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Tacrolimus
In Heart Transplant Recipients

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Contents

Abstract

▲ Tacrolimus is a calcineurin inhibitor recently approved in the US and throughout the EU for the prevention of allograft rejection in heart transplant recipients. It is commonly administered orally for long-term immunosuppression.

▲ The incidence of mild to severe acute rejection in the first 6 months following heart transplantation was significantly lower in tacrolimus recipients than in ciclosporin recipients (54% vs 66%) in a large, phase III trial conducted in Europe.

▲ A large, phase III trial conducted in the US did not show a significant difference between tacrolimus and ciclosporin in the incidence of severe rejection or haemodynamic compromise rejection requiring treatment within the first 6 months post-transplant (22% vs 32%), but did show a significant difference in the incidence at 1 year (23% vs 37%).

▲ In phase III trials, 1-year patient survival was similar between tacrolimus and ciclosporin recipients in the EU (93% vs 92%) and the US (95% vs 90%).

▲ Tacrolimus was shown to be effective in the prevention of rejection in paediatric and African American heart transplant recipients.

▲ The tolerability profile of tacrolimus in heart transplant recipients was broadly similar to that of ciclosporin, although tacrolimus was usually associated with lower incidences of post-transplant hypertension and dyslipidaemia.

Features and properties of tacrolimus (FK506; Prograf®)	
Indication (focus of this profile)	
Prevention of allograft rejection in heart transplant recipients	
Mechanism of action	
Immunosuppression by inhibition of T-cell activation	
Dosage and administration	
Starting dosage in adults	0.075 mg/kg/day
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (single oral dose of 0.0375 mg/kg; mean values)	
Bioavailability	≈25%
Maximum whole blood concentration (C_{max})	15 ng/mL
Time to C_{max}	2.1h
Area under the whole blood concentration-time curve from time 0 to 12 hours	78 ng • h/mL
Elimination half-life	10.9h
Adverse events	
Most frequent, clinically relevant events	Infection, post-transplant hypertension, abnormal renal function, anaemia, dyslipidaemia, post-transplant diabetes mellitus, leukopenia, thrombocytopenia and tremor

Heart transplantation has become a standard treatment modality for end-stage heart disease, consisting predominantly of ischaemic and non-ischaemic cardiomyopathy in adults.[1] While cardiac allograft survival during the first 6 months has improved dramatically in recent decades, the survival of heart transplants beyond the first year continues to decrease at a linear rate of approximately 3.4% per year with a half-life of 9.6 years.[1] Allograft rejection and cardiac allograft vasculopathy remain major causes of graft failure.[1] Effective immunosuppressive therapy is crucial to cardiac allograft survival and the calcineurin inhibitor ciclosporin has been the mainstay of these immunosuppressive regimens for the past 20 years.

Tacrolimus (FK506; Prograf®)[1] is a calcineurin inhibitor, normally given orally during long-term administration, that has proven to be effective for primary immunosuppression in liver, kidney and lung transplantation and as rescue therapy for reversing acute rejection episodes refractory to ciclosporin.[2] Tacrolimus has recently become available in the US and throughout the EU for primary immunosuppression in heart transplant recipients.[3,4] It is also approved in the EU for the treatment of allograft rejection resistant to treatment with other immunosuppressants.[5] This review focuses on the use of oral tacrolimus as primary prophylaxis to prevent acute allograft rejection in heart transplant recipients.

