Techniques

When considering studies dealing with the pharmacokinetic behaviour of cyclosporin, it is important that the fluids and assays used are taken into account.[31] Determination of relationships between cyclosporin concentrations in biological fluids and therapeutic and/or toxic effects is complicated by the influence on pharmacokinetic results of the fluid (plasma or serum *vs* whole blood) and assay method [radioimmunoassay *vs* high performance liquid chromatography (HPLC)]. This subject is covered in detail elsewhere,[36] but measurement of whole blood concentrations of cyclosporin is generally recommended. Distribution of cyclosporin into erythrocytes is temperature- and concentration-dependent, and plasma determinations may also be affected by the patient's lipoprotein status and haematocrit. Furthermore, the higher concentrations of cyclosporin in whole blood (relative to plasma or serum) can be measured more precisely and accurately than those in other fluids.

Radioimmunoassay and HPLC do not yield comparable results, and the former has been used most frequently because HPLC determination of cyclosporin is technically difficult and the results variable.[36] Other techniques that may be used include fluorescence polarisation immunoassay (FPIA), a specific enzyme multiplied immunoassay technique (EMIT), and a cloned enzyme donor immunoassay (CEDIA). Any of the currently available immunoassays is suitable for routine cyclosporin concentration monitoring in whole blood, although differences have been shown between these methods in ease of handling, specificity (for the parent compound rather than metabolites) and precision.[37-40] For example, results to date suggest greatest ease of handling with CEDIA,[38,40] and highest cross reactivity with metabolites with CEDIA and a monoclonal FPIA method,[37,38] although the last mentioned is also associated with high levels of precision.[38,40] Because of these differences between assays, standardisation between laboratories is needed, and reference ranges for different groups of transplant patients and assay methods must be known, for meaningful interpretation of results. HPLC may also be appropriate, but differences in results obtained with this method relative to immunoassay must be borne in mind when comparing studies. Immunoassay of cyclosporin in whole blood was used in studies discussed in this and other sections.

3.2 Clinical Monitoring of Cyclosporin and Patient Outcomes

The introduction of cyclosporin microemulsion has prompted much research into the monitoring of therapy, with the aim of identifying methods that predict exposure to the drug accurately and thereby assist in the optimisation of therapeutic outcomes. High intrapatient variability in exposure to cyclosporin is associated with adverse clinical outcomes (particularly chronic rejection),[41-43] and the underlying stimulus for this research has been the clinical potential of the more predictable pharmacokinetic behaviour of the microemulsion relative to the original formulation.

The methods used for clinical monitoring of cyclosporin therapy have been reviewed comprehensively by Dumont and Ensom.[44] These authors indicate that trough concentration (C_0) monitoring, the traditional method used in patients receiving cyclosporin, remains standard practice in many centres, despite its failure to indicate clearly total drug exposure or outcomes (see section 3.2.1). Other methods have also been developed, however, as part of ongoing efforts to identify techniques that consistently yield clinically relevant data and that are most useful in the prediction of outcomes (table I).

3.2.1 Trough Concentration (C_0) Monitoring

As reviewed previously in *Drugs*,[11] trough concentrations of cyclosporin in blood have little predictive value with respect to the actual systemic exposure to the drug [in terms of area under the curve of drug concentration in blood versus time (AUC)] in patients receiving the original oil-based formulation. In addition, the concentration of cyclosporin in blood has been reported not to be an optimal indicator of actual clinical events.[11] In one study in 92 recipients of renal transplants who received triple immunosuppressive therapy,[45] 63% of nephrotoxicity episodes and 59% of acute rejections were seen in patients with mean levels of cyclosporin in blood (12 to 14 hours after a single evening dose) within the desired therapeutic range of 150 to 400 μg/L. Furthermore, there was no apparent significant relationship between pharmacokinetic parameters and nephrotoxicity in a 1-year study in 160 patients undergoing renal transplantation, although correlations were reported between graft survival and average or steady-state concentrations of cyclosporin.[41]

Table I. Cyclosporin therapeutic monitoring. Advantages and disadvantages of methods used in conjunction with whole blood assays to manage therapy in patients receiving cyclosporin immunosuppression after organ transplantation[44]

Method	Characteristics
Trough concentration (C_0) monitoring	Involves measurement of single trough blood concentration of drug. Simple to carry out and practical for routine clinical use in all patients. Poor indicator of total drug exposure and clinical outcome, however
Area under the blood concentration versus time curve (AUC) monitoring	Multiple blood samples taken to show full AUC. Precise indicator of drug exposure. Appears to predict outcomes and allows calculation of oral pharmacokinetic parameters, but is costly and inconvenient for patients and clinicians. Not suitable for routine clinical use
Limited sampling strategies	Calculation of regression equation from AUC determination in a sample population to allow subsequent estimation from sampling at 2 to 3 time points. Better indicator of exposure to cyclosporin than C_0 measurements, and easier and more practical than full AUC determination. Some concern over validation and predictive power of equations generated
Monitoring of single concentrations other than troughs (most notably 2-hour concentrations)	Better correlation with full AUC than C_0 measurements, with evidence of improved overall clinical outcome, shown in some studies. Practical and convenient in the clinical setting. Research ongoing
Bayesian forecasting	Calculation of dosage regimens and pharmacokinetic parameters and prediction of drug concentrations by blending population and patient-specific values. Calculations now facilitated by availability of desktop computers with appropriate software. Population databases not available for cyclosporin and must be created by the researcher
Pharmacodynamic monitoring	Monitoring of *in vivo* markers of immunosuppression. Not widely used because assays are cumbersome, and because of difficulty in distinguishing rejection from infection. Attention currently focused on calcineurin inhibition

3.2.2 Absorption Profiling and 2-Hour Concentration (C_2) Monitoring

Attention has recently been focused on sampling during the absorption phase in patients undergoing immunosuppression with cyclosporin microemulsion. This approach, which is termed 'absorption profiling', has the underlying rationale that the 4-hour absorption phase following administration provides measurements that are more informative than C_0 monitoring in the assessment of likely cyclosporin exposure and subsequent clinical response. Proponents of absorption profiling state also that the limited sampling required overcomes objections that alternatives to C_0 measurement (notably AUC and pharmacodynamic monitoring) involve unacceptable increases in patient management workloads (see review by Belitsky et al.[46]).

An abbreviated AUC (taken from 0 to 4 hours after administration of cyclosporin; AUC_4) was shown to correlate with full AUC (0 to 12 hours; AUC_{12}) in whole blood in a study in 156 patients undergoing *de novo* kidney transplantation.[47] Trough concentrations showed poor correlation with both AUC_4 and AUC_{12} ($r = 0.42$ and 0.61, respectively), and failed to predict acute rejection episodes during the first 90 days. Stepwise regression analysis showed AUC_4, AUC_{12} and delayed graft function to predict acute rejection (all $p < 0.05$). The authors recommended a target AUC_4 of 4.4 to 5.5 mg/L □h (measured by a parent drug-specific radioimmunoassay) for optimal immunosuppression with minimal risk of nephrotoxicity. Adoption of this protocol with 4-hour absorption profiling in further series of 89[48] and 59[49] renal allograft recipients resulted in acute rejection rates of 3[49] or 4[48] and 41[48] or 45%,[49] respectively, in patients who did and did not achieve AUC_4 values above 4.4 mg/L □h by day 3 ($p = 0.0003$)[48] or day 3 to 5 ($p = 0.0002$).[49]

Feasibility of 2-point blood cyclosporin monitoring in patients receiving cyclosporin microemulsion has also been suggested by several groups of authors.[50-52] Amante and Kahan[50] showed close correlation ($r^2 > 0.9$) between full 12-hour AUCs and those predicted from blood cyclosporin concentrations taken at 2 and 6 hours in a series of 118 patients undergoing primary renal transplantation (details of assay used not available).

C_2 Monitoring

Further research has shown the potential of concentrations measured 2 hours after administration (C_2) as an approximation of maximum concentrations of cyclosporin in blood (C_{max}) after GI absorption. A randomised and double-blind fully published comparison of the oil-based and microemulsion formulations in 188 Canadian patients undergoing primary liver transplantation showed a strong correlation between freedom from graft rejection during the first month after surgery and AUC_6 ($p = 0.026$) or C_{max} ($p = 0.019$) on days 5 and 10 in patients receiving the microemulsion.[53] No significant correlation was observed in recipients of the original oily formulation. Most interestingly, in patients receiving the microemulsion, a close correlation was observed between C_2 and AUC_6 ($r^2 = 0.93$). Concentrations of drug in whole blood were measured by a parent-drug specific radioimmunoassay or EMIT.

Data from a 3-month nonblind parallel-group study carried out in 307 liver transplant recipients in 29 centres showed graft loss (retransplantation or death) in 7% of patients managed with C_0 ($n = 158$) and 6.8% of those managed with C_2 monitoring ($n = 149$) [assay method not stated in the published abstract].[54] However, among patients with biopsy-proven acute rejection (21.6 and 30.4% of C_2- and C_0-managed patients, respectively), there was a significant 36% reduction in moderate to severe acute rejection with C_2 monitoring (47 *vs* 73%; $p = 0.01$).[54,55]

Although C_0, C_1, C_2 and C_4 measurements all showed significant ($p < 0.0001$) correlations with AUC_4 in a study in 30 heart transplant recipients ($r = 0.64$, 0.76, 0.91 and 0.59, respectively), the highest correlation coefficient was obtained with C_2 measurement.[56] Similar results were obtained in 35 liver transplant patients, with correlation coefficients of 0.4, 0.79, 0.92 and 0.43 being reported for C_0, C_1, C_2 and C_4, respectively (all $p < 0.0001$ with respect to AUC_4).[57] Both studies involved patients who were transferred to cyclosporin

microemulsion from the oil-based formulation more than 1 year after transplantation.

Clinical outcomes after C_0 and C_2 monitoring were compared in a further study comprising two consecutive 10-month surveillance periods in 114 patients who had undergone heart transplantation at least 1 year previously.[58] C_2 monitoring (target range 300 to 600 mg/L) was associated with reductions from baseline in mean cyclosporin microemulsion dosage, cyclosporin C_0 and C_2, and serum creatinine levels (26, 56, 45 and 2.3% reductions, respectively). Over the 10-month C_0 monitoring period (target range 100 to 200 mg/L), the same variables increased by 24, 56, 38 and 10% ($p < 0.0001$ between periods for all variables). Rejection rates and mortality were similar, and left ventricular ejection fraction remained stable, across both periods. However, overall clinical benefit (defined as the absence of acute rejection or mortality, or lack of decrease in ejection fraction or increase in serum creatinine level of more than 10%) was reported in 69.3 and 43.3% of patients during the C_2 and C_0 monitoring periods, respectively ($p < 0.00001$).

For further information, the reader is referred to the recent review by Levy[59] that deals in detail with C_2 monitoring in patients receiving cyclosporin microemulsion.

3.3 General Pharmacokinetic Properties of Cyclosporin

After GI absorption or intravenous administration, cyclosporin undergoes extensive distribution into body fluids and tissues, with most of the drug being distributed outside the bloodstream.[36,60] The volume of distribution at steady state after intravenous administration has been reported to be between 3 and 5 L/kg in recipients of solid organ allografts. Of the 90 to 98% of circulating cyclosporin bound to plasma proteins, 85 to 90% is carried on lipoproteins. Distribution of the drug in whole blood is dose-dependent, with 33 to 47% of the cyclosporin remaining in the bloodstream being present in plasma, 4 to 9% in lymphocytes, 4 to 12% in granulocytes and 41 to 58% in erythrocytes. At high concentrations, leucocytes and erythrocytes become saturated. Cyclosporin crosses the placenta and passes into human milk.[36,60]

Blood concentrations of cyclosporin generally decline in a biphasic manner. In adults with normal renal and hepatic function, the initial elimination half-life ($t_{½\alpha}$) has been reported to average 1.2 hours, with an average terminal elimination half-life ($t_{½\beta}$) of 8.4 to 27 hours (range 4 to 50 hours).[36] Clearance from blood is approximately 0.3 to 0.4 L/h/kg in adults undergoing renal or hepatic transplantation, but is slightly lower after cardiac transplantation. Clearance in infants appears to be several times higher than in adults, and is approximately doubled in older children.[36]

Cyclosporin is extensively metabolised by the hepatic cytochrome P (CYP) 450 3A enzyme system and to a lesser extent in the GI tract and the kidney to at least 30 metabolites, all of which are considerably less active than the parent compound.[36] First-pass metabolism after oral administration is extensive. Major metabolic pathways that have been identified include hydroxylation of the C_γ-carbon of two leucine residues, C_λ-carbon hydroxylation and cyclic ether formation (with double bond oxidation) in the 3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl group and *N*-demethylation of the *N*-methyl leucine residues.[36] Oxidation of cyclosporin yields the major metabolites AM1, AM4N and AM9 which account for approximately 70, 21 and 7.5%, respectively, of the total AUC of cyclosporin. The percentages of each dose present as these metabolites are similar for the original and microemulsion formulations.[60]

Metabolites of cyclosporin are found in bile, faeces, blood and urine. Elimination is primarily biliary. Only around 6% of each dose is excreted in the urine, with 0.1% undergoing urinary excretion as unchanged drug. Neither haemodialysis nor renal failure have any significant effect on the clearance of cyclosporin.[36,60]

3.4 Pharmacokinetic Properties of Cyclosporin Microemulsion

The pharmacokinetic characteristics of the microemulsion formulation of cyclosporin were evaluated in 48 healthy male volunteers by Mueller

and colleagues.[61] These authors reported more rapid absorption of cyclosporin from the microemulsion than from the original formulation: mean times to C_{max} (t_{max}) were 1.5, 1.4, 1.7 and 2.1 hours after respective single doses of 200, 400, 600 and 800mg. Corresponding t_{max} values for the oil-base formulation were 2.1, 2.1, 2.3 and 2.4 hours. C_{max} and AUC values were increased by 70 to 135% in volunteers receiving the microemulsion.

Improved pharmacokinetics of the microemulsion relative to the older formulation were also reported in two further studies, each of which involved 24 healthy male volunteers. In one investigation,[62] intraindividual variability in primary pharmacokinetic parameters (AUC, C_{max}, t_{max} and $t_{½\beta}$) ranged from approximately 9 to 22% after a 180mg dose of the microemulsion; this was compared with a range of 19 to 41% with a 300mg dose of the oil-based formulation (doses were selected to provide equivalent AUCs on the basis of bioavailability data obtained in fasting volunteers). Corresponding ranges for interindividual variability were 3 to 22% and 20 to 34%.

In the other study,[63] in which the same doses of cyclosporin were used, mean t_{max} was increased from 2.5 (fasting) to 4.8 hours after a fat-rich meal with the original formulation ($p < 0.05$). The increase in t_{max} associated with food was only 15 minutes (increase from 1.5 to 1.8 hours) with the microemulsion and was not statistically significant. Relative to fasting conditions, AUC and C_{max} were decreased by 15 and 26%, respectively, when the microemulsion was given after the fat-rich meal in this study; in contrast, the mean AUC was increased by 37% after a fat-rich meal when the oil-based formulation was given. In general, the presence of food in the GI tract appears to decrease AUC and C_{max} of cyclosporin when the drug is given as the microemulsion, although data are conflicting.[36]

3.4.1 Renal Transplantation

Dosage-normalised data from stable renal transplant patients and recipients of new allografts have shown significantly greater mean systemic exposure (in terms of increased AUC and C_{max} in whole blood) to cyclosporin and more rapid absorption with the microemulsion relative to the oil-based formulation (table II). These results are concordant with those from a series of randomised comparisons and conversion studies summarised by Friman and Bäckman,[31] which showed AUC increases ranging from 13 to 64% with the microemulsion. The mean AUC increases shown in table II ranged from 37 to 50%, and were all statistically significant.[42,64,65] In addition to measuring 12-hour profiles in 30 patients over 3 months, Keown et al.[65] determined AUC_4 after 3 and 6 months in 386 and 421 patients, respectively. Overall, these authors

Table II. Comparative pharmacokinetics of the microemulsion (MF) and oil-based (OF) formulations of cyclosporin. Dosage-normalised mean whole-blood data from crossover or randomised parallel group studies in renal transplant patients who received oral cyclosporin by either formulation twice daily

Reference (study design; duration)	No. and type of patients	AUC (μg/L □h)[a]		C_{max} (μg/L)		t_{max} (h)		C_{min} (μg/L)	
		MF	OF	MF	OF	MF	OF	MF	OF
Kahan et al.[42] (co; 3wk)[b]	55 with stable transplants	18.17*	13.29	4.09*	2.60	1.69*	2.70	0.67*	0.55
Keown & Niese[64] (r, db; pg; 12wk)[b]	28 with *de novo* transplants[c]	24.4*	16.3	6.2*	4.7	1.7*	4.5	NA	NA
Keown et al.[65] (r, pg; 3mo)[d]	30 with stable transplants	3525*	2556	721*	422	1.5	2.8	151	121

a AUCs shown are for 12-hour administration intervals.

b Data adjusted per milligram of cyclosporin administered.

c Subset of patients from a study in 167 individuals.

d Data expressed in terms of twice-daily dose of cyclosporin. Subset analysis from 6-month study in 1097 patients.

AUC = area under the blood concentration versus time curve for cyclosporin; **C_{max}** = maximum blood concentration of cyclosporin; **C_{min}** = minimum (trough) blood concentration of cyclosporin; **co** = crossover; **db** = double-blind; **NA** = dosage-normalised data not available; **pg** = parallel-group; **r** = randomised; **t_{max}** = time to C_{max}; * $p < 0.01$ *vs* OF.

showed mean exposure to the drug to be approximately 40% higher in patients receiving the microemulsion than in those receiving the original formulation. This was attributable chiefly to a marked increase in exposure in patients previously classified as poor absorbers, whereas there was no clinically significant change in patients initially classified as good absorbers. By month 6, the number of poor absorbers in the microemulsion group had decreased from 32 patients to none; with the older formulation, this number increased from 15 to 19. These results are in agreement with Friman and Bäckman's earlier report of greatest benefit of cyclosporin microemulsion in terms of drug exposure in poor absorbers of the original oil-based formulation.[31]

In a further 12-week study in 89 patients with *de novo* transplants, Barone et al.[66] reported mean 16 to 31% increases in AUC and 32 to 42% increases in C_{max} (dosage-normalised) with the microemulsion relative to the older formulation after 1, 4, 8 and 12 weeks. Mean t_{max} values were 32 to 38% lower in patients receiving the microemulsion.

