Tacrolimus

Section: 8. Immunomodulators and antineoplastics > 8.1. Immunomodulators for non-malignant disease

EMLc | Codes ATC: L04AD02

Indication	Failure or rejection of transplanted organs or tissues — Code ICD11: NE84
INN	Tacrolimus
Type de médicament	Chemical agent
Type de liste	Liste complémentaire
Formulations	**Parenteral > General injections > IV:** 5 mg per mL in 1 mL vial **Oral > Liquid:** 0.2 mg granules for oral suspension ; 1 mg granules for oral suspension **Oral > Solid:** 0.5 mg (immediate-release) ; 0.75 mg (immediate-release) ; 1 mg (immediate-release) ; 2 mg (immediate-release) ; 5 mg (immediate-release)
Historique des statuts LME	Ajouté pour la première fois en 2021 (TRS 1035)
Sexe	Tous
Âge	Aussi recommandé pour les enfants
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Patents have expired in most jurisdictions Lire la suite sur les brevets.
Wikipédia	Tacrolimus
DrugBank	Tacrolimus

Recommandation du comité d'experts

The Expert Committee noted the unmet public health need for prevention and treatment of rejection in organ transplantation. Tacrolimus has been studied for over 25 years as an immunosuppressant specifically focused on reducing graft rejection after transplantation. Originally studied in liver transplant patients, a series of trials has expanded its use to a wide range of other types of organ transplants. Tacrolimus has been in wide clinical use for many years and it is licensed for use in children and adults in several countries. The EML currently lists azathioprine and ciclosporin as immunomodulators for use in organ transplantation. The Committee acknowledged that the available evidence suggests that tacrolimus is superior to ciclosporin with regard to graft loss and acute rejection. Based on these considerations and the overall favourable efficacy and toxicity profile of tacrolimus, the Committee recommended the inclusion of immediate-release tacrolimus on the complementary list of the EML and EMLc for use in organ transplantation. The Committee recognized that as the indication is for organ transplantation, tacrolimus would only be used in settings where organ transplantation is available and affordable. The Committee also recognized that avoiding transplant rejection and graft loss is very important in these settings given the considerable resources invested in transplantation and the scarcity of donor organs. The Committee also noted that given its narrow therapeutic window, therapeutic drug monitoring of tacrolimus blood levels is important in the context of transplantation and recommended by most international guidelines. The Committee therefore requested that therapeutic drug monitoring for tacrolimus should be evaluated for inclusion in the next edition of the WHO model list of essential in vitro diagnostics.

Contexte

The calcineurin inhibitor tacrolimus has not been previously considered for individual listing on the Model Lists. However, in 1999 a square box symbol was added to the EML-listing of the calcineurin inhibitor ciclosporin for organ transplant rejection which indicated that tacrolimus could serve as an alternative to ciclosporin (1). Following a review of square box listings on the Model Lists in 2003, this square box was removed from the listing for ciclosporin (2). Ciclosporin was added to the EML in 1991 for use following organ transplantation. The Expert Committee recognized that immunosuppressant drugs were essential for use in organ transplant programmes, where such programmes exist (3). Ciclosporin was included on the first EMLc in 2007 (4).

Pertinence pour la santé publique

Optimal maintenance immunosuppression after organ transplant is important so that transplanted organs and transplant recipients can survive for the longest time possible. This is particularly important given the shortage of donor organs (5). According to Eurotransplant statistics, in 2019, 668 hearts, 1375 lungs, 1571 livers, 176 pancreases and 3191 kidneys were transplanted in Eurotransplant member countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands and Slovenia), with tens of thousands of people on an active waiting list (6). Transplantation is the best therapy for end-stage renal failure as it improves the patient's length and quality of life, encourages occupational rehabilitation and is more cost-effective than the alternative of dialysis (5,7). Chronic liver failure is the most common indication for liver transplantation (8). Other important indications are acute liver failure and hepatocellular carcinoma (8). The median survival after liver transplantation is more than 10 years (9,10), and there may also be an improvement in the quality of life of people with chronic liver disease after liver transplantation (11). Lung transplantation has become a treatment for many people with end-stage lung diseases. Currently, more than 2700 lung transplantations are reported annually worldwide, with a 1-year survival of over 80%, and 5-year survival of 60% (12). Achieving long-term survival after lung transplantation is still challenging because of the occurrence of bronchiolitis obliterans syndrome and late graft failure, which are responsible for more than 40% of deaths after the first year of transplantation (12). The therapeutic success of heart transplantation has been largely attributable to the development of effective and balanced immunosuppressive treatment regimens (13,14).