1. Pharmacodynamic Profile

- Tacrolimus acts primarily by suppressing T-cell activation.[2,6,7] It binds to the intracellular protein FK506 binding protein-12 (FKBP-12), which forms a complex with calcium and calmodulin. This complex inhibits calcineurin, a serine-threonine phosphatase enzyme involved in the signal transduction pathway in T cells. Inhibition of calcineurin prevents translocation into the nucleus of the transcription factor NF-AT (nuclear factor of activated T cells), which is required for the production of interleukin (IL)-2 and other cytokines, thus inhibiting IL-2-mediated T-cell activation.[2,6,7]
- Ciclosporin and tacrolimus had similar inhibitory effects on type 1 T helper cell (T_h1) type cytokines (IL-2 and interferon-γ), inflammatory cytokines (IL-1β and tumour necrosis factor-α) and cytotoxic factors (granzyme B and perforin) that were found to be upregulated 5 days post-transplant in Lewis rats.[8] However, the drugs had different effects on T_h2 type cytokines (IL-4 and IL-10): IL-4 was increased by ciclosporin and unaffected by tacrolimus ($p < 0.05$), while IL-10 was suppressed to a significantly ($p < 0.05$) greater extent by tacrolimus than by ciclosporin.[8]
- Tacrolimus and ciclosporin microemulsion therapies for 18 months were shown to induce apoptosis of peripheral blood T cells in heart transplant patients (n = 18) to an equivalent extent and rate.[9]
- Tacrolimus has an established adverse-event profile (see section 4), which includes abnormal renal function, cardiovascular effects, impaired glucose metabolism, gastrointestinal disturbances and neurological disorders, but the mechanism for these effects is not known.[7,10]
- In heart transplant recipients treated with ciclosporin microemulsion, conversion to tacrolimus (n = 65) for 6 months resulted in a significantly greater mean reduction in total cholesterol levels than in patients remaining on ciclosporin therapy (n = 64) [−0.63 vs −0.23 mmol/L; $p < 0.01$], predominantly as a result of a reduction in low-density lipoprotein (LDL)-cholesterol (−0.43 vs −0.10 mmol/L; $p < 0.01$) without a significant change in high-density lipoprotein-cholesterol.[11] The reduction in apolipoprotein B at 6 months was also significantly greater with tacrolimus than with ciclosporin (−0.19 vs −0.07 g/L; $p < 0.001$), while the reduction in triglycerides was similar between groups (−0.45 vs −0.34 mmol/L).[11]
- Conversion from ciclosporin to tacrolimus in stable cardiac allograft recipients (n = 10) or because of adverse reactions to ciclosporin (n = 45) resulted in a significant ($p < 0.001$) mean reduction

1 The use of trade names is for product identification purposes only and does not imply endorsement.

in systolic/diastolic blood pressure of 10/8mm Hg at 8–12 weeks after conversion.[12] Total cholesterol levels also significantly ($p < 0.001$) improved in both the stable allograft patients (from 6.6 to 5.7 mmol/L) and those intolerant of ciclosporin (from 7.1 to 6.1 mmol/L). Serum creatinine levels did not change significantly following conversion.[12] The expression of transforming growth factor (TGF)-β_1 receptor on peripheral blood T cells and monocytes decreased significantly after conversion, suggesting a role for TGF-β_1 in these cardiovascular effects.[12]

- A prospective, randomised study in African American heart transplant recipients treated with tacrolimus (n = 20) or ciclosporin microemulsion (n = 22) demonstrated that at 1 year post-transplant, changes in total cholesterol (−0.88 vs +1.09 mmol/L; $p < 0.001$) and LDL-cholesterol (−0.36 vs +0.75 mmol/L; $p = 0.01$) levels significantly favoured tacrolimus recipients, despite similar use of statins (73% vs 78%).[13] There were no significant differences between groups in indices of hyperglycaemia or hypertension.[13]
- Increases in serum potassium levels observed during therapy with tacrolimus were found to significantly ($p = 0.03$) correlate with blood concentrations of tacrolimus, but the observed reductions in serum magnesium levels were not dose related.[14]
- A randomised study of 44 heart transplant recipients over 12 months post-transplant showed that, while epicardial endothelial function was similar in patients treated with tacrolimus or ciclosporin, tacrolimus was superior ($p < 0.05$) to ciclosporin with regard to microvascular endothelial function, intimal thickening and vascular remodelling.[15] Circulating levels of endothelin-1 decreased over 12 months in tacrolimus recipients, but increased in ciclosporin recipients (−25% vs +17%; $p < 0.05$).[15]

2. Pharmacokinetic Profile

The pharmacokinetic properties of orally administered tacrolimus in heart transplant recipients have been assessed in a number of clinical studies and are the focus of this section.[16-22] The pharmacokinetics of oral tacrolimus in healthy volunteers and in renal, liver and lung transplant recipients have been extensively reviewed elsewhere.[2,10]