Comparison of variances of logarithmically transformed data showed significantly (defined as $p < 0.04$) less intrapatient variability in terms of AUC, C_{max}, C_{min} and t_{max} with the microemulsion than with the oil-based formulation when data from all follow-up visits were pooled, although use of the microemulsion did not reduce interpatient variability to a statistically significant extent.[66] However, both intra- and interpatient variability in exposure to cyclosporin during the first 4 hours covered by the absorption curve (AUC_4) were reduced with the microemulsion relative to the oil-based formulation at 3- and 6-month follow-up in the study of Keown et al.[65] (fig. 2). These reductions in intra- and interpatient variability in absorption profiles in patients receiving cyclosporin microemulsion are in agreement with data previously reported by Noble and Markham[11] and Friman and Bäckman.[31] In a randomised double-blind study in 57 stable renal transplant recipients, 45 of whom were transferred from the original formulation to the microemulsion, results obtained at 8 and 12 weeks and 1 year showed respective reductions in intraindividual variability [percentage coefficients of variation (%CV)] of 63, 36 and 28% for t_{max}, C_{max} and AUC in patients receiving the microemulsion.[67] All these reductions were statistically significant ($p < 0.001$ *vs* oil-based formulation).

Paediatric Patients

The limited data available at the time of the previous review in *Drugs*[11] suggested that the pharmacokinetic effects of the microemulsion relative to the original formulation (increased C_{max} and AUC and shorter t_{max}) in children are similar to those seen in adults. In general, studies published since that time continue to show these effects,[68-70] although publications relating to paediatric renal transplant recipients remain few in number. Improvement of cyclosporin absorption in children and infants is of particular interest, because this group of patients has shown decreased absorption and increased elimination of the drug relative to adults.[71]

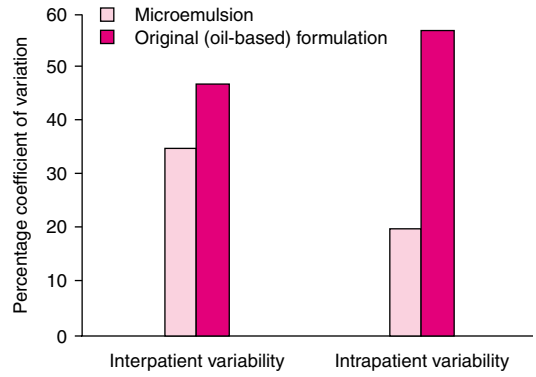

Fig. 2. Effect of cyclosporin microemulsion on intra- and interpatient variability. Percentage coefficients of variation of areas under curves of cyclosporin concentrations in whole blood versus time for the first 4 hours after administration in patients receiving the microemulsion and oil-based formulations. The results shown were calculated from data obtained after 6 months in 421 patients from a Canadian multicentre study in which 1097 patients with renal allografts who were stabilised on the original formulation were randomised to continue this treatment or to conversion to microemulsion.[65] Statistical significance was not stated.

Median AUC and C_{max} were increased by 71 and 48%, respectively ($p < 0.001$ *vs* oil-based formulation), after 6 months in a series of 25 stable renal transplant recipients of mean age 14.1 years who were transferred from the original to the microemulsion formulation of cyclosporin in a blood concentration-controlled manner.[69] t_{max} was reduced by 50%. The mean dosage of cyclosporin remained unchanged after 6 months (6.9 mg/kg/ day). Similar results were reported in a small study in nine children aged from 4.8 to 10.9 years with stable renal allografts.[68]

Other investigators showed no statistically significant effect of transfer to the microemulsion in terms of C_{max} and AUC after 4 weeks.[70] However, this study involved 12 patients stabilised on the original formulation, only six of whom were transferred to microemulsion treatment. Inspection of individual pharmacokinetic profiles showed increases in AUC_{12} and C_{max} in four individuals. The median age of the patients who received the microemulsion was 14.8 years, although it should be noted that one participant was aged 20.6 years.

3.4.2 Liver Transplantation

Data reported previously[11] showed significant increases in AUC and C_{max}, and decreases in t_{max}, with cyclosporin microemulsion relative to the oil-based formulation. Food intake had little effect on AUC (9% decrease compared with fasting) and no effect on t_{max} after administration of the microemulsion in a study in 39 patients undergoing liver transplantation.[72] t_{max} was increased by 93% after food with the oil-based formulation in this trial, although there were no clinically relevant changes in AUC or C_{max}.

Since the previous review, several small studies comparing the two formulations in patients undergoing liver transplantation have been published, all of them in children and adolescents with *de novo*[73,74] or stable existing[75-77] allografts (table III). These studies showed significant increases, or strong trends toward increases, in AUC and C_{max} with the microemulsion relative to the oil-based formulation, although statistical power was limited by sample sizes, particularly in three of the trials in which only eight to 12 patients were evaluable for pharmacokinetics.[74,76,77] Data were normalised according to dosage before statistical analysis in two studies.[73,75]

The most notable of these studies was the Canadian NOF-11 trial,[73] in which 32 children were randomised to receive the microemulsion (n = 17) or the original formulation (n = 15) in the early post-transplant period (days 1 to 7) [see section 4.1.2 for further details]. Daily doses of cyclosporin were divided into three in this study in order to conserve renal function. Biliary anastamoses were similar in both groups (Roux-en-Y in most patients). At 3 weeks, exposure to cyclosporin (shown by mean 8-hour AUC) was increased by over 200% in patients receiving the microemulsion ($p < 0.01$ *vs* original formulation). In addition, there were strong trends towards increased C_{max} and 3-hour AUC when oral cyclosporin was administered after an 8-hour fast (borderline significance for AUC: 2234 *vs* 1664 mg/L □h; $p = 0.05$), and trends towards lower AUC and C_{max} were observed in patients aged under 2 years relative to older children. Results from the other study in *de novo* transplant recipients are less reliable because the pharmacokinetic profiles of the oral formulations were taken under non–steady-state conditions, and two of the nine participants showed significant deviations from the group mean in respect of bioavailability of the microemulsion.[74]

In two studies in patients with existing stable transplants who were transferred from one formulation to the other, mean AUCs over dosage intervals were increased relative to the oil-based formulation by 44[76] and 81%[75] ($p \leq 0.001$). A nonsignificant median increase of 25% was reported in a further small series of children (table III).[77] These authors also showed greater increases in AUC with the microemulsion in patients with Roux-en-Y (mean increase of 37% over oil-based formulation) than in those with duct-to-duct anastomoses (16%).

Generally, systemic exposure to cyclosporin has been shown to be greater when the drug is given as the microemulsion than when the oil-based formulation is used in patients with open T tubes in the first few days after transplantation.[11] Two pre-

Table III. Comparative pharmacokinetics of the microemulsion (MF) and oil-based (OF) formulations of cyclosporin in children and adolescents undergoing liver transplantation. Mean whole-blood data from randomised studies comparing formulations in *de novo* transplantation or series of patients with stable transplants who were transferred from one oral formulation to the other

Reference	AUC (μg/L □h)[a]		C_{max} (μg/L)		t_{max} (h)		C_{min} (μg/L)		Comments
	MF	OF	MF	OF	MF	OF	MF	OF	
***De novo* transplants**									
Alvarez et al.[73]	950**[b]	300[b]	210*[b]	70[b]	NA	NA	NA	NA	db (for 1mo after enrolment of last patient) pg study. 32 children randomised to either oral formulation started during wk 1 to replace IV post-transplant treatment. Biliary anastamoses similar between groups (mainly Roux-en-Y). Dosage-adjusted results at day 22. Fasting 8-hour AUC shown
Dunn et al.[74]	NA	NA	1356	834	2.6	4.4	NA	NA	db co study. 9 children aged 6mo to 11y; all Roux-en-Y anastamoses. Comparison of 2 single oral doses (one of each formulation) given to patients stabilised on IV treatment
Existing stable transplants									
Hoppu et al.[75]	3475***	1920	963.9†	430.6	1.6**	2.9	117.3	87.3	22 children aged 1.9 to 15.6y transferred from OF to MF on a 1 : 1 dosage basis. MF data obtained 5 days after conversion. Significance calculated by ANOVA on dosage-adjusted data (not shown); dosages were similar between formulations
Melter et al.[76]	3484***	2423	673***	337	2*[b]	4[b]	134	118	38 patients aged 4.9 to 19y transferred from OF to MF on a 1 : 1 dosage basis; 12 evaluated for pharmacokinetics. MF data obtained after ≥3 doses. Data not adjusted for dosage
van Mourik et al.[77]	4542.5[c]	3629[c]	790.5[c]	589.4[c]	1.8**[c]	2.5[c]	179[c]	185.5[c]	8 children aged 1.2 to 12y on either formulation transferred to the other. 2 duct-to-duct anastomosis; 6 Roux-en-Y. Pharmacokinetic profiles were taken before and 4 days after conversion, but were not adjusted for dosage

a AUCs shown are for administration intervals unless stated otherwise.

b Estimated from graph.

c Median results.

ANOVA = analysis of variance; **AUC** = area under the blood concentration versus time curve for cyclosporin; $\mathbf{C_{max}}$ = maximum blood concentration of cyclosporin; $\mathbf{C_{min}}$ = minimum (trough) blood concentration of cyclosporin; **co** = crossover; **db** = double-blind; **IV** = intravenous; **NA** = data not available; **pg** = parallel-group; $\mathbf{t_{max}}$ = time to C_{max}; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, † $p < 0.0001$ *vs* OF.

viously reviewed studies, however, indicated that absorption of cyclosporin from the microemulsion is not fully independent of bile flow. A statistically significant inverse correlation between the volume of externally drained bile and the bioavailability of cyclosporin was reported in a series of eight patients receiving the microemulsion.[78] In a further three individuals, the highest C_{max} and AUC values and the shortest t_{max} were seen in patients with no T-tube in place.[79]

3.4.3 Heart and/or Lung Transplantation

Enhancement of absorption of cyclosporin from the microemulsion relative to that seen with the oil-based formulation was reported previously in small numbers of patients undergoing heart transplantation and those with cystic fibrosis who were candidates for heart-lung transplantation.[11]

Two parallel-group comparative studies in *de novo* transplantation have since become available, one in 50 patients receiving lung allografts (nine

of whom had cystic fibrosis)[80] and one in 35 heart transplant recipients.[81] One study[81] was carried out in a double-blind manner, and both followed patients for up to 1 year after randomisation to treatment with either the microemulsion or oil-based formulation of cyclosporin.

In the lung transplantation study,[80] there were no differences between groups in mean blood concentrations of cyclosporin immediately before (trough) or 6 hours after each dose of the drug. However, mean 2-hour blood concentrations and 6-hour AUCs were significantly greater ($p < 0.001$) with the microemulsion at all follow-up visits for patients with and without cystic fibrosis (increase in mean 6-hour AUC of just over 70% relative to the oil-based formulation in both patient types at the 12-month visit). Patients with cystic fibrosis required dosages two to three times those needed by patients without this disorder to maintain trough concentrations of cyclosporin in blood, regardless of formulation.

Results in heart transplant recipients followed a similar pattern,[81] although differences between formulations were less pronounced than in the previously described study. The dosage-normalised mean AUC for the 12-hour administration interval was 35% higher after 1 week in patients receiving the microemulsion ($p = 0.023$); this increase was still apparent at weeks 12 and 52, although the difference between groups was smaller (respective 16 and 13% increases with microemulsion) and statistical significance was lost. Increases in mean C_{max} in the microemulsion relative to the oil-based formulation group were statistically significant ($p < 0.05$) at weeks 1 and 12, but not at week 52. A trend towards reduced t_{max} in week 1 was lost by week 52. In both of these studies, statistically significant reductions in intra-[80,81] and interpatient[80] variability (in terms of AUC values) were reported.

A statistically significant increase in mean AUC_{12} from 3792 to 4899 μg/h □L was noted after 1 week in a series of 172 patients with stable heart and/or lung allografts who were converted to microemulsion treatment from the original formulation.[82] After a reduction in cyclosporin microemulsion dosage (see section 3.5.3), the AUC_{12} was reduced to 4231 μg/L □h at week 4. Mean t_{max} was 4.7 hours before conversion and 1.9 hours 1 week thereafter.

Two reports of small series of patients transferred from the oil-based formulation to the microemulsion are also available. One of these showed a statistically significant 24% increase in mean AUC_{12} 4 weeks after conversion in 20 patients with existing stable heart transplants;[83] there were no clinically relevant changes in mean cyclosporin dosage or trough concentration of drug in whole blood between formulations. In a similar study in 11 evaluable stable lung transplant recipients (all of whom had had end-stage cystic fibrosis),[84] mean AUC_{12} was increased from 4164 to 5318 μg/L □h, although statistical significance was not attained.

3.4.4 Other Patient Groups and Special Considerations

Limited data are available to show the pharmacokinetic characteristics of cyclosporin microemulsion in patients undergoing bone marrow transplantation (BMT),[85,86] and comparisons with the original oil-based formulation are lacking. A two-dose study showed substantially reduced absorption as shown by whole blood concentrations of drug and AUC values in children ($n = 5$) relative to those in adults ($n = 20$).[85] Interpatient variability was high (%CV = 48 and 63 for AUC after doses one and two, respectively), but intrapatient variability was lower (%CV = 32).

A further study in 20 adults and seven children carried out in the first month after BMT showed substantially lower systemic exposure to cyclosporin with the microemulsion formulation in children than in adults (mean AUC_{12} values of 861 *vs* 2629 μg/L □h; $p = 0.001$).[87] Absorption was delayed and reduced relative to that seen in solid organ allograft recipients. Intra- and interpatient variabilities were high, and AUCs were significantly increased by the presence of GI inflammation caused by mucositis or graft-versus-host disease. The presence of liquids or food had no clinically relevant effect.

Renal transplantation in patients with diabetes mellitus is characterised by poor outcomes, high

mortality and progression of secondary complications. The pharmacokinetics of cyclosporin may be influenced in these patients by disturbances in GI motility, impaired microcirculation in the intestinal mucosa, altered biliary flow and changes in lipid metabolism. These factors have given rise to interest in the potential pharmacokinetic advantages of the microemulsion formulation in patients with diabetes mellitus who require organ transplantation. Results are available from two small studies, one in 17 stable recipients of simultaneous pancreas and kidney allografts[88] and the other in 18 stable renal allograft recipients with diabetes mellitus before and after conversion.[89]

Both studies showed increased systemic exposure to cyclosporin upon conversion from the oil-based formulation to the microemulsion, although changes in AUC and C_{max} were statistically significant in one study only.[88] Interestingly, however, mean AUC and C_{max} values increased to a smaller extent in eight patients with insulin-dependent diabetes mellitus than in ten individuals who had developed diabetes mellitus after transplantation and who were controlled with oral hypoglycaemic therapy.[89] Conversion to the microemulsion normalised mean t_{max} (as shown by comparison with a control group of patients without diabetes) in both groups.[89]

The pharmacokinetics of cyclosporin in elderly patients have been reviewed in detail by Kovarik and Koelle,[90] who conclude that the disposition of the drug in this patient group does not differ to any clinically significant extent from that seen in younger individuals.

3.5 Effect of Formulation on Cyclosporin Dosage

The implications of use of the microemulsion formulation in terms of dosage needed to maintain therapeutic blood concentrations of cyclosporin while avoiding toxicity have been investigated extensively in large numbers of studies carried out since the mid-1990s. Many of these have been non-blind sequential studies in series of patients transferred from the old to the new formulation, and have generally shown either mean dosage reductions to maintain blood concentrations of cyclosporin within desired ranges and/or increases in trough or mean blood concentrations upon transfer to the microemulsion. The effect of formulation conversion on transplant rejection rates is discussed in section 4.4.

3.5.1 Renal Transplantation

Series of stable renal allograft recipients undergoing conversion from the original to the microemulsion formulation of cyclosporin have been followed for up to 12 months,[91-100] with the exception of one study in which follow-up was continued for up to a mean 26.5 months.[95] A simple 1 : 1 initial dosage conversion was used in all studies but one, in which this ratio was compared with a 1 : 0.8 conversion (original formulation : microemulsion).[95] Dosage adjustments after conversion were based on C_0 or mean blood cyclosporin concentrations, with adverse events also being taken into account (this applies additionally to sections 3.5.2 and 3.5.3).

Cyclosporin dosages were reduced after conversion to microemulsion in 12.3 to 87.2% of patients in studies in which this information was given.[91-94,96,97,99,100] A reduction in mean dosage of 4.7% over 90 days ($p < 0.001$) was reported by Løkegaard et al.[97] in their study in 809 patients; mean dosage reductions ranged from 6.6 to 14.7% in other studies ranging in duration from 8 weeks to 12 months and involving a total of 572 individuals.[91,96,98] These reductions were statistically significant ($p < 0.05$[91] and $p < 0.001$[98]) in two series of patients. The mean dosage of cyclosporin was unchanged over 3 months in one study in 167 renal allograft recipients,[94] but the mean trough concentration of drug in blood increased slightly (from 145 to 153 μg/L). In some studies,[91,92,94,96,97] increased dosages were required in a minority of patients (0.9 to 18.4%). The reasons for this were given by one group of authors only ('rounding up' of dosages after conversion or detection and correction of suboptimal therapy with the original formulation).[92]

The only significant predictor of dosage reduction after 52 weeks was the original dosage of cyclosporin as oil-based formulation in the single

study in which this information was given.[92] Patients receiving 4 mg/kg/day or more at the time of recruitment were significantly more likely ($p < 0.0001$) than those receiving smaller dosages to need reductions after conversion to microemulsion therapy.

In one study,[95] patients were allocated to either 1 : 1 or 1 : 0.8 conversion to cyclosporin microemulsion (26 patients in each group). Of patients in the first group, 65% required a dosage reduction (mean follow-up 26.5 months); 11% of patients in the second group required further dosage reductions after the initial 20% reduction at conversion (mean follow-up 16.1 months).