Bénéfices

Kidney transplantation A systematic review and meta-analysis of 21 studies compared immunosuppression with tacrolimus and ciclosporin in adults (15). Tacrolimus was significantly superior to ciclosporin for graft loss (relative risk (RR) 0.09, 95% confidence interval (CI) 0.06 to 0.12), acute rejection (RR 0.64, 95% CI 0.57 to 0.71) and hypercholesterolaemia (RR 0.63, 95% CI 0.54 to 0.75). No significant differences were observed between treatment groups for mortality (RR 1.07, 95% CI 0.79 to 1.45), hypertension (RR 0.96, 95% CI 0.85 to 1.08) or the frequency and type of infections (RR 1.05, 95% CI 0.92 to 1.94). An increased but non-significant risk of diabetes was seen in the tacrolimus group compared with the ciclosporin group (RR 1.89, 95% CI 1.52 to 2.35). A systematic review and meta-analysis of 10 studies (2357 patients) compared immunosuppression with tacrolimus combined with sirolimus and tacrolimus combined with mycophenolate mofetil in adults (16). The authors concluded that the two treatment combinations were equally safe and effective. No significant differences were seen between treatment groups in the rates of delayed graft function, acute rejection, graft survival, infectious complications, anaemia or seroma. The tacrolimus + sirolimus group was associated with higher rates of diabetes, hyperlipidaemia and lymphocele compared to the tacrolimus + mycophenolate mofetil group. A systematic review of 21 studies made an indirect comparison of the clinical effectiveness of tacrolimus and belatacept in adults (17). The authors concluded that both immediate- and prolonged-release tacrolimus were significantly superior to belatacept for acute rejection (RR 0.22, 95% CI 0.13 to 0.39 and RR 0.44, 95% CI 0.20 to 0.99, respectively). The two treatments were comparable for graft and patient survival. A systematic review and network meta-analysis of 28 studies compared immunosuppressive efficacy of belatacept, ciclosporin and tacrolimus (18). Belatacept was associated with significant improvement in glomerular filtration rate compared with ciclosporin. Compared with tacrolimus, this difference was clinically meaningful but not statistically significant. The probability of being the