- The absorption of tacrolimus from the gastrointestinal tract is highly variable and incomplete.[2,10] The mean oral bioavailability of tacrolimus is only about 25%; it is unpredictable and highly variable between individuals, ranging from 5% to 93%.[10] Tacrolimus is a substrate of P-glycoprotein, which pumps absorbed drug from intestinal cells back into the intestinal lumen.[10] Therefore, dosages of tacrolimus are commonly adjusted for each patient to maintain target trough blood concentrations (see section 5). Food decreases both the rate and extent of tacrolimus absorption.[5,7]
- The mean time (t_{max}) to reach the maximum whole blood concentration (C_{max}) of tacrolimus in heart transplant patients was approximately 2 hours (range 1.8–2.8 hours) after oral doses of usually 0.01–0.3 mg/kg/day in two divided doses 12 hours apart designed to attain target trough blood concentrations of usually 5–20 ng/mL.[16-20,22]
- In heart transplant recipients (n = 25) receiving the recommended starting oral dosage of 0.075 mg/kg/day (section 5), the mean C_{max} was 15 ng/mL following the first dose and 27 ng/mL at steady state.[18] Corresponding mean t_{max} values were 2.1 and 1.9 hours and mean values for the area under the blood concentration-time curve over the 12-hour dosage interval (AUC_{12}) were 78 and 186 ng • h/mL.[18]
- The mean apparent volume of distribution (Vd/F) of tacrolimus in heart transplant recipients after a single oral mean dose of 0.052 mg/kg was 2.0–2.4 L/kg.[17] Mean steady-state Vd/F values of 1.69 and 1.13 L/kg were estimated over the first 10 days and at 2 months post-transplant, respectively, in adult heart transplant recipients receiving a mean tacrolimus dosage of 0.1 mg/kg/day.[21] Tacrolimus is highly bound to erythrocytes and plasma protein binding may be as high as 99%.[2,10]
- Tacrolimus is extensively metabolised by cytochrome P450 (CYP) 3A isoenzymes, predominantly CYP3A4, mostly in the liver, but also in the intestinal wall.[2,10] Less than 0.5% of unchanged drug is

excreted in urine or faeces; >95% of tacrolimus metabolites are excreted by the biliary route.[2,10]

- The mean oral clearance of tacrolimus in adult heart transplant recipients has been variously estimated at 0.19–0.23 L/h/kg or 11.63 L/h.[17,20,21] One study found a significant inverse correlation between oral clearance and bodyweight.[21] The mean elimination half-life ($t_{1/2}$) of tacrolimus was 10.9 hours in heart transplant recipients after administration of the first dose of the recommended starting dosage of 0.075 mg/kg/day in two divided doses.[18] Estimates of $t_{1/2}$ have varied from 4 hours to 14 hours, with most in the 9–11 hours' range.[16-19,22]

- Paediatric transplant recipients generally require 2- to 4-fold higher weight-related doses of tacrolimus than adults in order to achieve similar trough drug concentrations, probably as a result of differences in the expression of particular CYP3A isoenzymes.[10] In addition, particular polymorphisms in the CYP3A5 gene or the multiple drug resistance gene *MDR1* that encodes P-glycoprotein were found to result in significantly ($p < 0.05$) lower blood concentrations of tacrolimus per dose/kg/day than in those without the polymorphisms.[23]

- African Americans appear to require higher absolute and weight-related doses of tacrolimus than Caucasians to achieve the same trough blood concentrations of tacrolimus.[24] African Americans achieved t_{max} later than Caucasians (6 vs 2 hours) and had higher C_{max} values (35 vs 28 ng/mL).[24]

- Since tacrolimus is a substrate of P-glycoprotein and CYP3A isoenzymes, pharmacokinetic drug interactions may occur with other drugs that interact with (induce or inhibit) these proteins.[2,7,10] Interactions may also occur with agents having high binding affinity for plasma proteins.[7]

- Coadministration of tacrolimus and the immunosuppressant mycophenolate mofetil (MMF) increases the bioavailability of the active metabolite of MMF, mycophenolic acid, presumably by inhibiting the glucuronidation of mycophenolic acid, an effect not seen with coadministration of ciclosporin and MMF.[25]

3. Therapeutic Efficacy

The immunosuppressive efficacy of tacrolimus has been extensively studied in patients undergoing heart transplantation, with much of the data being published in preliminary form as abstracts. Where possible, the source of information for this section has been restricted to fully published, randomised, controlled trials focusing on the the use of tacrolimus as primary immunosuppression,[26-33] rather than rescue or adjunct therapy.

Most studies have been conducted in adults (aged ≥18 years),[26-32,34,35] but the efficacy of tacrolimus has also been specifically assessed in paediatric heart transplant recipients.[33,36] The efficacy of tacrolimus in African American patients has also been studied.[35]

The efficacy of tacrolimus has been compared with that of conventional ciclosporin[30,32] and the microemulsion form of ciclosporin,[26,28,29,31,33,35] which has higher oral bioavailability and reportedly greater efficacy than conventional ciclosporin.[37] In addition to the primary immunosuppressive agents being assessed, trials also included adjunctive therapy with azathioprine,[26,27,29,30,32-34,38] MMF[28,31,35] or sirolimus,[31] usually together with corticosteroids.