Data are also available from a number of comparative studies (most of which were nonblind) in which patients with *de novo* or established renal transplants were followed for up to 3 years after being randomised to treatment with the microemulsion or the original formulation. Dosages were adjusted according to C_0 results. As shown in table IV, mean dosages needed to maintain required trough blood concentrations of cyclosporin were significantly lower with the microemulsion in two studies in *de novo* transplant recipients (12-month[101] and 3-year[102] follow-up). The difference in mean dosage between formulations was not significant at the end of years 1 and 2 in the 3-year study; however, mean trough concentrations of cyclosporin in whole blood were significantly higher in patients receiving the microemulsion throughout the study.

There was no statistically significant difference in mean daily dosage between formulations in other studies summarised in table IV,[64,65,103] including the very large trial by Keown et al.,[65] or in a further trial in 123 patients with existing stable allografts (although actual dosages were not stated).[104] However, the proportion of patients needing dosage increases to maintain trough cyclosporin concentrations within the desired range was significantly higher with the oil-based formulation than with the microemulsion during the first 3 months in the study of Frei et al.[103] Studies in which rejection rates were analysed in addition to dosage requirements are discussed in more detail in sections 4.1.1 and 4.4.1.

3.5.2 Liver Transplantation

Mean daily dosages of cyclosporin were reduced by 11.4% over 12 months[105] and 16.1% over 12 weeks[106] in two series of patients (n = 64[105] and 46[106]) with stable existing liver allografts who were converted (on a 1 : 1 basis) from the oil-based formulation to the microemulsion (see also section 4.4.2). In one study,[106] 73% of patients required dosage reduction to maintain blood cyclosporin concentrations within the desired range, and it was noted that these reductions were needed particularly in patients receiving more than 4 mg/kg/day of cyclosporin as oil-based formulation at study entry.

Dosage reductions were also significant in two randomised, double-blind, blood cyclosporin concentration-controlled clinical trials in patients undergoing *de novo* liver transplantation (see section 4.1.2),[107,108] but not in a third, small, trial.[109]

3.5.3 Heart/Lung Transplantation

Statistically significant dosage reductions were reported over follow-up periods ranging from 1

Table IV. Comparison of dosages of cyclosporin oil-based formulation (OF) or microemulsion (MF)

Reference; duration of follow-up	No. of patients	Mean dosage at final follow-up (mg/kg/day)[a]
Frei et al.[103]	373 MF	3.3
(STA);[b] 12mo[c]	93 OF	3.5
Gracida & Melchor[102]	65 MF	2.9*
(NEW);[b] 3y	67 OF	3.6
Keown et al.[65]	737 MF	3.5
(STA); 6mo	356 OF	3.6
Keown & Niese[64]	86 MF	4.5
(NEW); 12wk[a]	81 OF	4.9
Pollard et al.[101]	195 MF	3.65*
(NEW); 12mo	98 OF	4.53

a Dosages required to maintain target blood concentrations of cyclosporin.

b In all STA studies, patients with stable existing transplants were randomised to continue OF or to conversion to MF. In NEW studies, patients were randomised to begin either treatment after transplantation.

c Double-blind study.

NEW = Patients with *de novo* transplants; **STA** = patients with existing stable transplants; * $p < 0.04$ *vs* OF.

Table V. Effect on dosage of conversion from cyclosporin oil-based formulation (OF) to microemulsion (MF) in series of patients with stable existing heart and/or lung allografts

Reference (duration of follow-up)	No. of patients	Mean dosages (conversion[a] → final follow-up[b])
Aziz et al.[82] (1wk)	172	293 → 259 mg/day**
Dorent et al.[113] (3mo)	81	3.9 → 3.6 mg/kg/day
Pethig et al.[110] (9mo)	70	3.8 →3.1 mg/kg/day**
Svendsen et al.[111] (90 days)	153	389 → 353 mg/day**
Zaldonis et al.[112] (3mo)	185	307 → 260 mg/day*

a Patients were transferred from OF to MF on a 1 : 1 dosage conversion basis.

b Dosages required to maintain target blood concentrations of cyclosporin.

* $p < 0.05$, ** $p < 0.001$ *vs* baseline (i.e. dosage at conversion).

week to 9 months in four series of 70 to 185 patients with existing stable heart and/or lung allografts who were transferred to cyclosporin microemulsion on the basis of an initial 1 : 1 dosage conversion (table V).[82,110-112] Statistical significance was not reported in a further series,[113] although these authors noted a need for dosage reduction in 93.3% of patients over 3 months. Other authors reported dosage reductions in 35[112] and 57%[111] over the same period. Dosages were increased in small proportions of patients (less than 4%) in two studies,[111,113] although possible reasons for this were not discussed. The relationship between mean concentrations of cyclosporin in whole blood and mean daily dosage in the largest of these series of patients is shown in figure 3.

3.5.4 Paediatric Patients

Kelles et al.[69] reported no change in mean daily cyclosporin dosage requirements 6 months after conversion of 25 children and adolescents (mean age 14.1 years) with stable renal allografts from the oil-based formulation to the microemulsion (see section 3.4.1). However, in a non-randomised comparison in paediatric patients undergoing *de novo* kidney transplantation, Holm et al.[114] reported a reduction in dosage from 10 mg/kg/day with the original formulation (n = 102) to 6 mg/kg/day in 'most' patients converted to microemulsion treatment (n = 68).

In a randomised comparison (double-blind for 1 month after enrolment of the last patient) in 32 *de novo* paediatric recipients of liver transplants,[73] the weight-adjusted dosage of the oil-based formulation needed to maintain target trough concentrations of cyclosporin in blood was approximately twice that needed with the microemulsion from day 22 onwards (see section 3.4.2 for effect of formulation on drug exposure to day 22, and section 4.1.2 for clinical details of this study). Similarly, conversion of a series of 53 children with stable liver allografts from oil-based to microemulsion cyclosporin treatment resulted in a re-

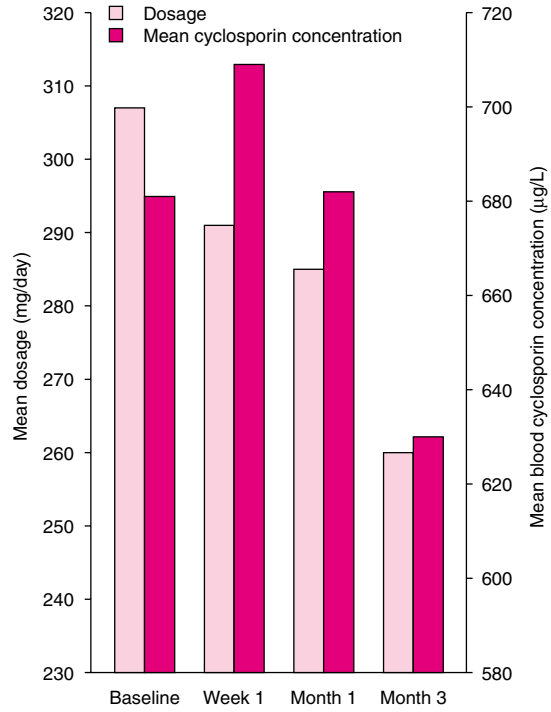

Fig. 3. Effect of conversion to cyclosporin microemulsion on dosage and concentration of drug in whole blood. 185 patients with existing stable heart and/or lung allografts were converted on a 1 : 1 dosage basis from the original oil-based formulation to the microemulsion, and daily dosages adjusted to maintain blood concentrations of cyclosporin within a prespecified therapeutic range. The mean daily dosage of cyclosporin microemulsion and the mean concentration of the drug in blood was determined 1 week, 1 month and 3 months after formulation conversion. Mean daily dosages were statistically significantly ($p < 0.05$) lower than at baseline at all time points.[112]

Table VI. Interactions between cyclosporin (as microemulsion) and other agents

Effect	Agents (known and suspected)	References
Increased plasma or whole blood concentrations of cyclosporin	**Calcium channel blockers:** diltiazem; nicardipine; verapamil	116-121
	Antifungals: fluconazole; itraconazole; ketoconazole	116-119; 122; 123
	Antibacterials: erythromycin and some other macrolides; doxycycline; quinupristin/dalfopristin	116-119
	Glucocorticoids: methylprednisolone	116-119
	Reproductive hormones: danazol; methyltestosterone; oral contraceptives	116-118
	Antidiabetic agents: glipizide (but not consistently; see Sagedal et al.[124])	116
	Other agents: amiodarone; allopurinol; bromocriptine; colchicine; grapefruit and its juice; metoclopramide; propafenone; tacrolimus; sirolimus; HIV protease inhibitors (potential)	116-119; 125-127
Decreased plasma or whole blood concentrations of cyclosporin	**Antibacterials:** rifampicin; nafcillin; sulfadimidine/trimethoprim (intravenous only); rifabutin (potential)	116-119
	Anticonvulsants: carbamazepine; phenobarbital; phenytoin; primidone	116-119
	Antiplatelet drugs: ticlopidine	116-119
	Other agents: octreotide; orlistat; St John's Wort	118; 119
Interacting drugs associated with enhanced nephrotoxicity	**Antibacterials:** aminoglycosides; ciprofloxacin; trimethoprim/sulfamethoxazole	116-119
	Antivirals: aciclovir	116
	Antineoplastics: melphalan	116-119
	Antifungals: amphotericin B; ketoconazole	116; 118; 119
	Other immunosuppressants: tacrolimus; sirolimus	119; 125
	NSAIDS: azapropazone; diclofenac; naproxen; sulindac	116; 118; 119
	Other agents: colchicine	116; 119

duction of the mean daily dosage from 13.75 to 7.22 mg/ kg in patients aged below 6 years[115] (see also section 4.4.2). In patients aged 6 years or over, the mean daily dosage was reduced from 7.3 to 5.42 mg/kg.

3.6 Drug Interactions

The subject of interactions of cyclosporin with other drugs was discussed in detail in a review published in 1996 that dealt with observations in patients receiving the original oil-based formulation.[116] This review described a wide variety of interactions documented in patients receiving this formulation; more recent data specific to the microemulsion are presented in the manufacturer's literature, standard reference sources and in case series published since the introduction of the newer formulation.

Various agents are known to either increase or decrease plasma or whole blood concentrations of cyclosporin by competitive inhibition or induction of hepatic enzymes involved in the metabolism of the drug (notably CYP 450). These interactions are summarised in table VI, together with drugs associated with enhancement of nephrotoxicity of cyclosporin.

A shift to the right of the plasma concentration versus time curve for orally administered diltiazem in patients receiving cyclosporin microemulsion has been noted.[121] This apparent lag in diltiazem absorption has not been reported with the oil-based formulation of cyclosporin, and an interaction me-

diated by P-glycoprotein was suggested by these authors.[121]

In addition to the above, a potential for cyclosporin to enhance the ability of HMG-CoA reductase inhibitors to induce rhabdomyolysis has been noted in the literature.[117,128,129] Reduced clearance of prednisolone and digoxin has also been reported in cyclosporin recipients.[116,117] Cyclosporin should not be given with potassium-sparing diuretics because of a risk of hyperkalaemia, and gingival hyperplasia and convulsions have been noted in patients receiving nifedipine and methylprednisolone, respectively, in addition to the drug. Cyclosporin also limits the effectiveness of vaccination, and live vaccines should be avoided in patients receiving the drug.[117,118]

Other data suggest that exposure to cyclosporin may be increased by coadministration of mycophenolate mofetil,[130] but that the proton pump inhibitor pantoprazole has no effect on the pharmacokinetic behaviour of the drug.[131,132]

4. Therapeutic Efficacy

Some of the trials reviewed in this section, although providing therapeutic efficacy results, were designed primarily to provide data on the pharmacokinetics of cyclosporin microemulsion (section 3). Nonetheless, in the interests of completeness, the clinical results have been included.

4.1 Comparisons with Other Cyclosporin Formulations

The efficacy of cyclosporin microemulsion (Neoral®) has been investigated in well designed trials in comparison with that of the oil-based cyclosporin formulation (Sandimmun®) in recipients of *de novo* renal, liver or heart transplants. Preliminary comparisons of the microemulsion with the alternative oral cyclosporin formulations Sangcya®, Consupren® and Neoplanta® have also been undertaken in renal transplantation.

4.1.1 Renal Transplantation

Oil-Based Formulation (Cyclosporin Sandimmun®)

Although prospective randomised and nonblind studies have investigated the efficacy of cyclosporin microemulsion in comparison with that of the oil-based formulation (Sandimmun®) in *de novo* renal transplant recipients,[102,133] this section discusses only randomised double-blind studies in this respect.

In general, the efficacy of these two formulations was statistically equivalent in *de novo* recipients of first or second renal transplants in double-blind, randomised, multicentre trials (table VII). Nonetheless (as also indicated by the nonblind studies referred to above), a trend towards lower cyclosporin dosages and a lower incidence of acute rejection over 3 to 12 months was apparent in patients receiving the cyclosporin microemulsion formulation compared with those receiving the oil-based formulation.

Dosages required to reach therapeutic cyclosporin concentrations were 8 to 16% lower in microemulsion recipients than in oil-based formulation recipients after 3 to 12 months of treatment[64,134,136,138] (the effects on dosage requirements of the different formulations in renal transplant recipients are discussed in more detail in section 3.5.1).

At these lower dosages, the incidence of biopsy-confirmed acute rejection tended to be lower in microemulsion recipients (25 to 44.2% over 3 to 24 months) than in those receiving the oil-based formulation (22 to 60.5%; table VII). The percentage of patients experiencing more than one acute rejection also tended to be lower among microemulsion recipients than among those receiving the oil-based formulation in the studies recording this (3.1 to 13.3% *vs* 4.0 to 26.8% over 3 to 24 months; table VII). Differences in both parameters reached statistical significance at 3 months in one of the larger studies (table VII).[64] There was also a trend for fewer microemulsion than oil-based formulation recipients to receive monoclonal antibody treatment for acute rejection in the first 3 months of treatment.[135,136,139] Graft (91 to 96% *vs* 89 to 98%) and patient (98 to 100% *vs* 99 to 100%) survival rates were high with both formulations (table VII).

Table VII. Efficacy of cyclosporin microemulsion (MF; Neoral®) versus the oil-based formulation (OF; Sandimmun®) in *de novo* recipients of first or second cadaveric or living renal transplants. Summary of randomised, double-blind, multicentre, concentration-controlled clinical trials. Studies used intent-to-treat analyses and acute rejection episodes were biopsy-confirmed unless stated otherwise

Reference	Study duration	Initial dosage (target trough concentrations in blood)[a]	Treatment and no. of patients (withdrawals)	No. of patients with acute rejection (%)	No. of patients with >1 acute rejection episode (%)	Graft survival (%)	Patient survival (%)
Abendroth et al.[134]	12mo	NR	MF: 28 (NR)	10 (35.7)	NR	NR	NR
			OF: 27 (NR)	15 (55.6)	NR	NR	NR
Barone et al.[135]	3mo (plus 12mo follow-up)	10 mg/kg/day (≤200 μg/L)	MF: 51 (31%)	13 (25.0) [NS at 12mo]	NR	96	100
			OF: 50 (30%)	11 (22.0)	NR	98	100
Frei et al.[136] [b]	3mo	Mean 6.1 mg/kg/day (NR)	MF: 45 (17.8%)	18 (40.0)[c]	5 (11.1)[c]	NR	NR
		Mean 6.4 mg/kg/day (NR)	OF: 41 (14.6%)	22 (53.7)[c]	8 (19.5)[c]	NR	NR
Hricik[137] [d]	24mo	10 mg/kg/day (≤350 μg/L)	MF: 128 (NR)	39 (30.5)	4 (3.1)	92.9	NR
			OF: 127 (NR)	37 (29.1)	10 (7.9)	89.4	NR
Keown & Niese[64]	3mo	Mean 7.2 mg/kg/day (NR)	MF: 86 (17.4%)	38 (44.2)*	11 (12.8)*	90.7	98.8
		Mean 6.6 mg/kg/day (NR)	OF: 81 (19.8%)	49 (60.5)	18 (22.2)	91.4	98.8
Niese[138] [e]	12mo	NR	MF: 45 (26.7%)	19 (42.2)[c]	6 (13.3)[c]	NR	NR
			OF: 41 (26.8%)	23 (56.1)[c]	11 (26.8)[c]	NR	NR
Pollak[139]	3mo	10 mg/kg/day (≤200 μg/L)	MF: 51 (31%)	16 (31.4)	2 (3.9)	96.1	98.0
			OF: 50 (30%)	12 (24.0)	2 (4)	98.0	100

a The overall immunosuppressant regimen [induction therapy and/or dual (plus corticosteroids) or triple (plus corticosteroids and azathioprine) therapy] followed the normal practice of the individual centre; patients were started on a 1 : 1 dosage ratio.

b Not stated whether intent-to-treat analysis.

c Not stated whether biopsy-confirmed.

d Abstract.

e Extension of study by Frei et al.[136]

NR = not reported; **NS** = no statistically significant difference; * $p < 0.05$ *vs* OF.

Other Modified Cyclosporin Formulations

There are preliminary indications of clinical equivalence between cyclosporin Neoral® and cyclosporins SangCya®, Consupren® and Neoplanta® in *de novo* renal transplant recipients (table VIII). Equivalence has also been demonstrated between Neoral® and Consupren® or SangCya® in two small studies in patients with stable existing transplants who were transferred from therapy with the original oil-based formulation of cyclosporin (table VIII). These trials were of limited size (39 to 72 patients), all but one[140] were carried out in a non-blind manner, and the data are available predominantly in abstracts or short reports only. Studies ranged in duration from 1 to 12 months, with one group of investigators[141] observing graft rejections for up to 18 months (table VIII).

4.1.2 Liver Transplantation

Oil-Based Formulation (Cyclosporin Sandimmun®)

In adult patients, the microemulsion and oil-based formulations of cyclosporin have equivalent efficacy in the prevention of acute rejection of orthotopic liver transplants. However, the microemulsion formulation may be more effective in paediatric patients.