best treatment was highest for belatacept for graft survival (68%), patient survival (97%) and renal function (89%). Tacrolimus was the immunosuppressive agent with the highest probability of being best for avoiding episodes of acute rejection (99%). Donor, recipient and trial characteristics varied across the included trials; however, little statistical heterogeneity was detected in the analysis of acute rejection, graft or patient survival, and none of the characteristics was significantly associated with the relative effect. Glomerular filtration rate in patients treated with tacrolimus was also significantly higher than in patients treated with ciclosporin (6.03 mL/min per 1.73 m2; 95% credible interval (CrI): 1.60 to 11.00). Belatacept had significantly higher odds of acute rejection than tacrolimus (OR 2.50, 95% CrI 1.21 to 4.81). Tacrolimus had the highest probability of being best for avoiding episodes of acute rejection (18). A systematic review of five studies compared immunosuppression with tacrolimus and ciclosporin in children (19). No significant differences were seen between treatment groups for mortality rate (RR 1.06, 95% CI 0.59 to 1.90), graft loss (RR 0.67, 95% CI 0.40 to 1.11) or acute rejection (RR 0.79, 95% CI 0.59 to 1.05). The authors concluded that tacrolimus was as effective as ciclosporin for the outcomes of graft loss and acute rejection. However, this systematic review was considered to be of poor methodological quality by the applicants. A systematic review of eight studies (1189 participants, age not reported) compared immunosuppression with tacrolimus and sirolimus (20). Pooled results did not show statistically significant differences between treatment groups for mortality (RR 0.94, 95% CI 0.46 to 1.91) or graft loss (RR 1.23, 95% CI 0.76 to 1.97). Significantly more patients treated with sirolimus experienced acute rejection (RR 2.08, 95% CI 1.47 to 2.95). The risk of infection was significantly lower with sirolimus (RR 0.43, 95% CI 0.26 to 0.72). Patients treated with sirolimus were significantly more likely to be withdrawn from treatment because of adverse events (RR 1.93, 95% CI 1.32 to 2.83) than patients treated with tacrolimus. A Cochrane systematic review of 30 studies (4102 participants) compared immunosuppression with tacrolimus and ciclosporin in adults and children (21). At 6 months, the risk of graft loss was significantly lower in patients treated with tacrolimus (RR 0.56, 95% CI 0.36 to 0.86) and this effect persisted up to 3 years. At 1 year, tacrolimus patients had a lower risk of acute rejection (RR 0.69, 95% CI 0.60 to 0.79) and steroid-resistant rejection (RR 0.49, 95% CI 0.37 to 0.64), but more diabetes mellitus requiring insulin (RR 1.86, 95% CI 1.11 to 3.09), and tremor (RR 2.18, 95% CI 1.50 to 3.17), headache (RR 1.23, 95% CI 1.00 to 1.52), diarrhoea (RR 1.98, 95% CI 1.03 to 3.83), dyspepsia (RR 1.31, 95% CI 1.00 to 1.70) and vomiting (RR1.41, 95% CI 1.05 to 1.89). Patients treated with ciclosporin experienced significantly more constipation and cosmetic side-effects. There was no difference in infection or malignancy between patients treated with tacrolimus or ciclosporin. Compared with ciclosporin, recipients of kidney transplants treated with tacrolimus showed substantial improvement in graft survival, with a 44% reduction in graft loss (censored for death) within the first 6 months of transplantation. Treatment with tacrolimus led to 31% fewer patients experiencing acute rejection and 51% fewer experiencing severe rejection episodes that required more intensive therapy than steroids, within the first year of transplantation. Liver transplantation A Cochrane systematic review of 23 trials (3693 participants) evaluated the benefits and harms of maintenance immunosuppression interventions in adults with liver transplants (22). The pair-wise meta-analysis of ciclosporin and tacrolimus showed that ciclosporin was associated with more retransplantation than tacrolimus (very low quality evidence, hazard ratio (HR) 3.08, 95% CrI 1.13 to 9.90). Low-quality evidence from direct comparison of ciclosporin and tacrolimus showed similar results (HR 3.07, 95% CrI 1.12 to 8.38). The combination of tacrolimus and sirolimus showed higher mortality and graft loss (HR 2.76, 95% CrI 1.30 to 6.69 and HR 2.34, 95% CrI 1.28 to 4.61, respectively) compared with tacrolimus alone. However, this finding was from a direct comparison in a single trial including 222 participants (low-certainty evidence). No differences were found between the two treatments based on network meta-analysis results (very low-certainty evidence). A systematic review of 11 trials compared tacrolimus versus ciclosporin as primary immunosuppression in adults with liver transplants (23). Mortality in patients given ciclosporin was significantly higher than in patients treated with tacrolimus (RR 1.26, 95% CI 1.01 to 1.58) as was the risk of hypertension (RR 1.26, 95% CI 1.07, 1.47). Ciclosporin was associated with a lower risk than tacrolimus of developing new-onset diabetes after transplantation (RR 0.60, 95% CI 0.47 to 0.77). No significant differences were found for graft loss or acute rejection. These findings are consistent with the findings of an earlier systematic review and meta-analysis of 16 randomized trials comparing tacrolimus and ciclosporin (3813 participants) (24). Most of the trials restricted enrolment to adults, but one included children and one was restricted to children. At 1 year, mortality (RR 0.85, 95% CI 0.73 to 0.99) and graft loss (RR 0.73, 95% CI 0.61 to 0.86) were significantly lower in patients treated with tacrolimus. Patients treated with tacrolimus also had a lower