In most studies, tacrolimus was administered orally at initial doses of 0.05–0.3 mg/kg/day in two divided doses, usually in overlap with antilymphocyte antibody induction therapy (antithymocyte globulin or muromonab-CD3), although in some studies tacrolimus was administered intravenously in the immediate post-operative period before switching to oral administration once normal gastric motility had resumed (after 1–2 days). The dosage of tacrolimus was adjusted to maintain target whole blood trough concentrations, normally 10–20 ng/mL in months 1–3, then 5–15 ng/mL from month 3 onwards. Similarly, ciclosporin dosages were adjusted to maintain whole blood trough concentrations of usually 200–400 ng/mL for the first 3 months, then 100–300 ng/mL. MMF and sirolimus dosages were adjusted to achieve target whole blood trough concentrations of 3–5 and 4–12 ng/mL, respectively, while azathioprine dosages were adjust-

ed according to the white cell count. Corticosteroid dosages were tapered over the first 4 weeks and often discontinued at 6 months, if possible.

The primary efficacy endpoint, where stated, was usually the time to and/or the incidence of first biopsy-proven acute rejection (BPAR) [or freedom from BPAR] during the first 3, 6, 12 or 24 months.[27-32,35] The definition of a rejection episode varied between studies, but was generally either an episode of International Society for Heart and Lung Transplantation (ISHLT)[39] severity grade 1B or greater (mild to severe), an episode of ISHLT grade 3A or greater (multifocal moderate to severe) or any episode requiring treatment.

Early Trials

- In initial noncomparative[34,38] or dose-finding[27] studies in heart transplant recipients (n = 72–122), patient survival rates of 93–98% (3 months)[27] or 90% (1 year)[38] were reported after immunosuppression with tacrolimus. Rates of freedom from BPAR at 3 months of 41–47% (ISHLT grade ≥3A)[34,38] or 57–66% (ISHLT grade ≥1B)[27] were observed. In two studies, 30%[34] and 48%[38] of patients were able to be weaned off all corticosteroids.
- Early, small (n = 82–85), randomised, comparative studies did not find any significant differences in efficacy between tacrolimus- and ciclosporin-based therapies for the primary prevention of acute allograft rejection in adult heart transplant recipients.[30,32]

Phase III Trials

- In contrast to earlier studies, two large, randomised, open-label, multicentre, phase III trials, one conducted in Europe[29] and the other in the US,[31] demonstrated that tacrolimus-based regimens were superior to ciclosporin-based regimens with regard to either the primary endpoint[29] or secondary endpoints.[31]
- In the European phase III study, tacrolimus at an initial oral dosage of 0.075 mg/kg/day (n = 157) and ciclosporin microemulsion at an initial dosage of 4–6 mg/kg/day (n = 157) were each combined with azathioprine and corticosteroids for 18 months.[29] The incidence of first BPAR (ISHLT grade ≥1B) within the first 6 months (primary endpoint) was significantly lower in tacrolimus recipients than in ciclosporin recipients (figure 1). Likewise, the incidence of BPAR of grade ≥3A was also significantly lower with tacrolimus, although the 1-year patient/allograft survival rate did not significantly differ between treatments.[29]
- The US phase III study compared tacrolimus (n = 108) at an initial dosage of 2–4 mg/day with ciclosporin microemulsion (n = 115) at an initial dosage of 3–5 mg/kg/day, each in combination with MMF (3 g/day). A third treatment arm consisting of tacrolimus in combination with sirolimus 6 mg/day initially, then 2 mg/day (n = 111) was also included.[31]
- Although there was no significant difference between groups for the primary endpoint of incidence of BPAR of ISHLT grade ≥3A or haemodynamic compromise rejection requiring treatment at 6 months, the incidence of rejection at 1 year was significantly ($p < 0.05$) lower with tacrolimus plus

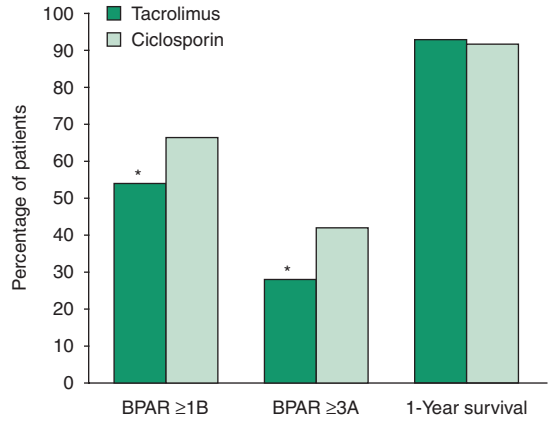

Fig. 1. Efficacy of tacrolimus compared with ciclosporin microemulsion in the primary prevention of graft rejection in adult heart transplant recipients. One-year patient/allograft survival and incidence within 6 months of first biopsy-proven acute rejection (BPAR) of International Society for Heart and Lung Transplantation severity grade ≥1B (primary endpoint) or ≥3A in patients treated with oral tacrolimus (n = 157) or oral ciclosporin (n = 157), both in combination with azathioprine and corticosteroids, in a randomised, open-label, multicentre, phase III study.[29] * $p < 0.05$ vs ciclosporin.