A large prospective, randomised, nonblind study indicated a similar incidence of acute rejection in adult patients receiving cyclosporin microemulsion to that in patients receiving the oil-based formulation.[145] In support of this, randomised, double-blind trials in adults showed no difference in the incidence of biopsy-confirmed acute rejection between the microemulsion and oil-based formulations over 4 to 24 months (45.9 to 62.7% *vs* 49.2 to 59.1%), although the number of patients with more severe rejection episodes tended to be lower in groups receiving the microemulsion formulation (0 to 18.5% *vs* 10.8 to 20.0%) [table IX]. In one 12-month trial, a significant difference between groups in the incidence of biopsy-confirmed acute rejection was seen at week 2 (33.2% in microemulsion recipients *vs* 44.8% in those receiving the oil-based formulation; $p < 0.05$) and in the incidence of severe acute rejection at weeks 2 (2.0 *vs* 6.3%; $p < 0\ 05$) and 3 (3.1 *vs* 10.1%; $p < 0.05$).[107]

In contrast, in the randomised, concentration-controlled, intent-to-treat Canadian NOF-11 study in 32 children and adolescents (aged 4 months to 15.6 years; initial dosage 5 mg/kg/day, target trough concentration in blood ≤400 μg/L) which was double-blind for only a month after enrolment of the last patient, significantly fewer microemulsion than oil-based formulation recipients had episodes of biopsy-confirmed acute rejection (35 and 80%, respectively; $p = 0.01$) or corticosteroid-resistant acute rejection (6 and 53%; $p = 0.004$) after 12 months' follow-up.[73] Cyclosporin was given three times daily in this study to conserve renal function (see also section 3.4.2).

There were no differences in graft and patient survival rates between recipients of microemulsion and oil-based formulations in adults (graft 90 to 94.1% and 86 to 93.8%; patient 84.2 to 100% and 85.8 to 94%) [table IX] or children (graft 94.1 and 86.7%; patient 82.4 and 93.3%).[73]

Table VIII. Summary of comparisons of the Neoral® microemulsion formulation (NEO) of cyclosporin with other oral formulations in patients with renal transplants

Reference (study design)	Treatment and mean dosage at final follow-up (mg/kg/day) [study duration]	No. & type of patients	No. of patients with biopsy-confirmed acute rejection (%)	Graft survival (%)	Patient survival (%)
Barbari et al.[141] (r[a], nb)	NEO 2.73 [12mo][b]	46 STA	0	96[c]	NR
	CON 3.41 [12mo][b]	26 STA	0	93[c]	NR
Gaston et al.[140] (r, db)	NEO [3mo][d]	20 STA	0	100	100
	SAN [3mo][d]	19 STA	0	100	100
Kim & Han[142] (r, nb)	NEO [1mo]	20 NEW	10[e]	100	NR
	PLA [1mo]	20 NEW	5[e]	100	NR
McCune et al.[143] (r, nb)	NEO [6mo]	57 NEW[f]	NEO ≡ SAN[g]	100	97
	SAN [6mo]	51 NEW[f]		96	97
Stephan et al.[144] (r[h], nb)	NEO 2.89 [12mo]	20 NEW	30	100	100
	CON 3.37 [12mo]	32 NEW	16	100	100

a First 14 patients transferred to NEO only; patients randomised to NEO or CON thereafter.

b Patients converted from treatment with original oil-based formulation on a 1 : 1 dosage basis.

c Rejections observed over 12 to 18mo.

d Interim report of 12mo study. Basis of initial dosage conversion from oil-based formulation and dosages at follow-up not stated in the abstract available.

e Whether confirmed by biopsy not stated.

f Data available for first 65 patients (total for both groups) only.

g Numerical data not reported in the abstract available.

h First 12 patients received CON as part of unit protocol; patients randomised to NEO or CON thereafter.

CON = cyclosporin Consupren®; **db** = double-blind; **nb** = nonblind; **NEW** = patients receiving *de novo* transplants; **PLA** = cyclosporin Neoplanta®; **r** = randomised; **SAN** = cyclosporin SangCya®; **STA** = patients with stable existing transplants; ≡ indicates statistical similarity between treatments.

Table IX. Efficacy of cyclosporin microemulsion (MF; Neoral®) versus the oil-based formulation (OF; Sandimmun®) in *de novo* recipients of orthotopic liver transplants. Summary of randomised, double-blind, concentration-controlled, clinical trials. Acute rejection episodes were biopsy-confirmed and studies were multicentre and used intent-to-treat analyses unless stated otherwise

Reference	Study duration	Initial dosage (target trough concentrations in blood)[a]	Treatment and no. of patients (withdrawals)	Duration of IV cyclosporin (days)	No. of patients with acute rejection (%)	No. of patients with severe[b] acute rejection (%)	Graft survival (%)	Patient survival (%)
Donovan et al.[146] [c]	24mo	10 mg/kg/day (NR)	MF: 161 (41%)	6*[d]	98 (62.7)	(18.5)	90.7	84.2
			OF: 164 (38%)	7[d]	94 (59.1)	(20.0)	92.3	86.6
Graziadei et al.[109] [e]	12mo	10 mg/kg/day (≤400 μg/L)	MF: 17 (24%)	2.0[f]	9 (52.9)	0	94.1	100
			OF: 16 (25%)	2.1[f]	9 (56.3)	2 (12.5)	93.8	94
Otto et al.[107]	12mo	10 mg/kg/day (≤350 μg/L)	MF: 198 (33.8%)	4.0**[d]	(50.1)	(13.6)	93.9	85.4
			OF: 192 (35.9%)	6.5[d]	(53.5)	(17.0)	89.1	85.8
Roy et al.[108] [g]	4mo	10 mg/kg/day (≤400 μg/L)	MF: 95 (27.4%)	5.8***[f]	(45.9)	(9.5)	90	93
			OF: 93 (31.2%)	8.7[f]	(49.2)	(10.8)	86	91

a All patients received intravenous cyclosporin induction, and all received concomitant azathioprine 1 to 2 mg/kg/day and tapering corticosteroids.

b Corticosteroid-resistant.

c Abstract.

d Median.

e Single-centre study; evaluable-patient analysis.

f Mean.

g Patients receiving the MF were significantly younger than those receiving the OF.

IV = intravenous; **NR** = not reported; * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ *vs* OF.

Patients received intravenous cyclosporin induction and concomitant maintenance (tapered) corticosteroids and azathioprine. The duration of intravenous cyclosporin treatment was significantly shorter in microemulsion recipients than in those receiving the oil-based formulation in most trials (4 to 6 days *vs* 6.5 to 8.7 days; table IX).

Increased systemic exposure to cyclosporin was reported in microemulsion recipients in one trial[73] (see section 3.4.2). Reduced dosage requirements were also noted in patients receiving the microemulsion in some studies[73,107,108] (section 3.5.2).

4.1.3 Heart Transplantation

Oil-Based Formulation (Cyclosporin Sandimmun®)

There were no statistically significant differences in efficacy between the microemulsion and oil-based formulations of cyclosporin in recipients of *de novo* heart transplants in a randomised, double-blind, multicentre trial (3 consecutive reports published over 24 months as shown in table X).[147-149] 86.2 and 84.9% of patients in the microemulsion and oil-based formulation groups, respectively, had acute rejection episodes in the first 6 months. Patient/graft survival rates were 88.3 and 85.4%, respectively, and the rates of severe acute rejection [International Society for Heart and Lung Transplantation (ISHLT) grade ≥3A] were 46.3 and 45.8%, respectively, after 2 years of follow-up.

Although there were no differences between the groups in the primary end-points in this study, several secondary end-points favoured the microemulsion formulation. Antilymphocyte antibody treatment for rejection was required by fewer recipients of the microemulsion formulation (5.9 *vs* 14.1%, $p = 0.010$ at 6 months;[147] 6.4 *vs* 16.7%, $p = 0.002$ at 12 months;[148] 6.9 *vs* 17.7%, $p = 0.002$ at 24 months[149]), and none required more than one course in the first 6 months (*vs* 2.6% of the oil-based formulation recipients; $p = 0.007$).[147] Similarly, the incidence of rejection was significantly lower among women with ISHLT rejection grade ≥3A who received the microemulsion formulation than among women receiving the oil-based formulation at 6 months (31.3 *vs* 57.6%, $p = 0.032$).[147]

4.2 Comparisons with Tacrolimus

The comparative efficacy of cyclosporin microemulsion and tacrolimus in recipients of renal, liver or heart transplants has been investigated in randomised nonblind studies; comparisons in recipients of pancreas-kidney transplants were less well designed.

4.2.1 Renal Transplantation

There were no statistically significant differences in the incidence (10 to 39% *vs* 9 to 40%) or severity (incidence of corticosteroid-resistant acute rejection 0 to 14% *vs* 0 to 7%) of acute rejection between *de novo* renal transplant recipients of cyclosporin microemulsion 8 to 10 mg/kg/day or tacrolimus 0.15 to 0.2 mg/kg/day for 3 to 24 months in the majority of randomised nonblind studies shown in table XI. Most studies included additional corticosteroids plus azathioprine or mycophenolate mofetil, although one had additional corticosteroids only.[151] Graft (78 to 97% *vs* 83 to 100%) and patient (86 to 100% *vs* 90 to 100%) survival were similar for cyclosporin microemulsion and tacrolimus recipients in most studies (table XI), but graft survival was significantly ($p < 0.05$) lower in recipients of cyclosporin microemulsion plus azathioprine plus corticosteroids (85%) than in those receiving tacrolimus plus azathioprine plus corticosteroids (100%) in one study.[152]

Tacrolimus 0.3 mg/kg/day was associated with significantly lower incidences of acute (20 *vs* 37%; $p < 0.001$) and severe acute rejection (9 *vs* 21%; $p < 0.001$) in the largest nonblind comparative 6-month study in 577 patients in 50 European centres.[159] Patients also received azathioprine and corticosteroid treatment in this trial, which also involved a small proportion (7%) of individuals undergoing a second or third transplant. Graft and patient survival over 6 months were similar between treatments.

Black patients receiving tacrolimus tended to do better than those receiving cyclosporin microemulsion plus azathioprine (all patients received corticosteroids; table XI) in a small randomised nonblind study.[158] Biopsy-confirmed acute rejection occurred in 14% of tacrolimus recipients and 38% of those receiving cyclosporin microemulsion in the first year after transplantation. The incidence of corticosteroid-resistant acute rejection (7 and 14%, respectively) was also lower in tacrolimus recipients. The small number of patients involved (35) should be borne in mind, however, when considering the results of this trial.

Table X. Efficacy of cyclosporin microemulsion (MF; Neoral®) versus the oil-based formulation (OF; Sandimmun®) in *de novo* heart transplantation. Randomised,[a] double-blind, multicentre, concentration-controlled, intent-to-treat clinical trial with results reported at 6,[147] 12[148] and 24[149] months

Reference	Study duration	Treatment and no. of patients (withdrawals)[b]	No. of patients with biopsy-confirmed acute rejection[c] (%)	No. of patients with severe acute rejection[d] (%)	Patient/graft survival (%)
Eisen et al.[147]	6mo	MF: 188 (10.6%)	162 (86.2)	80 (42.6)	93.1
		OF: 192 (17.2%)	163 (84.9)	80 (41.7)	92.7
Eisen et al.[148]	12mo	MF: 188	NR	85 (45.2)	90.4
		OF: 192	NR	83 (43.2)	90.1
Eisen et al.[149]	24mo	MF: 188	NR	87 (46.3)	88.3
		OF: 192	NR	88 (45.8)	85.4

a There were significantly more patients with a pretransplant diagnosis of idiopathic dilated cardiomyopathy, coronary artery disease or hypertension in the OF group and a significantly higher baseline serum creatinine level in the MF group.

b All patients received concomitant azathioprine and tapered corticosteroids; antilymphocyte antibody induction therapy followed the normal practice of the individual centre; initial dosage was 10 mg/kg/day in both groups, titrated to whole blood trough concentrations of ≤375 μg/L.

c With any ISHLT rejection severity grading.[150]

d ISHLT rejection severity grade ≥3A.

ISHLT = International Society for Heart and Lung Transplantation; **NR** = not reported.

Table XI. Summary of randomised nonblind studies of the efficacy of cyclosporin microemulsion (CYC; Neoral®) versus tacrolimus (TAC) in *de novo* renal transplant recipients. Acute rejection episodes were biopsy-confirmed

Reference	Concomitant immunosuppression (study duration)	Treatment (target trough concentrations in blood): no. of patients	No. of patients with acute rejection (%)	No. of patients with severe[a] acute rejection (%)	Graft survival (%)	Patient survival (%)
Busque et al.[153] [b]	MMF[c] + CS (6mo)	CYC (200-400 μg/L): 21	2 (10)	0	NR	100
		TAC (8-16 μg/L): 23	2 (9)	0	NR	100
Gonwa et al.[154] [b,d]	MMF[c] + CS (24mo)	CYC (NR): 75	17 (23)	NR	78	88
		TAC (NR): 72	12 (17)	NR	83	94
Johnson et al.[155] [b]	MMF[c] + CS (12mo)	CYC 8-10 mg/kg/day (100-400 μg/L): 75	15 (20)	8 (11)	NS	89
		TAC 0.15-0.2 mg/kg/day (5-16 μg/L): 72	11 (15)	3 (4)		93
Morris-Stiff et al.[152]	AZA + CS (3mo)	CYC 8 mg/kg/day (100-200 μg/L): 40	13 (33)	NS	85*	93
		TAC 0.2 mg/kg/day (5-15 μg/L): 40	16 (40)		100	100
Morris-Stiff et al.;[156] Jurewicz[157]	AZA + CS[e] (≥6mo)	CYC 8 mg/kg/day (NR): 89	35 (39)	NR	NR	NR
		TAC 0.2 mg/kg/day (NR): 90	29 (32)	NR	NR	NR
Raofi et al.[158] [f]	AZA + CS (12mo)	CYC (150-200 μg/L): 21	8 (38)	3 (14)	NR	86
	CS (12mo)	TAC (10-15 μg/L): 14	2 (14)	1 (7)	NR	95
Sperschneider[159] (*de novo* transplants in 93% of patients)	AZA + CS (6mo)	CYC 8-10 mg/kg/day (100-400 μg/L): 271	101 (37)**	57 (21)**	92	99
		TAC 0.3 mg/kg/day (10-20 μg/L): 286	56 (20)	27 (9)	95	99
White et al.[151]	CS (12mo)[g]	CYC (NR): 24	6 (24)	2 (8)	NR	NR
		TAC (NR): 29	8 (28)	1 (3)	NR	NR
Yang et al.[160]	MMF[h] + CS (12mo)	CYC 8 mg/kg/day (NR): 30	4 (13)	3 (10)	97	100
		TAC 0.16 mg/kg/day (NR): 30	4 (13)	1 (3)	90	90

a CS-resistant.
b A third group received azathioprine + tacrolimus (not reviewed).
c MMF dosage 2 g/day.
d Two-year follow-up of Johnson et al.;[155] abstract.
e CS eliminated by 3mo unless the patient had acute rejection.
f Black patients.
g Duration of study not clear.
h Low-dosage MMF (1 g/day).

AZA = azathioprine; **CS** = corticosteroid(s); **MMF** = mycophenolate mofetil; **NR** = not reported; **NS** = no statistically significant difference; * $p < 0.05$, ** $p < 0.001$ *vs* TAC.

4.2.2 Simultaneous Pancreas-Kidney Transplantation

Two small (n = 51 and 27) nonrandomised and nonblind studies of cyclosporin microemulsion versus tacrolimus in recipients of simultaneous pancreas-kidney transplants also receiving mycophenolate mofetil and corticosteroids have indicated superiority [fewer acute rejection episodes (45 and 45% *vs* 26 and 0%)[161,162] and significantly fewer patients with more than one episode (36 *vs* 3.7%; $p < 0.005$)[161] at 6 months] for the tacrolimus-containing regimen. However, in a prospective randomised and nonblind study in 36 recipients of simultaneous pancreas-kidney transplants, acute rejection episodes occurred in 11% each of those receiving cyclosporin microemulsion (initial dosage 600 mg/day) or tacrolimus (initial dosage 6 mg/day) in conjunction with mycophenolate mofetil and corticosteroids at 3 months.[163] The difference between this rate and that in a historical control group receiving the oil-based formulation of cyclosporin plus azathioprine (77%) was significant ($p < 0.01$).

4.2.3 Liver Transplantation

There were no statistically significant differences in the incidence (23 to 65% *vs* 17 to 66%) or severity (incidence of severe acute rejection 6 to 25% *vs* 0 to 19%) of acute rejection (table XII) or the percentage of patients with more than one acute rejection episode (6 to 45% *vs* 2 to 25%)[164-166] between *de novo* liver transplant recipients of cyclosporin microemulsion 8 to 15 mg/kg/day or tacrolimus 0.1 to 0.15 mg/kg/day for 1 to 30 months in most randomised nonblind studies. There was, however, a trend for superiority associated with tacrolimus in many,[164,166-169] reaching statistical significance in one.[170] In this study, biopsy-confirmed acute rejection and severe acute rejection rates at 12 to 26 (mean 18) months were 82.5 versus 50% and 22.5 versus 12.5% of cyclosporin and tacrolimus recipients, respectively ($p < 0.01$ for both comparisons). The dosages of cyclosporin microemulsion and tacrolimus were not, however, recorded in this short report.