MMF than with ciclosporin plus MMF (figure 2).[31] The incidence of any treated rejection was lower with tacrolimus plus MMF (42.1%) and tacrolimus plus sirolimus (35.1%) than with ciclosporin plus MMF (59.6%), with the differences between the groups being significant ($p < 0.001$).[31]

Longer-Term Follow-Up

- A randomised, open-label, single-centre study in 60 adult heart transplant recipients found that freedom from acute rejection (BPAR grade ≥2 or ≥1B-treated) [primary endpoint] at 2 years using Kaplan-Meier analysis was significantly higher with tacrolimus plus MMF than with ciclosporin microemulsion plus MMF (0.75 vs 0.26 proportional probability [values estimated from a graph]; $p = 0.0001$).[28] In addition, the incidence of acute rejection episodes per 100 patient days was significantly lower with tacrolimus plus MMF (0.03 vs 0.15; $p < 0.0001$).[28]
- With respect to longer-term results, a randomised, single-centre study comparing tacrolimus (n = 33) with ciclosporin microemulsion (n = 34) found no significant differences in efficacy at 5 years between the two agents when both were given in combination with azathioprine and corticosteroids.[26] Values at 5 years with tacrolimus and ciclosporin were similar for patient survival (79% vs 71%), freedom from BPAR of grade ≥3A (76% vs 79%), any treated rejection (70% vs 68%) and freedom from cardiac allograft vasculopathy (54% vs 64%).[26] Circulating anti-HLA antibodies were detected during the first year of treatment in 37% of tacrolimus recipients and 59% of ciclosporin recipients ($p = 0.09$).
- A retrospective analysis of 273 adult heart transplant recipients followed for >5 years post-transplant, indicated that the rate of development of cardiac allograft vasculopathy, a major cause of long-term allograft failure, was significantly slower in patients treated with tacrolimus plus MMF ($p = 0.0002$) or tacrolimus plus azathioprine ($p = 0.005$) than in those receiving ciclosporin plus azathioprine.[40] The mean annual score of cardiac allograft vasculopathy over the follow-up period (≤8 years) was 0.22 for tacrolimus plus MMF recipients, compared with 0.45 for ciclosporin plus MMF recipients, 0.62 for tacrolimus plus azathioprine recipients and 1.93 for ciclosporin plus azathioprine recipients.[40]

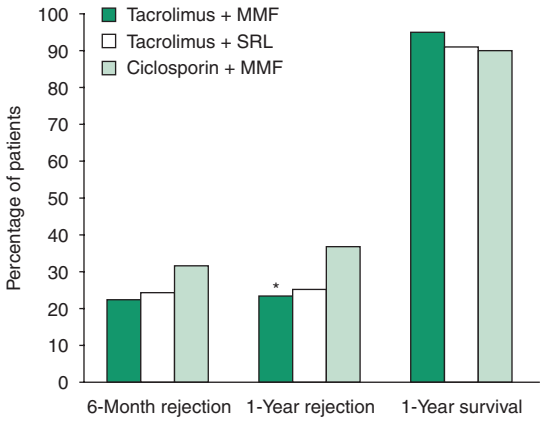

Fig. 2. Efficacy of oral tacrolimus in combination with mycophenolate mofetil (MMF) [n = 108] or sirolimus (SRL) [n = 111] compared with that of oral ciclosporin microemulsion plus MMF (n = 115) in adult heart transplant recipients. One-year patient/allograft survival and incidence of biopsy-proven acute rejection of International Society for Heart and Lung Transplantation severity grade ≥3A or haemodynamic compromise rejection requiring treatment within 6 months (primary endpoint) or 1 year in a randomised, open-label, multicentre, phase III study.[31] * $p < 0.05$ vs ciclosporin plus MMF.

Special Patient Populations

- The comparative efficacy of tacrolimus and ciclosporin microemulsion, both combined with azathioprine and prednisone, was assessed in paediatric patients (aged 0–19 years) in a small randomised, open-label trial, but deaths unrelated to allograft rejection (2 vs 5) and treatment crossovers (2 vs 4) meant that only 3 of 12 ciclosporin-randomised and 10 of 14 tacrolimus-randomised patients remained on their assigned treatment at 15 months.[33] Of these, one ciclosporin recipient and six tacrolimus recipients experienced BPAR of grade ≥3A in the first 3 months, although three patients initially randomised to ciclosporin switched to tacrolimus within the first 3 months after experiencing corticosteroid-resistant rejection.[33]
- An early, noncomparative clinical trial in 19 paediatric patients, aged 5 days to 17 years, under-

going heart transplantation found an actuarial freedom from rejection (ISHLT grade ≥3A) rate of 60% at 3, 6 and 9 months for tacrolimus combined with corticosteroids.[36] Patient survival was 89% (17/19) over a median follow-up of 304 days and the incidence of rejection at 3 months was 0.7 episodes per patient, with half of the episodes occurring in two patients.[36]

- Tacrolimus in combination with MMF and corticosteroids was shown to be equally effective in African American (n = 20) and Caucasian (n = 21) patients for primary immunosuppression following heart transplantation in a prospective, open-label study.[35] There were no significant differences between African Americans and Caucasians at 1 year for the rate of freedom from allograft rejection requiring treatment (64% vs 67%) [primary endpoint], the number of episodes per patient of acute allograft rejection requiring treatment (0.6 vs 0.5) or haemodynamic compromise rejection (0.33 vs 0.14), or the rate of patient/allograft survival (95% vs 95%).[35]
- In African American patients, tacrolimus (n = 20) was significantly more effective than ciclosporin microemulsion (n = 22) when both were combined with MMF and corticosteroids.[35] The rate of freedom from allograft rejection requiring treatment at 1 year was 37% with ciclosporin microemulsion compared with 64% for tacrolimus ($p = 0.01$). Compared with tacrolimus recipients, ciclosporin microemulsion recipients at 1 year had more episodes per patient of rejection requiring treatment (0.65 vs 1.3; $p = 0.01$) or rejection with haemodynamic compromise (0.35 vs 1.1; $p = 0.02$) and had a lower 1-year patient/allograft survival rate (95% vs 73%; $p = 0.04$).[35]

Health-Related Quality-of-Life Considerations

- In a randomised, open-label trial of heart transplant recipients, health-related quality-of-life (HR-QOL) scores assessed by the Medical Outcome Short Form (36 item) Health Survey (SF-36) questionnaire were numerically higher at 12 months post-transplant in all eight domains in patients treated with tacrolimus (n = 24) than in those treated with ciclosporin (n = 46).[41] Tacrolimus was superior ($p \leq 0.05$) to ciclosporin with respect to improvements in the 'mental health' and 'vitality' domains, as well as the combined 'mental component' score.[41]
- HR-QOL results for heart transplant recipients treated with tacrolimus plus corticosteroids (n = 24) were compared with those for an historical control group of patients treated with ciclosporin plus corticosteroids and azathioprine (n = 22).[42] At 7 months post-transplant, tacrolimus recipients were two to five times more likely than recipients of conventional therapy to have optimal quality for most HR-QOL measures over the physical well-being, psychological well-being and social well-being domains, although the incidence of any rejection episode was similar between tacrolimus and ciclosporin recipients (54.2% vs 59.1%).[42]

4. Tolerability

The tolerability of tacrolimus-based immunosuppression in heart transplant recipients has been assessed in a number of clinical trials,[26-35,38] several of which have compared tacrolimus with ciclosporin,[26,28-33,35] including two large phase III studies.[29,31]

- The most common, clinically relevant adverse events observed with tacrolimus in controlled clinical trials include abnormal renal function, post-transplant hypertension, infections, anaemia, dyslipidaemia, post-transplant diabetes mellitus or hyperglycaemia, leukopenia, tremor and thrombocytopenia (see figures 3 and 4).[7,29,31]
- In comparative studies, the incidence of most adverse events, including major infections and malignancies, was similar between tacrolimus and ciclosporin recipients.[29,31] However, tacrolimus has been reported to have a more favourable adverse-event profile than ciclosporin in most comparative studies. Several studies have found tacrolimus to be associated with a significantly ($p = 0.009$–0.05) lower incidence of post-transplant hypertension[29,32] or significantly ($p = 0.015$–0.05) lower use of antihypertensive medication[28,30,35] and significantly