Graft (62 to 92% *vs* 68 to 95%) and patient (67 to 98% *vs* 72 to 98%) survival rates were similar for cyclosporin microemulsion and tacrolimus re-

Table XII. Summary of randomised nonblind studies of the efficacy of cyclosporin microemulsion (CYC; Neoral®) versus tacrolimus (TAC) in *de novo* liver transplant recipients. Acute rejection episodes were biopsy-confirmed

Reference	Concomitant immunosuppression: study duration	Treatment (target trough concentrations in blood): no. of patients	No. of patients with biopsy-confirmed acute rejection (%)	No. of patients with severe acute rejection (%)	Graft survival (%)	Patient survival (%)
Canadian Liver Transplant Study Group[166]a	AZA 1 mg/kg/day + CS: 12 mo	CYC (200-300 μg/L): 72	(43)	NR	NR	92
		TAC (5-15 μg/L): 71	(34)	NR	NR	97
Fisher et al.[164]	MMF 1-3 g/day + CS: 6mo	CYC 8-10 mg/kg/day (300-400 μg/L): 49	11 (23)	3 (6)[b]	92	98
		TAC 0.15 mg/kg/day (10-15 μg/L): 48	8 (17)	0[b]	94	98
Klupp et al.[170]	MMF + CS[c]: 12-26mo	CYC (NR): 40	33 (82.5)**	9 (22.5)**	72*	82
		TAC (NR): 40	20 (50)	5 (12.5)	95	95
Mühlbacher[169]	CS: 3mo	CYC 8-15 mg/kg/day (150-300 μg/L): 305	122 (40)	42 (14)[b]	90	92
		TAC 0.15 mg/kg/day (5-20 μg/L): 310	112 (36)	36 (12)[b]	88	91
Rolles et al.[165]	None: 30mo	CYC 10 mg/kg/day (100-300 μg/L): 34	22 (65)	5 of 45 episodes (11)[d]	62	74
		TAC 0.1 mg/kg/day (5-15 μg/L): 30	20 (66)	5 of 30 episodes (17)[d]	73	80
Stegall et al.[167]	MMF 1-2 g/day + CS (eliminated over 14 days): 6mo	CYC 600 mg/day (200-350 μg/L): 32	15 (46)	8 (25)[b]	92	94
		TAC 6 mg/day (8-15 μg/L): 26	11 (42)	5 (19)[b]	86	87
Zervos et al.[168]e	CS + interferon-α 1.5-3 × 10^6 units 3×/wk: 1-21mo	CYC (300-400 μg/L): 25	12 (48)	2 (8)[f]	64	67
		TAC (15 μg/L): 25	6 (24)	0[f]	68	72

a Abstract.

b CS-resistant.

c A third group received TAC + CS (not reviewed).

d Royal Free Hospital scoring system score of 9 to 10.

e Patients with hepatitis C virus infection.

f Not defined.

3×/wk = 3 times per week; **AZA** = azathioprine; **CS** = corticosteroids; **MMF** = mycophenolate mofetil; **NR** = not reported; * $p < 0.05$, ** $p < 0.01$ *vs* TAC.

cipients in most trials (table XII), but the difference achieved statistical significance in favour of tacrolimus in the trial mentioned above for graft survival (72 *vs* 95%; $p < 0.05$).[170] Follow-up data from one study[164] showed similar rejection rates over 2 years in patients receiving either cyclosporin microemulsion or tacrolimus in combination with mycophenolate mofetil.[171]

Across the studies, patients had received liver transplants for hepatitis B or C cirrhosis, sclerosing cholangitis, alcoholic liver disease, cryptogenic cirrhosis, primary and secondary biliary cirrhosis, hepatocellular carcinoma or autoimmune hepatitis. There were no significant differences in the numbers of patients undergoing retransplantation in any study. In a study in which the patients received monotherapy with cyclosporin microemulsion or tacrolimus, 36 and 13%, respectively, required additional immunosuppressive therapy (not statistically significant).[165]

Early data from 425 of 606 liver transplant recipients taking part in a multicentre, randomised, nonblind study in the UK and Ireland indicate a lower incidence of death, retransplantation or treatment failure for immunological reasons with tacrolimus than with cyclosporin microemulsion (17 *vs* 28%; $p = 0.01$).[172] These interim 6-month data, presented in an abstract in which further details are unavailable, precede an awaited report of 1-year outcomes.

4.2.4 Heart Transplantation

One-year follow-up results of a randomised and nonblind trial (published in abstract form) comparing the efficacy of the microemulsion formulation of cyclosporin ($n = 34$) with that of tacrolimus ($n = 33$) in recipients of *de novo* heart transplants indicated no significant differences between the drugs.[173] Dosages were not reported, but all patients received concomitant azathioprine and corticosteroids. There were no differences in patient survival (85 and 85% in cyclosporin and tacrolimus recipients, respectively), incidence of ISHLT grade ≥3A acute rejection (30 and 21%), incidence of any treated acute rejection (30 and 24%) or incidence of muromonab CD3-treated rejection.

In a randomised nonblind trial in Black *de novo* heart transplant recipients, the incidence of acute rejection requiring treatment (1.3 *vs* 0.65 per patient in 12 months; $p = 0.01$) and the incidence of acute rejection with haemodynamic compromise (1.1 *vs* 0.35 per patient in 12 months; $p = 0.02$) were significantly higher in recipients of cyclosporin microemulsion (target trough concentrations 200 to 300 μg/L; $n = 22$) than in those receiving tacrolimus (target concentrations 10 to 20 μg/L; $n = 20$).[174] Kaplan-Meier survival curves indicated significantly improved patient/graft survival among tacrolimus recipients ($p = 0.04$) in this population.

4.3 Comparisons with Sirolimus

Data comparing the efficacy of cyclosporin microemulsion and sirolimus are few. Two 12-month multicentre, randomised, nonblind studies are currently available to show similar efficacy of the two agents in a total of 161 patients undergoing *de novo* renal transplantation (table XIII).[175,176] The same target blood concentrations of cyclosporin and sirolimus were specified in both trials, although concomitant immunosuppression differed (corticosteroid therapy was combined with azathioprine in one study[175] and with mycophenolate mofetil in the other[176]).

Nineteen and 24 patients were withdrawn from the cyclosporin and sirolimus groups, respectively, during the 12 months' follow-up in the first study shown in table XIII;[175] corresponding withdrawal numbers in the second trial were ten and 17.[176] Rates of graft and patient survival ranged from 89.5 to 98% and from 95 to 100%, respectively, and were similar between treatments across both studies. Biopsy-proven acute rejection rates were also not statistically significantly different, although there was a trend in favour of cyclosporin (18 *vs* 27.5%) in the study of Kreis et al.[176]

4.4 Conversion to Cyclosporin Microemulsion

The design of studies investigating the rate of acute rejection after conversion of stable transplant

Table XIII. Summary of randomised, nonblind, 12-month studies of the efficacy of cyclosporin microemulsion (CYC; Neoral®) versus sirolimus (SIR) in recipients of *de novo* renal transplants. Acute rejection episodes were biopsy-confirmed

Reference	Concomitant immunosuppression	Treatment (target trough concentration in blood): no. of patients)	No. of patients with acute rejection (%)	Graft survival (%)	Patient survival (%)
Groth et al.[175]	AZA + CS	CYC (200-400 μg/L × 2mo, then 100-200 μg/L): 42	16 (38)	90	98
		SIR (30 μg/L × 2mo, then 15 μg/L): 41	17 (41)	98	100
Kreis et al.[176]	MMF 2 g/day + CS	CYC (200-400 μg/L × 2mo, then 100-200 μg/L): 38	7 (18)	89.5	95
		SIR (30 μg/L × 2mo, then 15 μg/L): 40	11 (27.5)	92.5	97.5

AZA = azathioprine; **CS** = corticosteroids; **MMF** = mycophenolate mofetil.

recipients from the oil-based to the microemulsion cyclosporin formulations ranges from randomised and double-blind (in renal transplantation) to nonblind sequential (in liver, heart or lung transplantation) [see section 3.5 for a detailed discussion of the effect of formulation on dosage]. A few small nonblind sequential treatment studies have investigated the conversion of patients from tacrolimus to cyclosporin microemulsion.

4.4.1 Renal Transplantation

From the Oil-Based Formulation

No substantial changes in dosage or incidence of acute rejection were apparent in stable recipients of renal transplants switched from the oil-based formulation to the microemulsion in a prospective randomised and nonblind study (n = 123) [section 3.5.1][104] or a randomised and double-blind 3-month study and its 12-month extension.[103,136]

Cyclosporin dosages and the incidence of acute rejection did not change significantly over 3 to 12 months in 373 patients who had previously [≥6 (mean 38) months ago] received a first or second renal transplant, who had stable graft function on the oil-based cyclosporin formulation and who were switched (1 : 1 initial dosage ratio, altered to keep blood concentrations in the therapeutic range) to the microemulsion formulation, compared with those remaining on the oil-based formulation (n = 93), in the randomised double-blind multicentre study.[103,136] 0.8 and 0% of patients receiving the microemulsion and oil-based formulations had acute rejection episodes in the first 12 months.

From Tacrolimus

Conversion from tacrolimus is occasionally necessary because of neurotoxicity (for example, mental status changes, coma, confusion, aphasia, cognitive changes, headache, Guillain-Barré syndrome, status epilepticus, depression, peripheral neuropathy), hyperglycaemia/diabetes mellitus, GI intolerance, nephrotoxicity or lack of efficacy.

In two small and nonblind sequential treatment trials, acute rejection rates after conversion from tacrolimus to cyclosporin microemulsion were 0 of 19 renal transplant patients over 3 months[177] and 12% of 49 patients over 2 months.[178] Reconversion to tacrolimus was required in three of 19 patients within 33 months for acute rejection or hirsutism in one trial.[177]

4.4.2 Liver Transplantation

From the Oil-Based Formulation

Available evidence indicates no clinically relevant changes in the rate of acute rejection on conversion from the oil-based to the microemulsion formulation in liver transplant recipients.

There were no acute rejection episodes in 46 stable (≥3 months post-transplant) adult liver transplant recipients during the first 3 months after conversion from the oil-based cyclosporin formulation to the microemulsion (1 : 1 dosage ratio) in a nonblind sequential treatment trial.[106] All patients received concomitant corticosteroids, and 42 also received azathioprine. The mean cyclosporin dosage was reduced by 16.1% (to 2.3 mg/kg/day; see section 3.5.2).

A similar lack of acute rejection was seen in a nonblind sequential treatment study of 22 children (aged 1.9 to 15.6 years; 0.5 to 6.9 years after orthotopic liver transplantation) 6 months after conversion from the oil-based formulation to the microemulsion (1 : 1 dosage ratio); total drug exposure was increased in recipients of the microemulsion formulation (section 3.4.2).[75] Eight percent of 50 children (mean age 6.4 years; mean 3.6 years after orthotopic liver transplantation) had acute rejection episodes in 18 months' follow-up after conversion to the microemulsion formulation (1 : 1 dosage ratio except those previously receiving 10 mg/kg/day who were converted to 0.8mg of the microemulsion formulation per milligram of the oil-based formulation) in another nonblind sequential treatment study; dosage reductions were required in many during follow-up (see section 3.5.4).[115]

From Tacrolimus

The rates of acute rejection in two nonblind sequential treatment trials of patients converted from tacrolimus to cyclosporin microemulsion for adverse effects or lack of efficacy were 39% of 23 patients over 23 months[179] and 26% of 108 patients over 2 months (7 patients had inadequate cyclosporin blood concentrations at the time of rejection in the latter study).[178] Adverse effects from tacrolimus resolved in most patients, although reconversion to tacrolimus was necessary in six individuals (26%) for persistent rejection (3 patients), retransplantation (2) or persistent nausea and vomiting (1) in one study.[179]

4.4.3 Heart/Lung Transplantation

From the Oil-Based Formulation

A lack of well-designed clinical trials precludes any conclusion on the efficacy of converting from the oil-based to the microemulsion formulations of cyclosporin after thoracic organ transplantation. Nonetheless, retrospective comparisons with pretransplant data 3 and 26 months after conversion in recipients of heart (n = 109 and 170)[111,180] or lung (n = 34)[111] transplants indicated no change in the incidence of acute rejection (see section 3.5.3 for discussion of effects on dosage of formulation change).

4.5 Use of Other Agents with Cyclosporin Microemulsion-Based Immunosuppression

4.5.1 Renal Transplantation

The incidence of acute rejection (assessed using clinical criteria, response to treatment and histology) in cyclosporin recipients is linked to the choice of total immunosuppressive regimen. Acute rejection occurred more often in the first 3 months in recipients of *de novo* first or second renal transplants who had cyclosporin microemulsion alone or with corticosteroids (54.2% of 24) than in those receiving triple therapy (cyclosporin, corticosteroids and azathioprine; 46.7% of 45) and more often in recipients of triple therapy than in those receiving quadruple therapy (cyclosporin, corticosteroids, azathioprine plus induction with antilymphocyte antibodies; 23.5% of 17).[64] There were no statistically significant differences in this respect between the microemulsion and oil-based formulations in this randomised and double-blind trial, although there was a trend for a lower incidence of acute rejection in the group receiving the microemulsion formulation as part of quadruple therapy (23.5 *vs* 52.6% with the oil-based formulation).

Addition of Mycophenolate Mofetil

Significantly fewer episodes of acute renal transplant rejection (15% at 4 to 31 months' follow-up) occurred in 68 patients receiving *de novo* maintenance corticosteroid-free immunosuppression comprising the microemulsion formulation of cyclosporin (target blood trough concentrations 200 to 400 nmol/L) plus mycophenolate mofetil 2 g/day than in 190 historical controls (37%; p = 0.0006) receiving corticosteroid-free cyclosporin microemulsion alone (all patients received antithymocyte globulin induction).[181]

This result was supported by data from randomised nonblind studies in a total of 173 renal transplant patients receiving cyclosporin microemulsion plus corticosteroids with or without mycophenolate mofetil 2 g/day.[182,183] Significant decreases in rates of presumed[182] or biopsy-

Table XIV. Summary of randomised, double-blind, 12-month studies assessing the combination of cyclosporin microemulsion (CYC) with other immunosuppressants in patients undergoing *de novo* renal transplantation

Reference	Treatment regimen[a]	No. of patients	No. of patients with biopsy-confirmed acute rejection (%)	No. of patients with severe[b] acute rejection (%)	Graft survival (%)	Patient survival (%)
Combination with mycophenolate mofetil (MMF)						
Wiesel & Carl[184]	CYC + MMF 2 g/day	165	29 (18)***		91.5[c]	
	CYC + MMF 3 g/day	160	22 (14)***		90[c]	
	CYC + PL	166	77 (46)		89[c]	
Combination with anti–interleukin-2 receptor monoclonal antibodies						
Kahan et al.[186] (abstract)	CYC + BAS 40mg	173	61 (35)**	43 (25)***	95	97
	CYC + PL	173	85 (49)	73 (42)	93	96
Nashan et al.[187]	CYC + BAS 40mg	190	51 (30)*[d]	19 (10)***[d]	88	95
	CYC + PL	186	73 (44)[d]	43 (23)[d]	87	97
Nashan et al.[188]	CYC + DAC 1 mg/kg every 2wk × 5	140	39 (28)***[d]		83	99**
	CYC + PL	133	63 (47)[d]		88	94
Combination with sirolimus (SIR)						
Kahan & the Rapamune US Study group[189]	CYC + SIR 2 mg/day	284	58 (17)†[d]	1 (0.4)[e]	94	97
	CYC + SIR 5 mg/day	274	33 (12)‡[d]	6 (2.2)[e]	93	96
	CYC + AZA 2-3 mg/kg/day	161	48 (30)[d]	3 (1.9)[e]	94	98
MacDonald & the Rapamune Global Study Group[190]	CYC + SIR 2 mg/day	227	56 (25)**[d]		90	96.5
	CYC + SIR 5 mg/day	219	42 (19)***[d]		91	95
	CYC + PL	190	54 (41.5)[d]		88	95

a All patients also received corticosteroids as part of their immunosuppression regimen. CYC dosages were adjusted according to centre protocols in all studies.

b Corticosteroid-resistant.

c Combined end-point of graft and patient survival.

d 6-month results.

e 'Refractory' acute rejection (not defined).

AZA = azathioprine; **BAS** = basiliximab; **DAC** = daclizumab; **PL** = placebo; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ *vs* PL; † $p < 0.01$, ‡ $p < 0.001$ *vs* AZA.

proven[183] rejection were reported in patients receiving mycophenolate mofetil. The need for antilymphocyte antibody for acute rejection was also significantly reduced in mycophenolate mofetil recipients in one study.[182]

The addition of mycophenolate mofetil 2 or 3 g/day to cyclosporin microemulsion (initial daily dosage 5 to 15 mg/kg/day) plus corticosteroid-based immunosuppression significantly reduced the incidence of biopsy-proven rejection or treatment failure over 1 year in a randomised, multicentre, double-blind and placebo-controlled study in 491 recipients of first or second renal allografts (table XIV).[184] Proportions of patients experiencing rejection or withdrawing from treatment were 30.3 and 38.8% with mycophenolate mofetil 2 and 3 g/day, respectively, and 56% with placebo ($p < 0.001$ *vs* mycophenolate mofetil). Graft and patient survival rates were similar between groups. Additional results from 34 patients at a single centre showed the beneficial effect of mycophenolate mofetil on acute rejection to be maintained over 5 years.[185]

Concomitant immunosuppression with mycophenolate mofetil may allow reductions in the dosage of cyclosporin microemulsion in renal transplant recipients. There were no episodes of acute rejection during 6 months of follow-up in 16 ca-

daveric renal transplant recipients suspected of nephrotoxicity whose mean cyclosporin microemulsion dosage was reduced from 3.8 mg/kg/day (whole blood trough concentration 148 μg/L) to 2.2 mg/kg/day (42% reduction, $p < 0.01$ *vs* baseline; trough concentration 53 μg/L, $p < 0.001$ *vs* baseline) on the addition of mycophenolate mofetil 2 g/day to the regimen; corticosteroid dosages remained unchanged.[191]

Addition of Anti–IL-2 Receptor Monoclonal Antibodies

The addition of intravenous basiliximab 20mg on days 0 and 4 of renal transplantation to baseline *de novo* immunosuppressive therapy with cyclosporin microemulsion (blood concentrations 100 to 450 μg/L) plus corticosteroids significantly decreased rates of acute and corticosteroid-resistant acute rejection at 6 months in a randomised double-blind trial in 376 European and Canadian patients (table XIV).[187] A similarly designed US study in an intent-to-treat population of 346 showed a statistically significant reduction in the rate of biopsy-proven acute rejection after 12 months when basiliximab was added to cyclosporin microemulsion therapy (table XIV). This result was accompanied by first acute rejection rates of 38 and 55% in the basiliximab and placebo groups, respectively ($p = 0.001$).[186] There were also significantly fewer second rejections (12 *vs* 23%; $p = 0.005$) and rejection episodes requiring treatment with augmented immunosuppression (other than corticosteroids) [25 *vs* 42%; $p = 0.001$] among patients receiving basiliximab. Patient and graft survival rates were similar between groups.

A significant reduction in the incidence of biopsy-confirmed acute rejection was associated with addition of the humanised monoclonal antibody daclizumab (1 mg/kg given every 2 weeks for up to five doses) to cyclosporin microemulsion (10 mg/kg/day initially, with the option to switch to intravenous therapy if patients were unable to take the drug orally) plus corticosteroids in *de novo* renal transplantation (table XIV).[188] Need for additional antilymphocyte therapy and cumulative corticosteroid requirements were also significantly lower in the daclizumab group. There was no significant difference between groups in graft survival after 1 year, but the rate of patient survival was significantly higher in the daclizumab group (99 *vs* 94%; $p = 0.01$) [table XIV].