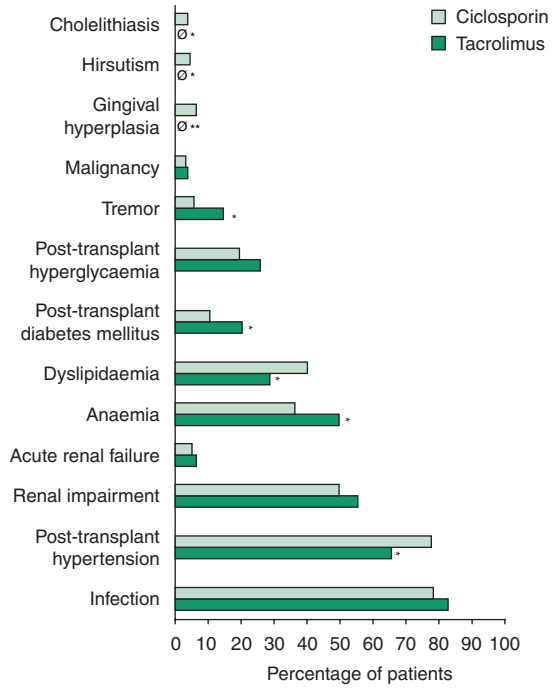

Fig. 3. Tolerability of tacrolimus compared with ciclosporin in adult heart transplant recipients. Most common, clinically relevant adverse events reported in a large, phase III trial conducted in Europe comparing immunosuppression for 18 months post-transplant with tacrolimus (n = 157) or ciclosporin (n = 157), both in combination with azathioprine and corticosteroids.[29] **Ø** = zero value; * $p < 0.05$, ** $p < 0.01$ vs ciclosporin.

($p = 0.001–0.05$) lower levels of serum lipid factions.[26,28,29,31,32,35] Gingival hyperplasia and hirsutism were notably lacking with tacrolimus.[28,29,31,33,34,38]

- The incidence of renal dysfunction associated with tacrolimus therapy in clinical trials was generally similar to that observed with ciclosporin.[28-30,32,35] However, the US phase III study found a significantly lower median serum creatinine level at 1 year in tacrolimus plus MMF recipients than in ciclosporin plus MMF recipients (1.3 vs 1.5 mg/dL; $p = 0.032$).[31] In another 5-year study, the mean serum creatinine level was also significantly lower in tacrolimus recipients than in ciclosporin recipients (1.2 vs 1.5 mg/dL; $p = 0.044$), although a similar number of patients in each group required dialysis.[26]

- In the US phase III trial comparing sirolimus with MMF as adjunctive therapy in combination with tacrolimus, 21.6% of tacrolimus plus sirolimus recipients discontinued their calcineurin inhibitor compared with 8.3% of tacrolimus plus MMF recipients and 21.7% of ciclosporin plus MMF recipients.[31] Renal dysfunction was the predominant reason for withdrawal of tacrolimus plus sirolimus. The proportions of patients discontinuing their calcineurin inhibitor because of renal dysfunction were 8.1% in the tacrolimus plus sirolimus group, 0.9% in the tacrolimus plus MMF group and 4.3% in the ciclosporin plus MMF group.[31] Compared with patients receiving ciclosporin plus MMF, tacrolimus plus sirolimus recipients also had higher incidences of wound healing complications (12% vs 23%; p =

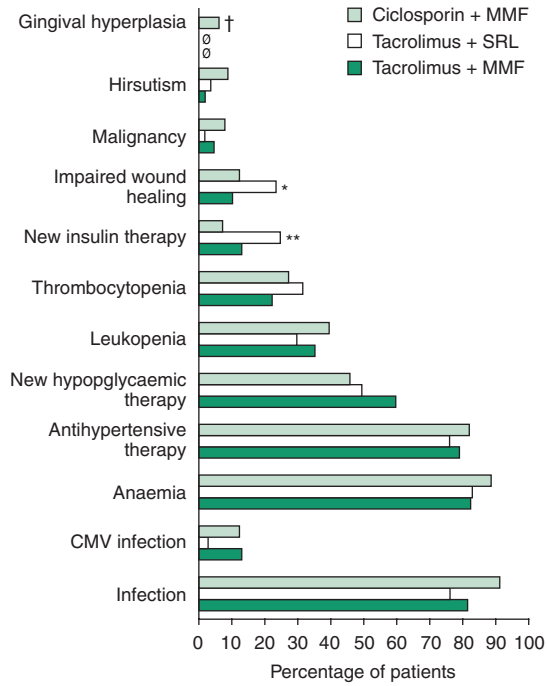

Fig. 4. Tolerability of tacrolimus compared with ciclosporin in adult heart transplant recipients. Most common, clinically relevant adverse events reported in a large, phase III trial conducted in the US comparing immunosuppression for 1 year post-transplant with tacrolimus plus mycophenolate mofetil (MMF) [n = 108], tacrolimus plus sirolimus (SRL) [n = 111] or ciclosporin plus MMF (n = 115).[31] **CMV** = cytomegalovirus; **Ø** = zero value; * $p < 0.05$, ** $p < 0.01$ vs ciclosporin plus MMF; † $p = 0.001$ vs tacrolimus plus MMF.