Addition of Sirolimus

The addition of sirolimus (2 or 5 mg/day) to blood concentration-controlled cyclosporin microemulsion plus corticosteroid immunosuppressive therapy has been investigated in two large, multicentre, double-blind, placebo-controlled studies in recipients of primary renal allografts (table XIV). One was a comparison of sirolimus with placebo in 576 patients,[190] and the other a comparison with azathioprine 2 to 3 mg/kg daily in 719 patients.[189] Target trough concentrations of cyclosporin in whole blood were 200 to 350 or 400 μg/L for the first month, 200 to 300 μg/L for the second month, and 150 to 250 μg/L thereafter.

The addition of sirolimus to cyclosporin microemulsion therapy was associated with statistically significant reductions in incidence of biopsy-confirmed acute rejection and a composite end-point comprising acute rejection, graft loss and death in both studies. The overall rates of the composite end-point at 6 months in the study in 576 patients were 30 ($p = 0.002$ *vs* placebo), 25.6 ($p < 0.001$) and 47.7% in the sirolimus 2 and 5 mg/day and placebo groups, respectively.[190] The frequencies of this end-point in the other study ($n = 719$)[189] were 18.7 ($p = 0.002$ *vs* azathioprine), 16.8 ($p < 0.001$) and 32.3% for sirolimus 2 and 5 mg/day and azathioprine, respectively. Patient and graft survival rates were similar for all treatment groups at 12 months in both studies (table XIV).

Corticosteroid Withdrawal

The elimination of corticosteroids from the immunosuppressive regimens of patients receiving concomitant cyclosporin microemulsion 3 to 10 mg/kg/day and mycophenolate mofetil 1.5 to 3 g/day appeared not to affect the rate of acute rejection of kidney transplants in a number of small ($n \leq 80$) randomised studies (one of which was double-blind and placebo-controlled[192]) with 6 to 9 months' follow-up.[192-194] Reported rates were 0

to 20% versus 0 to 10% with rapid steroid elimination compared with tapering.

However, larger placebo-controlled, double-blind studies have indicated an increase in risk of acute rejection when corticosteroids are withdrawn.[195,196] Patient enrolment was halted because of excess rejection in the corticosteroid withdrawal group in 266 recipients of *de novo* renal transplants.[195] Patients with no acute rejection 90 days after transplantation who were receiving cyclosporin microemulsion 5 to 15 mg/kg/day, mycophenolate mofetil ≥2 g/day and prednisone 10 to 15 mg/day were randomised to one of two prednisone regimens: tapering to 10 mg/day (maintenance) or prednisone withdrawal over 8 weeks. Cumulative 1-year incidences of rejection or treatment failure were 9.8 and 30.8% for the maintenance and withdrawal groups, respectively. Treatment differences in the distribution of time to event were significant ($p = 0.0007$). Notably, the risk of rejection or treatment failure was higher in Black (39.6%) than in non-Black patients (16%; $p < 0.001$). There were no statistically significant differences between groups in patient and graft survival.

A further double-blind, placebo-controlled study in 500 renal transplant recipients receiving cyclosporin (microemulsion in 447 patients) and mycophenolate mofetil plus corticosteroids compared maintenance of standard full-dosage corticosteroid therapy with a 50% taper over 12 weeks followed by complete withdrawal.[196] Rates of biopsy-proven acute rejection were 23 and 14% in the withdrawal and full dosage groups, respectively ($p = 0.008$) over 6 months, and 25 and 15% at 12 months. Overall, however, fewer than 3% of rejections were classified as severe, with no significant differences between groups in this respect, and there were significant reductions in corticosteroid-related adverse events in the withdrawal group. The authors concluded that early withdrawal of prophylactic corticosteroids is feasible, and does not carry an unacceptable increase in risk of severe rejection.

4.5.2 Liver Transplantation

Addition of Mycophenolate Mofetil

Clinical benefit of addition of mycophenolate mofetil to cyclosporine microemulsion plus corticosteroid-based immunosuppression has been shown in a nonblind study in 57 recipients of orthotopic liver transplants.[197] Of the participants, 28 were randomised to mycophenolate mofetil and 29 to azathioprine, both in combination with lymphocyte antibodies, cyclosporine microemulsion and methylprednisolone. After a median 10 months of follow-up, patient and graft survival were similar between groups, but the incidence of acute rejection was significantly lower with mycophenolate mofetil than with azathioprine (21.4 *vs* 44.8%; $p < 0.05$).

Corticosteroid Withdrawal

Corticosteroids were removed from the immunosuppressive regimen in recipients of liver transplants in two studies, with inconclusive results. In one study, 58 patients received cyclosporin microemulsion 600 mg/day or tacrolimus 6 mg/day plus mycophenolate mofetil 1 to 2 g/day; corticosteroids were eliminated from both regimens over 14 days from transplantation in both groups, and moderate acute rejection rates of 46 and 42% were noted over the following 6 months (table XII).[167] Patient and graft survival rates were high. In the other study, corticosteroids were withheld completely and the 64 patients received cyclosporin microemulsion 10 mg/kg/day or tacrolimus 0.1 mg/kg/day as monotherapy.[165] 65 and 66% of patients, respectively, had acute rejection episodes in the following 30 months (table XII).

5. Pharmacoeconomic Considerations

The pharmacoeconomic aspects of the use of cyclosporin microemulsion were examined in detail by Coukell and Plosker in 1998.[198] The studies available to these authors included patients with stable[199,200] or *de novo*[138,201] kidney or liver transplants[202-206] and were designed as cost-minimisation analyses, cost analyses or cost-consequence studies. Most compared the costs associated with use of the microemulsion with those

of the older oil-based formulation but did not link these to therapeutic outcomes. The studies were carried out from the perspective of the hospital, healthcare system or third party payer and therefore included direct healthcare costs only; indirect costs (e.g. lost productivity, etc.) were not accounted for. Most analyses included costs of hospitalisation, physician time and treatment and laboratory monitoring, but did not include the cost of cyclosporin. This was held to be of little consequence, however, as the acquisition costs of the two formulations were reported to be similar (in the US). Costs were not discounted; this was appropriate because of the short durations of the studies covered.

Overall, the studies reviewed at that time indicated the costs associated with the use of the microemulsion to be similar to those with the oil-based formulation in patients undergoing renal or hepatic transplantation (see Coukell and Plosker[198]). Several studies suggested cost savings with the microemulsion, but these observations did not attain statistical significance.

Since the last review of cyclosporin microemulsion in *Drugs*,[11] three further pharmacoeconomic studies of cyclosporin microemulsion have become available: one in renal[207] and two in liver transplantation.[208,209] One study[207] is a cost comparison between the oil-based and microemulsion formulations in patients with stable renal allografts, and one other[208] has been carried out to assess the potential for cost savings arising from elimination of the need for intravenous immunosuppressive therapy in liver transplant recipients. The other available study is a comparison with tacrolimus.[209]

5.1 Cost Comparisons with Cyclosporin Oil-Based Formulation

5.1.1 Renal Transplantation

Since the publication of the earlier studies, an analysis has been carried out in 181 French patients with stable existing renal allografts who were converted on a 1 : 1 dosage basis from treatment with the oil-based formulation of cyclosporin to the microemulsion.[207] Few details of the study design or methods used are available (abstract only), although this 6-month analysis appears to have been carried out from a healthcare provider's perspective. Costs accounted for and the year of costing were not stated, and sensitivity analyses did not appear to have been conducted. Overall, the microemulsion was associated with a monthly cost saving of $US52 per patient; this was extrapolated to a postulated total annual cost saving of $US6240 million (35 692 million French francs) for the French national healthcare system. Reasons for this saving were not stated, although the authors reported dosage reductions after 3 and 6 months' treatment with microemulsion.

5.1.2 Liver Transplantation

As previously reviewed,[198] prospectively gathered resource utilisation data from the MILTON study in 390 *de novo* liver transplant patients showed cost savings (healthcare system perspective) of 8 to 10% over the 4-month post-transplant period in patients receiving cyclosporin microemulsion relative to the oil-based formulation.[206] Absolute savings per patient (for Belgium, France and the UK) were not statistically significant, however. Overall, the greatest cost savings were achieved through a reduction in the time spent in hospital among microemulsion recipients; this was attributed partly to a more rapid discontinuation of intravenous cyclosporin in this group.

Intravenous cyclosporin therapy is required in the immediate postoperative period in patients undergoing liver transplantation who receive the original oil-based formulation of cyclosporin. This is because of the impairment of bile flow and GI motility, both of which affect the absorption of this formulation. The pharmacoeconomic implications of the use of the microemulsion in terms of reduced need for intravenous cyclosporin therapy has been explored further by investigators at a Canadian centre,[208] who identified an overall cost saving from the perspective of the transplant centre in patients receiving the newer formulation. This retrospective case control study compared 20 consecutive patients undergoing *de novo* liver transplantation with oral cyclosporin treatment (microemulsion) for induction of immunosuppression with a control

group of 21 individuals undergoing conventional induction with intravenous cyclosporin, with oral therapy (oil-based formulation) started from day 4 to 7.

Overall, healthcare utilisation was based on time in hospital and the cost of treatment of an acute rejection episode. Direct healthcare costs associated with in- and outpatient care (excluding physician fees) were included, with healthcare utilisation data being collected from patient charts and hospital records. The length of stay at specified care levels was recorded, and each level of care was assigned a per diem cost (previously evaluated by the centre's finance department). Hospital contract drug prices were used, and all patients were followed for 3 months. Although there was a nonsignificant trend towards reduced time in hospital in patients receiving the microemulsion, most savings were achieved through reductions in the cost of treatment of acute rejection. There were seven and 19 rejection episodes in the microemulsion and intravenous/oil-based formulation groups, respectively ($p < 0.05$), and decision tree analysis of the effect of reduced frequency of rejection showed a cost saving of 2162 Canadian dollars per patient (year of costing and statistical significance not stated). This result was robust when subjected to a sensitivity analysis.

Three other analyses of the use of cyclosporin emulsion in *de novo* liver transplantation suggested that the newer formulation was associated with cost savings.[202,204,210] Although few or no details of methods used were available at the time of the previous pharmacoeconomic review,[198] one of these studies[210] has since been published in full. Arumugam et al.[203] analysed the medical records of 66 children who underwent liver transplantation, of whom 22 received cyclosporin microemulsion and 44 the older formulation in the post-transplant period. Brief details only of methods were available: data collected included recuperation time in the intensive care unit, duration of intravenous cyclosporin therapy and duration of hospitalisation.

As shown in figure 4, there was a nonsignificant trend towards reduced mean time spent in intensive care (27%), and a statistically significant 40% reduction ($p < 0.001$ *vs* oil-based formulation) in mean time spent in hospital, in patients receiving the microemulsion. None of the patients in the microemulsion group required treatment with intravenous cyclosporin.[203] The overall excess cost associated with use of the oil-based formulation was $US3598 per patient ($p = 0.007$ between groups); this was calculated on the basis of the costs of a hospital room, infusion pump and extension tubing and intravenous administration of cyclosporin. Graft survival was similar in each group after 1 year, but the authors did not attempt to link this observation with cost data. Year of costing was not stated, and no sensitivity analyses appeared to have been carried out.

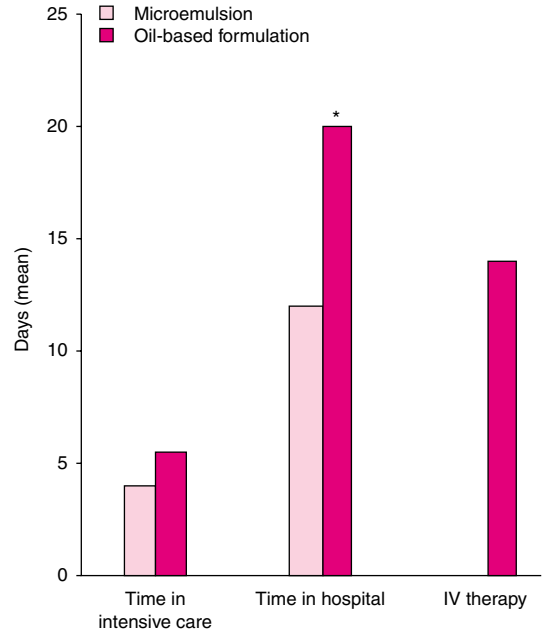

Fig. 4. Resource utilisation in liver transplant recipients receiving oral cyclosporin. Mean duration of stay in intensive care, overall duration of hospitalisation and days of intravenous (IV) cyclosporin therapy in children receiving *de novo* liver transplants.[203] Immunosuppression with cyclosporin in the post-transplant period was given as microemulsion (n = 22) or the original oil-based formulation (after IV therapy if required) [n = 44]. * $p < 0.001$ *vs* oil-based formulation.

5.2 Comparisons with Tacrolimus

Previously reported[198] data from a nonrandomised UK study carried out in 1996 and 1997 in 89 *de novo* renal transplant recipients showed similar 6-month direct healthcare costs for use of cyclosporin microemulsion (£13 216) and the macrolide immunosuppressant tacrolimus (£12 982) [year of costing not stated].[211] The cost of immunosuppression was considerably higher in the tacrolimus group, but patients receiving cyclosporin microemulsion had higher costs for intensive care stays and dialysis.

A further study,[209] based on a prospective randomised trial in 86 new liver transplant recipients, has shown the mean cost of cyclosporin microemulsion to be 22% lower than that of tacrolimus on the basis of dosages used over a 1-year follow-up period. The cost of the microemulsion was slightly greater than that of tacrolimus over the first 6 months ($US2851 *vs* $US2746; year of costing not stated), but was reduced over the subsequent 6 months ($US2030 *vs* $US2534). This change over the course of the study was attributed to improvements in the bioavailability of cyclosporin microemulsion, which was deemed to have been impaired in the early post-transplant period by cholestasis. Full details of costs and their derivation are not available for this study, however, which has been reported as an abstract only.

6. Tolerability

6.1 General Profile

The tolerability profile of cyclosporin is characterised by a number of potentially serious exposure-related adverse effects, including acute or chronic nephrotoxicity, hypertension and neurotoxicity.[11,119,212] Adverse effects associated with cyclosporin may be intensified by coadministered immunosuppressant drugs.[212] In the majority of clinical trials that evaluated the efficacy and tolerability of the microemulsion formulation of cyclosporin in the prevention of transplant rejection, patients received concomitant corticosteroid and azathioprine therapy. Most information on the tolerability of cyclosporin microemulsion in transplant recipients has been derived from studies that enrolled patients aged 18 years or over. The initial daily dosage of cyclosporin microemulsion was typically 10 mg/kg (administered in two divided doses).

The main dose-limiting adverse effect of cyclosporin is nephrotoxicity, which usually presents as a reversible decrease in glomerular filtration rate. Nephrotoxicity is reported to affect 25 to 37% of kidney, heart or liver transplant recipients being treated with cyclosporin and may progress to permanent renal dysfunction in up to 15% of patients.[212] Although the exact mechanism for the development of cyclosporin-related nephrotoxicity has yet to be established, it is known that the direct vasoconstrictive activity of cyclosporin on the renal circulation is involved in this process (section 2); alterations in endogenous vasoconstrictor and vasodilator mechanisms may be contributory factors.[213] Glomerular capillary thrombosis, progressing to graft failure in some patients, has also been reported in transplant recipients being treated with cyclosporin.[119]

Mild to moderate hypertension has been documented in up to 50% of renal transplant patients receiving treatment with cyclosporin[119] and has usually been managed effectively with antihypertensive drug therapy in clinical trials in transplant recipients. In controlled trials comparing cyclosporin microemulsion with the oil-based formulation in renal transplant recipients, hypertension was documented as an adverse event in less than 25% of patients treated with either formulation.[103,135,138,139,214-216] Hypertension was also reported in patients receiving treatment with cyclosporin microemulsion after primary liver transplantation[73,107,217,218] and developed in most cardiac transplant recipients treated with the microemulsion or oil-based formulation of cyclosporin in a large comparative trial (section 6.2.3).[147] Although sodium retention and renal dysfunction have been implicated in the initiation of cyclosporin-associated hypertension, neither of these factors was associated with the development of cyclosporin-related hypertension in 18 healthy adult volunteers who re-

ceived a single oral 10 mg/kg dose of cyclosporin microemulsion in a placebo-controlled trial.[213]

Neurological symptoms, including headaches, tremor, paraesthesia and convulsions, have also been frequently reported in transplant patients receiving cyclosporin therapy[212] (according to one official US source,[36] tremor has been reported in 12 to 21, 31 and 55% of patients receiving kidney, heart or liver transplants, respectively). Hypomagnesaemia, hypertension, high-dosage methylprednisolone therapy, nephrotoxicity and hypocholesterolaemia are among the many factors contributing to the development of convulsions in patients receiving cyclosporin treatment.[119]

Transplant patients (particularly those receiving liver allografts) treated with cyclosporin have been reported to exhibit signs and symptoms of neurotoxicity.[117,219,220] Seizures, confusion, disorientation, psychosis, ataxia and coma are among the many clinical features observed in affected patients, although it is not clear whether these are related to cyclosporin use or to the underlying clinical disorder.[117] Extrapontine myelinolysis and central pontine myelinolysis developed in five of 44 primary liver transplant recipients treated with cyclosporin in an investigation conducted in a Canadian transplant centre.[221] Extrapontine myelinolysis alone was identified in a further two patients. Neurological investigations were prompted by signs of impaired mentation in all seven patients and marked decreases in consciousness levels in five patients. Four patients showed substantial impairment of motor function, three had tonic-clonic seizures, one had severe ataxia and one had 'locked-in' syndrome.

Other potentially serious adverse effects associated with cyclosporin therapy include dosage-related hepatic dysfunction (predominantly cholestasis), hyperkalaemia, hyperuricaemia and hyperlipidaemia. Hirsutism, gingival hyperplasia, glucose intolerance and GI events are also commonly observed in patients receiving cyclosporin therapy, and were reported as adverse events in numerous trials that evaluated the efficacy and tolerability of cyclosporin microemulsion in the prevention of transplant rejection.[119,212]

6.2 Comparisons with the Oil-Based Formulation

A number of randomised double-blind or nonblind trials have compared the tolerability of cyclosporin microemulsion with that of the original oil-based formulation in recipients of renal[64,65,101,103,134-136,138,139,214-216,222-224] or liver transplants.[73,107-109,218] Numerous other noncomparative trials have reported data on the tolerability of cyclosporin microemulsion in stable renal,[91,93-96,98,99,225-230] liver[105,231] or heart transplant recipients[232,233] who were previously treated with the oil-based formulation. Data from these trials generally support the findings of previously reviewed early studies which showed that the original and microemulsion formulations have broadly similar tolerability profiles.

A meta-analysis of results of studies comparing the safety and tolerability of the microemulsion and oil-based formulations of cyclosporin found that the microemulsion was associated with a higher incidence of adverse events in blinded trials, whereas the original formulation was associated with a higher incidence of adverse events in nonblind trials.[234,235]

6.2.1 Renal Transplant Recipients

Evidence from a number of comparative double-blind or nonblind clinical trials, published as full papers, indicates that the increased bioavailability of cyclosporin and greater systemic exposure achieved with the microemulsion formulation does not result in an increase in incidence or severity of adverse events compared with the original formulation in stable renal transplant recipients, provided that the dosage of the microemulsion formulation is adjusted on the basis of target trough concentrations in whole blood.[64,65,101,103,134-136, 138,139,214-216,222-224] Similar findings were reported in most noncomparative trials that evaluated the tolerability of the microemulsion in stable renal transplant recipients previously treated with the oil-based formulation; in these trials, dosages of cyclosporin microemulsion required to produce therapeutic trough concentrations were typically lower than

those of the previously administered oil-based formulation (see section 7).[98,225-228,236]

Rates of treatment discontinuation did not differ significantly between the two groups across the studies reporting these data. In most comparative trials, there were no significant differences between the two formulations in the type, frequency or severity of documented adverse events. However, significantly fewer patients treated with the cyclosporin microemulsion [115 of 132 patients (87.1%)] than with oil-based formulation [124 of 130 (95.4%)] experienced adverse events in a randomised double-blind trial conducted over 1 year ($p = 0.03$).[214] Nevertheless, proportions of patients experiencing individual cyclosporin-related adverse events were similar in the cyclosporin microemulsion group and oil-based formulation group. Adverse event rates included headache: 17.4 *vs* 16.2%; hypertension: 14.4 *vs* 15.4%; increased serum cholesterol levels: 9.0 *vs* 10.0%; gingival hyperplasia: 8.3 *vs* 12.3%. Participants in this trial had received a renal transplant ≥6 months before enrolment and were stabilised on the oil-based formulation of cyclosporin.

Adverse events reported in a large randomised multicentre nonblind trial comparing the tolerability of cyclosporin microemulsion (n = 737) with the oil-based formulation (n = 356) in stable renal transplant recipients are shown in figure 5.[215]

Muscle weakness, oedema, epigastric pain, headache and hypertension were the most common events. No significant differences between the two treatment groups in the incidences of any of the adverse events shown in figure 5 were reported. In addition, during the 18-month duration of the trial, there were no significant between-group differences in liver function parameters, haematological values, serum levels of potassium, uric acid, triglycerides, or cholesterol.[215]

Episodes of worsening renal function (defined as ≥20% change in serum creatinine) occurred in 33.9 and 35.4% of patients in the microemulsion and oil-based formulation groups, respectively. In addition, the cyclosporin microemulsion-treated patients experienced a transiently higher increase in the incidence of cyclosporin-related nephrotoxicity than did the other group (12 *vs* 7%; $p = 0.008$) over the 18-month treatment period. Nevertheless, the renal function of the recipients of the microemulsion formulation was not adversely affected, despite the increased systemic cyclosporin exposure experienced by these patients compared with those treated with the oil-based formulation.[215]

Incidences of GI (26.9 *vs* 18.3%; $p < 0.05$) and neurological adverse events (21.7 *vs* 15.2%; $p < 0.05$) were also significantly higher in the cyclosporin microemulsion group than in the comparator group during the first month of treatment. There were no significant between-group differences in the incidences of these events at subsequent evaluation time-points.[215]

Adverse events described as serious were documented in 40.8% of patients who received the cyclosporin microemulsion formulation and in 40.4% of recipients of the oil-based formulation; the incidence of general cardiovascular adverse events was significantly higher in the recipients of the oil-based formulation than in the microemulsion group (4.1 *vs* 1.4%; $p = 0.003$).

6.2.2 Liver Transplant Recipients

In adults[107-109,218] or children[73] who had received orthotopic liver transplants, the types, frequency and severity of adverse events reported in patients treated with the microemulsion were generally similar to those reported in comparator groups who received treatment with the oil-based formulation in fully published randomised double-blind comparative trials. In individual trials, rates of treatment discontinuation did not differ significantly between the two treatment groups. Patients received concomitant corticosteroid and azathioprine therapy in all of these trials.

Most patients experienced adverse events in a large trial that compared cyclosporin microemulsion with the oil-based formulation in primary orthotopic liver transplantation.[107] Cyclosporin therapy was initiated within 24 hours of transplantation. The most common adverse events were infections, cardiovascular effects, hypertension, nervous system effects and renal failure (fig. 6).[107]

Markedly fewer recipients of the microemulsion formulation than of the oil-based formulation

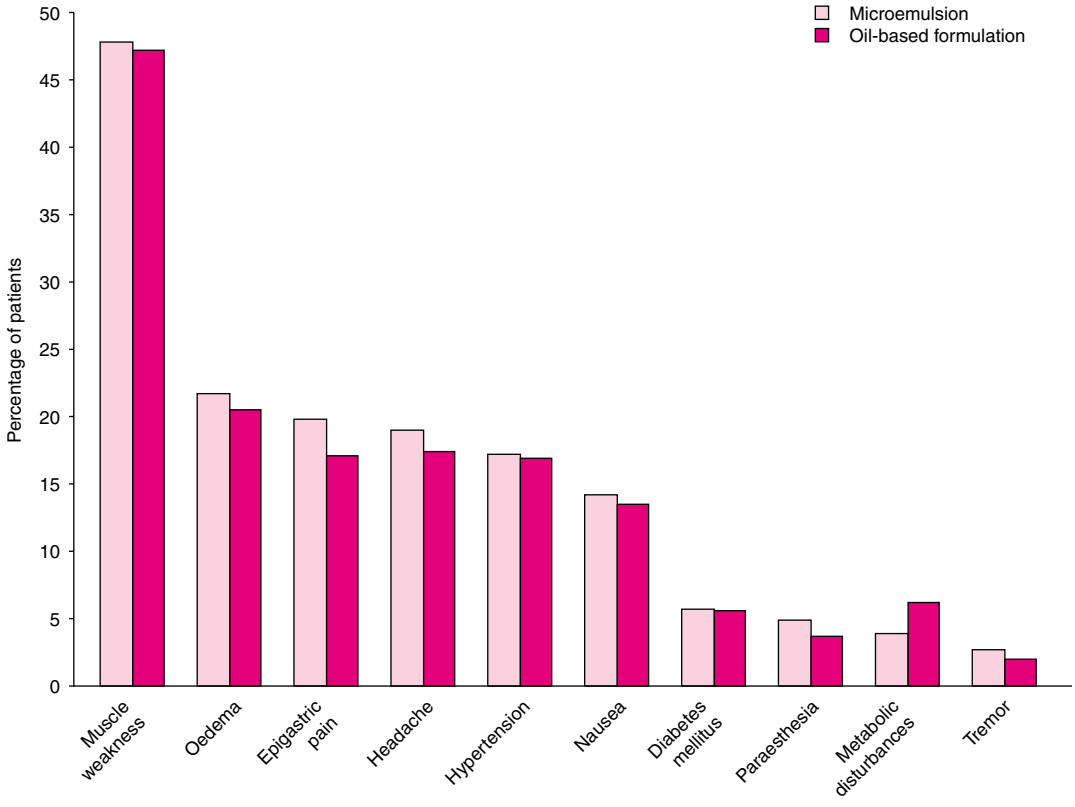

Fig. 5. Cyclosporin-related adverse events in stable renal transplant recipients treated with either cyclosporin microemulsion (mean ± SD dosage at study entry = 268 ± 100 mg/day, given in two divided daily doses; n = 737) or the oil-based cyclosporin formulation (mean ± SD dosage at study entry = 266 ± 104 mg/day; n = 356) for 18 months in a randomised, multicentre nonblind trial.[215] At enrolment, patients had 'acceptable graft function', which was defined as a serum creatinine level of <400 μmol/L (<4.4 mg/dl). Patients were aged ≥18 years and had been clinically stable for ≥3 months after receiving the living donor or cadaveric renal transplant; most patients were receiving concomitant treatment with prednisone and/or azathioprine.

experienced infections (72.2 *vs* 82.3%) or hepatitis (usually caused by hepatitis C virus) [11.6 *vs* 19.8%], but these differences did not attain statistical significance. Clinical diabetes mellitus, hirsutism and gum hyperplasia were documented in small numbers of patients in each treatment group. At least 20% of patients in each group were found to have abnormalities in biochemical and/or laboratory parameters. These included abnormal liver function tests, increased alkaline phosphatase levels and increased serum potassium levels.

All of the paediatric primary liver transplant recipients (mean age not reported) treated with either cyclosporin microemulsion (n = 17) or the oil-based formulation (n = 15) experienced adverse events in a small trial conducted over 12 months (NOF-11). However, the investigators reported that the drug was well tolerated overall.[73] Within 12 hours of receiving the transplant, patients were given intravenous cyclosporin (2 to 3 mg/kg/day) and were subsequently randomised to receive oral cyclosporin at a dose of about 5 mg/kg. Dosages of oral cyclosporin were adjusted thereafter to achieve target trough concentrations (e.g. 200 ± 50 μg/L during months 2 to 12), and each daily dose was divided into three rather than two in an attempt

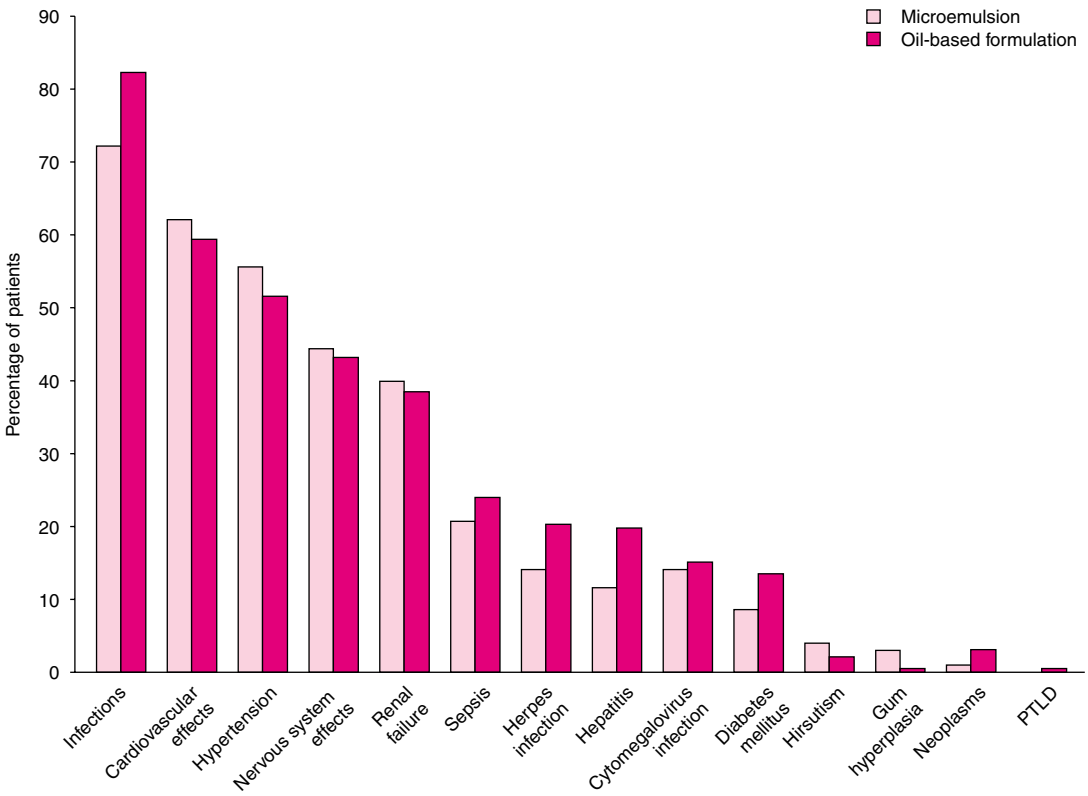

Fig. 6. Adverse events in primary orthotopic liver transplant recipients (aged ≥18 years) treated with cyclosporin microemulsion (median weight-adjusted daily dosage = 4.86 mg/kg) or the oil-based formulation (median weight-adjusted daily dosage = 5.42 mg/kg) for 52 weeks in a randomised, double-blind, multicentre trial.[107] Cyclosporin treatment was initiated within 24 hours of transplantation at a total daily dosage of 10 mg/kg/day (administered in two divided doses); all patients received concomitant treatment with a corticosteroid and azathioprine. **PTLD** = post-transplantational lymphoproliferative disorder.

to conserve renal function (see also sections 3.4.2 and 4.1.2). Reported incidences of adverse events in the microemulsion and standard formulation groups, respectively, were: diarrhoea (71 *vs* 80%), infection (59 *vs* 93%), hypertrichosis (82 *vs* 65%), vomiting (65 *vs* 53%), viral infection (35 *vs* 67%), anaemia (35 *vs* 67%), hypertension (35 *vs* 53%) and sepsis (35 *vs* 47%). No significant differences in the incidences of these adverse events were reported. Glomerular filtration rates were similar in the microemulsion and oil-based formulation groups at week 24 (5.28 *vs* 5.41 L/h/1.73m^2) and week 48 (5.36 *vs* 5.24 L/h/1.73m^2).

In a meta-analysis that included 4024 *de novo* liver transplant recipients treated with cyclosporin microemulsion and 3133 patients treated with the oil-based formulation, the incidence of adverse events was significantly ($p < 0.0001$) higher in recipients of the latter formulation.[217,237]

6.2.3 Heart Transplant Recipients

Data have also been reported on the tolerability of cyclosporin microemulsion compared with that of the standard formulation in patients who have received heart transplants.[147] Overall, the two formulations were equally well tolerated in a randomised double-blind trial in 380 *de novo* heart transplant recipients. However, there were differences in incidences of some individual adverse events. For example, compared with the standard formulation, patients treated with the microemul-

sion had a lower (not statistically significant) incidence of candidiasis (5.9 *vs* 10.9%), cytomegalovirus infections (10.1 *vs* 15.1%) and *de novo* diabetes mellitus (3.9 *vs* 8.5%). In contrast, incidences of gingival hyperplasia (3.2 *vs* 2.6%) and GI symptoms (81.9 *vs* 76.5%) were higher in the microemulsion treatment group than in the comparator group; these adverse events were transient and mild to moderate in severity. No significant changes from baseline in biochemical parameters or blood pressure were documented during the 2-year study period.[149]

6.3 Comparisons with Other Immunosuppressant Drugs

Information on the relative tolerability of cyclosporin microemulsion and other immunosuppressant drugs has been reported in several fully published comparative trials that enrolled recipients of renal or liver transplants.[152,157,238]

The tolerability profile of cyclosporin microemulsion was broadly similar to that of tacrolimus (both drugs were given in combination with a corticosteroid and azathioprine) in a randomised nonblind trial that enrolled cadaveric renal transplant recipients.[152] However, interim results of a larger trial in similar patients, also receiving concomitant corticosteroid and azathioprine therapy,[157] found significant differences in biochemical profiles of patients in the two treatment groups. Notably, after 12 months' treatment, median serum cholesterol and triglyceride levels had increased from baseline by 0.6 and 0.5 mmol/L, respectively, in the cyclosporin microemulsion group, whereas there was a gradual decrease from baseline in median triglyceride and cholesterol levels of 0.4 and 1.3 mmol/L in the tacrolimus group ($p < 0.05$ *vs* cyclosporin microemulsion).[157]

Serum urate levels increased from baseline in both treatment groups; however, at 12 months, the median urate level was significantly higher than baseline in the cyclosporin treatment group only. Diastolic blood pressure was significantly decreased in the tacrolimus treatment group and resulted in a significant reduction in the need for antihypertensive drug treatment, whereas diastolic blood pressure remained unchanged in the cyclosporin group and the use of antihypertensives did not decrease significantly.[157]

Notably, in the largest comparison to date in renal transplant recipients (n = 577; see section 4.2.1), the incidences of new-onset diabetes mellitus after 6 months' treatment were 4.5% in the tacrolimus group and 2% in patients receiving cyclosporin microemulsion (statistical significance not stated).[159] Mean serum creatinine levels were below 220 μmol/L (and were similar for both drugs) from the end of month 1 to the end of the study.

Cyclosporin microemulsion was associated with less neurotoxicity than tacrolimus in recipients of liver transplants in another trial reported as an abstract.[238] The incidence of severe speech impairment was significantly lower in the patients treated with cyclosporin microemulsion than in the tacrolimus treatment group (5.1 *vs* 24.1%; $p = 0.01$). Moreover, significantly fewer cyclosporin than tacrolimus recipients experienced neurological adverse events overall.

The adverse effect profile of cyclosporin microemulsion (n = 34) was similar to that of tacrolimus (n = 33) in recipients of heart transplants in a randomised trial.[239] Results of this trial have been published in an abstract and more detailed information on adverse events reported during treatment have not yet been reported. Therapy with cyclosporin microemulsion or tacrolimus was initiated after heart transplantation and dosages of each formulation were adjusted to achieve targeted drug concentrations.

The adverse event profile of cyclosporin microemulsion differed markedly from that of sirolimus in 83 cadaveric renal transplant recipients in a randomised multicentre nonblind trial.[175] Incidences of several laboratory abnormalities were significantly higher with sirolimus than with cyclosporin; these included hypertriglyceridaemia (51 *vs* 12%), hypercholesterolaemia (44 *vs* 14%), thrombocytopenia (37 *vs* 0%) and leucopenia (39 *vs* 14%). However, the incidence of hypertension was higher with cyclosporin than with sirolimus (33 *vs* 17%). In a randomised, nonblind study in 78

patients (see also section 4.3),[176] thrombocytopenia (45 *vs* 8%) and diarrhoea (38 *vs* 11%) were reported significantly more frequently with sirolimus than with cyclosporin microemulsion. Increased serum creatinine levels (18 *vs* 39%), hyperuricaemia (3 *vs* 18%), cytomegalovirus infection and tremor (both 5 *vs* 21%) were more frequent with cyclosporin.