0.015) and new insulin therapy for >30 days in the first 12 months (7% vs 25%; p = 0.005).[31]

- A 7-year follow-up study in paediatric heart transplant patients receiving tacrolimus (n = 70) or ciclosporin (n = 53) demonstrated that all patients had a steady increase over time in serum creatinine levels.[43] Four patients progressed to end-stage renal failure and there was no difference between tacrolimus and ciclosporin with respect to decline in renal function.
- The European phase III study found a significantly higher incidence of post-transplant diabetes with tacrolimus compared with ciclosporin (figure 3).[29] By contrast, other studies found no significant differences between tacrolimus and ciclosporin recipients with respect to post-transplant diabetes or glucose intolerance,[26,28,30,32,35] including the US phase III trial (figure 4).[31] In the latter study, the incidences of hypoglycaemic therapy (60% vs 46%) and insulin therapy for >30 days in the 12 months following transplantation (13% vs 7%) in patients nondiabetic at baseline were numerically higher in tacrolimus plus MMF recipients than in ciclosporin plus MMF recipients (figure 4), but the differences did not reach statistical significance.[31]

5. Dosage and Administration

The usual recommended starting dosage of tacrolimus in adult heart transplant recipients is 0.075 mg/kg/day orally in two divided doses 12 hours apart, beginning ≥6 hours post-transplant.[5,7] If intravenous therapy is necessary, the recommended starting dosage is 0.01–0.02 mg/kg/day as a continuous 24-hour infusion.[5] Patients should be switched to oral therapy as soon as it can be tolerated, starting 8–12 hours after discontinuing the infusion.[5,7]

Since blood concentrations of tacrolimus are highly variable and unpredictable, especially at the start of therapy, blood concentrations should be monitored and the dosage individually adjusted to maintain target trough blood concentrations.[7] The usually recommended target whole blood trough concentrations of tacrolimus in heart transplant recipients are 15–20 ng/mL in the first 2 months, 10–15 ng/mL in months 3–6 and then 5–10 ng/mL after 6–9 months.[44] Capsules should be administered on an empty stomach (≥1 hour before or 2–3 hours after a meal) to achieve maximum absorption.[5]

Paediatric heart transplant recipients require higher dosages than adults to achieve target blood concentrations of tacrolimus. If initiated orally, following antilymphocyte antibody induction therapy, the recommended starting dosage is 0.1–0.3 mg/kg/day in two divided doses 12 hours apart.[5] If initiated intravenously in paediatric patients not receiving antibody induction therapy, the recommended dosage is 0.03–0.05 mg/kg/day as a continuous infusion, targeted to a trough whole blood tacrolimus concentration of 15–25 ng/mL. Upon switching to oral therapy, the recommended first oral dosage is 0.3 mg/kg/day.[5]

It is recommended that tacrolimus be used in combination with azathioprine or MMF.[7] Combination with sirolimus is not recommended,[7] since this combination has been associated with an increased risk of wound healing complications, renal dysfunction and post-transplant insulin-dependent diabetes.[31]

Local prescribing information should be consulted for detailed information, including warnings, contraindications, precautions, potential drug interactions and use in special patient populations.

6. Tacrolimus in Heart Transplant Recipients: Current Status

Tacrolimus was approved in March 2006 in the US for the primary prevention of organ rejection in adult and paediatric heart transplant recipients.[4] It had been previously approved for use in kidney or liver transplant recipients. In April 2006, the European Medicines Agency harmonised the Summary of Product Characteristics for tacrolimus, which had differed in various European countries, to approve its use for the prophylaxis of transplant rejection and the treatment of allograft rejection resistant to other immunosuppressants in adult and paediatric heart transplant recipients in all EU countries.[3]

Tacrolimus is also approved in Japan for the prevention of rejection in heart transplant recipients.

In clinical trials, tacrolimus was effective in preventing acute rejection episodes in adult and paediatric heart transplant recipients. Tacrolimus was superior to ciclosporin in reducing rejection episodes within the first 6 months in one phase III study and within the first year in a second phase III trial. The tolerability of tacrolimus was generally similar to that of ciclosporin. Although tacrolimus may possibly be associated with a higher incidence of post-transplant diabetes, it is associated with lower incidences of post-transplant hypertension and/or dyslipidaemia.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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