6.4 Pregnancy

At present, there are no published well designed and controlled studies of the efficacy and tolerability of cyclosporin microemulsion in pregnant transplant recipients and their offspring. However, results of a retrospective analysis of 412 pregnancies in renal transplant recipients have been reported.[240] In this analysis, 13 of 412 pregnancies in 285 women who had undergone renal transplantation were in patients treated with either cyclosporin microemulsion (8 pregnancies) or the oil-based formulation and then the microemulsion (5 pregnancies) after transplantation.[240] Incidences of live birth were 75% in the cyclosporin microemulsion group and 80% in the oil-based formulation/microemulsion group; corresponding mean birthweights were 2481g (mean gestational age 36.3 weeks) and 2335g (mean gestational age 37 weeks), respectively, and were similar to results in the 392 pregnancies in women treated with the oil-based formulation of cyclosporin alone (mean birthweight 2465g, mean gestational age 35.9 weeks). Outcomes in the seven pregnancies in women treated with tacrolimus were slightly less favourable (live birth incidence 71%, birthweight 2211g, gestational age 32.8 weeks). No malformation trends of note were evident among the 175 children (mean age 4.4 years) of cyclosporin recipients who were available for long term assessment.[240]

Because cyclosporin is excreted in breast milk (section 3.3), the manufacturer advises caution in the use of the drug in breast-feeding recipients of cyclosporin microemulsion. Seven infants breast-fed by their cyclosporin-treated mothers [who were kidney transplant recipients (n = 5) or simultaneous kidney and pancreas transplant recipients] ingested less than 300 μg/day of cyclosporin and absorbed undetectable (limit of detection 30 μg/L) quantities of the drug.[241] The infants showed no signs of nephrotoxicity or other cyclosporin-associated adverse effects.

7. Dosage and Administration

Cyclosporin microemulsion is available in different countries variously as 10, 25, 50 and 100mg soft gelatin capsules, and as an oral solution containing 100 mg/ml. The oral solution may be made more palatable by diluting with orange or apple juice; after dilution, the resultant solution should be stirred well and the appropriate dose (measured using a syringe) taken at once. Dilution with milk is not advised as this mixture may be unpalatable. Blood cyclosporin concentrations increase when cyclosporin microemulsion is taken with grapefruit/grapefruit juice (see also section 3.6), which should therefore be avoided by patients taking the drug.[119]

Cyclosporin microemulsion is indicated for the prophylaxis of organ rejection in patients who have undergone renal, liver or heart allogeneic transplants.[119] Importantly, because cyclosporin is more bioavailable from the oral microemulsion than from the standard oral formulation, the two formulations cannot be interchanged without careful monitoring of the patient by a physician (see section 7.2). Cyclosporin microemulsion may be used in combination with corticosteroids and azathioprine.[119] Coadministration with anti–IL-2 receptor monoclonal antibodies, sirolimus or mycophenolate mofetil has also been studied in clinical trials (as discussed in section 4.5), although caution is recommended when using cyclosporin microemulsion in combination with other immunosuppressants because of the increased risk of overimmunosuppression, infection and lymphoma.[117]

In the prophylaxis of transplant rejection, cyclosporin microemulsion should be taken twice daily (in two equal doses). An optimal dosage of the drug will produce trough whole blood concentrations sufficient to achieve immunosuppression while preventing high peak blood concentrations and drug-related toxicity.[11] To avoid fluctuations in

plasma cyclosporin concentrations, it is recommended that the drug is administered in a consistent manner with regard to the time of administration and food intake. It is important that whole blood concentrations of cyclosporin are frequently measured, as lower than recommended therapeutic concentrations may result in rejection of the transplanted organ and higher concentrations are likely to produce drug-related toxicity. While there are no firm rules, and monitoring should be carried out whenever the need is clinically apparent, one source suggests monitoring from three to four times weekly to daily during the early post-transplantation period, with a reduction in frequency to once a month after 6 to 12 months.[36]

Renal function, liver function and blood pressure should be monitored closely in patients receiving treatment with cyclosporin microemulsion. In addition, levels of serum lipids, potassium and magnesium should be regularly checked during treatment with the drug.[119]

Although high doses of cyclosporin can result in increases in serum creatinine and blood urea nitrogen levels, changes in these biochemical parameters may also be characteristic of renal rejection episodes. To differentiate between overt cyclosporin-related nephrotoxicity and episodes of renal rejection, a full evaluation of the affected patient is advised before the dosage of cyclosporin microemulsion is adjusted. A number of clinical, laboratory, biopsy, cytology and radiological features may be used as an aid in differentiating between cyclosporin nephrotoxicity and rejection; the reader is referred to the manufacturer's prescribing information for a comprehensive list of these features. Notably, as many as 20% of patients treated with cyclosporin may experience simultaneous nephrotoxicity and renal transplant rejection.

7.1 *De Novo* Transplant Recipients

The first dose of cyclosporin microemulsion for *de novo* transplant recipients depends on the type of organ transplanted and on other immunosuppressive drugs included in the regimen. Initially, cyclosporin microemulsion may be administered either 4 to 12 hours before transplantation or postoperatively. According to the manufacturer's information, suggested initial dosages of the microemulsion formulation of cyclosporin are the same as those of the standard formulation. Initial mean dosages of the oil-based formulation (given in two equal divided daily doses) used in numerous hospitals in the US for adults were as follows:

- 9 ± 3 mg/kg/day for renal transplant recipients
- 8 ± 4 mg/kg/day for liver transplant recipients
- 7 ± 3 mg/kg/day for heart transplant recipients.

In randomised controlled trials discussed in section 4, initial dosages of cyclosporin emulsion typically ranged from 8 to 15 mg/kg/day, with 10 mg/kg/day being most commonly used. Dosages were adjusted thereafter to achieve target therapeutic trough concentrations in whole blood, and then further titrated according to assessments of transplant rejection and tolerability (see section 6). Maintenance dosages of cyclosporin emulsion may be lower than initial dosages of the drug.

In *de novo* kidney transplant recipients who participated in randomised controlled trials, dosages required to produce therapeutic cyclosporin concentrations were 8 to 16% lower in patients who received the cyclosporin microemulsion than in recipients of the oil-based formulation after 3 to 12 months of treatment (section 4.1.1). Differences in dosages were statistically significant at weeks 4 and 10 in a single 3-month trial.[136] Mean cyclosporin whole blood trough concentrations did not differ significantly between groups receiving the microemulsion or standard formulations at any time.[64,103,138,139]

Adjunctive corticosteroid treatment is recommended for patients receiving initial therapy with cyclosporin microemulsion. Various dosages of prednisone have been used and have shown similar efficacy. A representative regimen of prednisone is 2 mg/kg/day for 4 days, reduced to 1 mg/kg/day by the end of week 1, to 0.6 mg/kg/day by the end of 2 weeks, to 0.3 mg/kg/day by the end of 1 month and to 0.15 mg/kg/day by the end of 2 months, and continued at this dosage as maintenance therapy thereafter, although further dose adjustment may be necessary.[119]

7.2 Conversion from the Standard to the Microemulsion Formulation

Stable transplant recipients receiving the standard formulation of cyclosporin may have their therapy changed to the microemulsion formulation. In these patients, it is recommended that the initial dosage of cyclosporin microemulsion is the same as that of the previously administered standard cyclosporin formulation. Thereafter, the dose of cyclosporin microemulsion should be adjusted to produce a whole blood trough cyclosporin concentration the same as that achieved previously with the oil-based formulation. Of note, patients who show poor absorption of cyclosporin from the oil-based formulation may require an adjustment in dosage of the microemulsion after initial conversion.

Trough concentrations of cyclosporin should be measured every 4 to 7 days after conversion to the microemulsion formulation. Various clinical parameters, including serum creatinine levels and blood pressure, should also be closely monitored during the first 2 months of therapy.[119] In non-comparative clinical trials that evaluated the microemulsion in stable transplant recipients previously treated with the oil-based formulation, dosages of the microemulsion were typically lower than previous dosages of the original formulation.

7.3 Other Considerations

Cyclosporin interacts with a number of drugs (see section 3.6). In addition, information on the use of cyclosporin microemulsion in pregnancy is limited at present (section 6.4). Thus, the manufacturer recommends that the drug is not taken during pregnancy, unless the benefit to the patient outweighs the risk to the fetus.

Few clinical trials have evaluated the clinical efficacy and tolerability of cyclosporin microemulsion in paediatric patients, and dosage recommendations are therefore unavailable for this population. In a single controlled trial in paediatric recipients of liver transplants, patients received initial dosages of about 5 mg/kg/day.[73] Subsequently, dosages of oral cyclosporin were adjusted to produce target trough concentrations. According to prescribing information, no unusual adverse effects have been documented in children aged ≥1 year who have been treated with the drug for the prophylaxis of transplant rejection.[119]

8. Place of Cyclosporin Microemulsion in the Prevention of Organ Transplant Rejection

The original introduction of cyclosporin represented a major advance in transplant surgery, and markedly improved morbidity and mortality in patients undergoing organ transplantation. However, the oil-based formulation of the drug that was originally introduced was characterised by poor and variable bioavailability, and administered dosages could not be used to predict concentrations of the drug in blood, the probability of graft survival or the likelihood of nephrotoxicity. The microemulsion formulation was developed to address these problems and thereby improve clinical outcomes with this agent, which remains a standard therapy in the prevention of graft rejection.

As shown in section 3 of this review, extensive data, accumulated since the mid-1990s, are now available to show clearly the increased bioavailability of cyclosporin microemulsion relative to the original oil-based formulation. Data obtained in recipients of renal transplants (section 3.4.1) have shown this increase to be attributable predominantly to improved absorption in patients who absorb cyclosporin only poorly from the oil-based formulation. This, together with the reduced intra- and interpatient variability in absorption characteristics with the microemulsion, has led in many studies to reduced mean dosages (section 3.5). Interestingly, these pharmacokinetic changes have not resulted in clinically significant alterations in tolerability relative to the oil-based formulation, and the two can be considered to have similar tolerability profiles provided that therapeutic monitoring and dosage adjustments are carried out appropriately and as required (see section 6). In addition, drug interaction profiles appear unaffected to any significant extent by the widespread use of the microemulsion (section 3.6).

The enhanced bioavailability and pharmacokinetic predictability of the microemulsion relative to the older oil-based formulation has prompted renewed research into new methods of therapeutic monitoring in patients receiving cyclosporin (section 3.2). Monitoring of drug concentrations in whole blood during the absorption phase, with particular emphasis on abbreviated AUCs (AUC_4 or AUC_6) and predictions based on 2-hour blood sampling, has demonstrated the greatest potential to date for optimising therapy. Research in this area is ongoing, and although C_0 monitoring remains current practice in many centres, emerging data (section 3.2.2) suggest clinical advantages associated with C_2 monitoring that may lead to increasingly widespread adoption of this method.

The cyclosporin microemulsion (Neoral®) formulation is at least as effective as the oil-based (Sandimmun®) formulation in *de novo* renal, liver and heart transplant recipients. The incidence of biopsy-confirmed acute rejection and severe acute rejection tended to be lower in renal (section 4.1.1) and liver (section 4.1.2) transplant recipients, in several well designed trials, but there was no overall difference in patients undergoing heart transplantation (section 4.1.3). Graft and patient survival rates were similar for both formulations in all recipients. There is evidence of decreased dosage requirements with the microemulsion formulation in *de novo* patients. There is also good evidence that the rate of acute rejection in stable renal, liver and heart transplant recipients is not affected by conversion from cyclosporin Sandimmun® to the microemulsion formulation.

These results are of particular interest in liver transplantation. Because the oil-based formulation of cyclosporin is lipophilic in nature, oral absorption of this formulation is dependent on the availability of bile, which is compromised in patients receiving liver transplants. As discussed earlier in section 3.4, the microemulsion formulation has bioavailability advantages over the oil-based formulation and is less dependent on bile acids for absorption. The comparative effects of the microemulsion formulation on the incidence of and costs associated with drug monitoring to maintain therapeutic cyclosporin concentrations in these patients have yet to be confirmed. However, it is possible that the potential of the microemulsion for improving outcomes through the use of more clinically meaningful and predictive monitoring of cyclosporin therapy in all types of transplantation has not yet been realised (see section 3.2), and further work in this area is needed.

Similar efficacy of cyclosporin Neoral® and other novel cyclosporin formulations (SangCya®, Consupren® and Neoplanta®) has been indicated in renal transplant recipients (section 4.1.1). These conclusions are derived, however, from small and mainly nonblind studies, and it should be noted that concerns over bioequivalence have led to the withdrawal of cyclosporin SangCya® in the US.[242] Claims for bioequivalence of a further formulation (Gengraf®) are based on two small unpublished studies in healthy volunteers.[243]

Most trials comparing cyclosporin microemulsion with tacrolimus (including one nonblind comparison in more than 600 patients[169]) indicate that these drugs are equivalent in the prevention of biopsy-confirmed acute rejection and graft and patient survival rates in renal, pancreas-renal, liver and heart transplant recipients (section 4.2). However, there are indications of superiority of tacrolimus in some trials, particularly in the prevention of severe acute rejection and in Black transplant recipients, and in two large studies in renal[159] and liver[172] transplant recipients.

When comparing cyclosporin therapy with other immunosuppressive interventions, it is also necessary to consider the relative toxicities of the treatments under review. Tacrolimus therapy is associated with nephrotoxicity, neurotoxicity, disturbances in glucose metabolism, GI disturbance and hypertension.[244] The drug may also cause alopecia and pruritus in some patients. As discussed in section 6.3, cyclosporin was associated with less neurotoxicity and speech impairment than tacrolimus in one study in liver transplant recipients, but the tolerability profiles of the two drugs were similar in other studies. Changes in biochemical profiles (notably serum lipid levels) that differ from those seen in cyclosporin microemulsion recipi-

ents have also been noted in patients receiving tacrolimus, and further comparisons are needed to clarify fully the relative positions of these two agents. Of note is the difference in incidence of new-onset insulin-dependent diabetes mellitus seen in patients receiving cyclosporin microemulsion (2%) and those receiving tacrolimus (4.5%) in the largest (n = 577) comparison of the two agents available in renal transplant recipients (section 6.3).

In addition, available data suggest that cyclosporin microemulsion and sirolimus have equivalent efficacy in renal transplant recipients (section 4.3). Although a trend towards a lower frequency of acute rejection was noted in one study,[176] both available trials involved fewer than 100 patients, and data are limited to 12 months' follow-up. The pattern of adverse events differed between the two drugs in the comparative studies available (section 6.3), and further study is required to assess more fully the comparative efficacy and tolerability of cyclosporin microemulsion and sirolimus in a wider range of transplant types.

The addition of other immunosuppressant agents (e.g. mycophenolate mofetil and/or an anti–IL-2 receptor monoclonal antibody) to basal cyclosporin microemulsion therapy appears to decrease the rate of acute rejection and the necessity for antilymphocyte antibody treatment in recipients of renal transplants without affecting graft or patient survival rates (section 4.5). Mycophenolate mofetil has been shown to be superior to azathioprine in conjunction with cyclosporin and corticosteroids in patients undergoing kidney transplantation (see review by Bardsley-Elliot et al.[245]). However, mycophenolate mofetil is associated in particular with haematological toxicity and has a high acquisition cost relative to that of azathioprine. It is expected that the advantages and disadvantages of immunosuppression regimens that include these novel agents in addition to cyclosporin microemulsion will become fully apparent as clinical experience with such regimens increases.

The long term adverse effects of corticosteroids (for example diabetes mellitus, osteopenia, hypercholesterolaemia, skin fragility) are a tolerated disadvantage of these drugs. Recently, some success has been achieved in the total withdrawal of corticosteroids from renal transplant immunosuppressive regimens containing cyclosporin microemulsion and mycophenolate mofetil (and basiliximab in one trial), although increased risk of rejection after corticosteroid withdrawal has also been noted (section 4.5.1). Long term results in renal as well as other transplant recipients in whom corticosteroids have been eliminated are awaited with interest.

Pharmacoeconomic studies of cyclosporin microemulsion in patients undergoing solid organ transplantation continue to be limited to cost analyses carried out from the health provider's or third party payer's perspective, and to be restricted to direct costs of therapy (section 5). Cost-effectiveness studies, in which costs of therapy are expressed in terms of therapeutic outcomes (e.g. cost per acute rejection episode avoided), are currently not available. Although preliminary/brief details only are available for many studies, the replacement of the original oil-based formulation by the microemulsion has resulted in cost savings in kidney and liver transplantation. Cost comparisons with other agents are limited to two analyses of healthcare costs in patients receiving either cyclosporin microemulsion or tacrolimus (section 5.2): one showed equivalent costs with either drug, whereas the other indicated a mean cost saving with cyclosporin microemulsion.

It is to be expected that cyclosporin microemulsion will be compared increasingly in the future with newer immunosuppressants in patients undergoing organ transplantation. However, in contemporary healthcare systems, the allocation and use of resources attract ever-increasing scrutiny, and the recommendation or adoption of any agent depends not only on its efficacy and tolerability, but also on economic considerations. Thus, analyses are now required to show the wider cost implications of the use of the microemulsion formulation of cyclosporin relative to other treatments, particularly in terms of societal costs (i.e. indirect costs, such as those associated with reduced productivity) over the longer term.

In conclusion, the introduction of the microemulsion formulation has consolidated the place of cyclosporin as a mainstay of therapy in all types of solid organ transplantation; research into optimisation of outcomes through more effective therapeutic monitoring in patients receiving this formulation is ongoing. Several novel immunosuppressants have been introduced in recent years: further clinical and pharmacoeconomic research will be needed to clarify the relative positioning of these agents, particularly with respect to specific patient groups. Other new drugs (anti–IL-2 receptor monoclonal antibodies and mycophenolate mofetil) appear to offer particular advantages when used in combination with cyclosporin.

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