risk of acute rejection (RR 0.81, 95% CI 0.75 to 0.88) and steroid-resistant rejection (RR 0.54, 95% CI 0.47 to 0.74) in the first year. No differences were seen with lymphoproliferative disorder or new dialysis rates, but more new insulin-requiring diabetes mellitus occurred in the tacrolimus group (RR 1.38, 95% CI 1.01 to 1.86). The risk of withdrawal from the drug was lower for tacrolimus than ciclosporin (RR 0.57, 95% CI 0.49 to 0.66). A systematic review and meta-analysis of 14 studies (1814 participants) evaluated the efficacy of immunosuppression monotherapy in adults (25). Tacrolimus and ciclosporin monotherapy were found to be as effective as immunosuppression with steroid-based combination therapy and associated with fewer complications. Tacrolimus monotherapy did not increase hepatitis C virus infection recurrence in hepatitis C virus-infected liver transplant recipients. Lung transplantation A Cochrane systematic review of three studies (413 participants) compared tacrolimus with ciclosporin for primary immunosuppression in adult patients with lung transplant (26). No significant differences were seen between treatment groups for mortality (RR 1.06, 95% CI 0.75 to 1.49), incidence of acute rejection (RR 0.89, 95% CI 0.77 to 1.03), number of infections/100 patient-days (mean difference (MD) –0.15, 95% CI –0.30 to 0.00), cancer (RR 0.21, 95% CI 0.04 to 1.16), kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), kidney failure (RR 1.57, 95% CI 0.28 to 8.94), neurotoxicity (RR 7.06, 95% CI 0.37 to 135.19) and hyperlipidaemia (RR 0.60, 95% CI 0.30 to 1.20). Tacrolimus was significantly superior to ciclosporin regarding the incidence of bronchiolitis obliterans syndrome (RR 0.46, 95% CI 0.29 to 0.74), lymphocytic bronchitis score (MD –0.60, 95% CI –1.04 to –0.16), treatment withdrawal (RR 0.27, 95% CI 0.16 to 0.46) and arterial hypertension (RR 0.67, 95% CI 0.50 to 0.89). No significant difference was seen for arterial hypertension when analysed using a random-effects model (RR 0.54, 95% CI 0.17 to 1.73). Diabetes mellitus occurred more frequently in patients receiving tacrolimus than those receiving ciclosporin when the fixed-effect model was applied (RR 4.24, 95% CI 1.58 to 11.40), but no statistically significant difference was found using the random-effects model (RR 4.43, 95% CI 0.75 to 26.05). The included studies were considered to have a high risk of bias. A systematic review of three studies (297 participants) evaluated the benefits and harms of tacrolimus versus ciclosporin as primary immunosuppression in adults (27). No significant difference was found in 1-year mortality between treatment groups (odds ratio (OR) 0.94; 95% CI 0.42 to 2.10). Patients treated with tacrolimus had fewer incidences of acute rejection (MD –0.14, 95% CI –0.28 to –0.01). Pooled analysis showed a lower risk of bronchiolitis obliterans syndrome in the tacrolimus group, although this was not statistically significant (OR 0.53, 95% CI 0.25 to 1.12). Fewer treatment withdrawals were seen in the tacrolimus group (OR 0.12, 95% CI 0.03 to 0.48). The likelihood of new-onset diabetes was higher in the tacrolimus group (OR 3.69, 95% CI 1.17 to 11.62). The incidence of hypertension and renal dysfunction were comparable between tacrolimus and ciclosporin (OR 0.24, 95% CI 0.03 to 1.70 and OR 1.67, 95% CI 0.70 to 3.96, respectively). The point estimate suggested a lower risk of malignancy in patients treated with tacrolimus, although this was not statistically significant (OR 0.19, 95% CI 0.03 to 1.13). The incidence of infection was comparable between the two treatments (MD –0.29, 95% CI –0.68 to 0.11). Heart transplantation A systematic review and meta-analysis of 11 studies (952 participants) evaluated primary immunosuppression with tacrolimus versus ciclosporin in adults and paediatric patients with heart transplant (28). No significant differences were found between the treatments for mortality (RR 0.78, 95% CI 0.54 to 1.13), grade 3A or higher rejection (RR 0.86, 95% CI 0.62 to 1.20), infection (RR 1.01, 95% CI 0.84 to 1.21) or basal cell skin cancer (comparison with microemulsion ciclosporin) (RR 1.20, 95% CI 0.29 to 4.93). Patients treated with tacrolimus had significantly lower risk of hypertension (RR 0.80, 95% CI 0.69 to 0.93), hyperlipidaemia (RR 0.57, 95% CI 0.44 to 0.74) and hirsutism (comparison with microemulsion ciclosporin; RR 0.17, 95% CI 0.04 to 0.62). The risk of diabetes was higher in patients treated with tacrolimus but this was not statistically significant (RR 1.35, 95% CI 0.93 to 1.94). In addition, no significant differences were seen between treatment arms for renal failure requiring haemodialysis, chronic allograft vasculopathy or neurotoxicity. A systematic review and meta-analysis of seven studies (885 participants) compared the benefits and harms of tacrolimus and microemulsion ciclosporin for primary immunosuppression in adults and children (29). No statistically significant difference was found in mortality at 1 year between treatment groups (RR 0.70, 95% CI 0.45 to 1.08). Tacrolimus was associated with significantly lower risks of acute rejection at both 6 months and 1 year (RR 0.61; 95% CI 0.49 to 0.75 and RR 0.69, 95% CI 0.48 to 0.98, respectively). Fewer patients taking tacrolimus than microemulsion ciclosporin stopped treatment (RR 0.57, 95% CI 0.40 to 0.83) and experienced post-transplant hypertension (RR 0.88, 95% CI 0.81 to 0.96). The rate of new-onset diabetes mellitus requiring insulin treatment was higher with tacrolimus using a

fixed-effects model (RR 1.65, 95% CI 1.18 to 2.29), however no difference was found using a random-effects model. The incidence of malignancy and renal failure requiring dialysis were comparable between treatment groups.

Torts

The most frequently reported adverse effects of tacrolimus include new-onset diabetes mellitus following transplantation, neurological effects, gastrointestinal complications (nausea, vomiting, diarrhoea and dyspepsia), changes in renal function, cardiotoxicity, tremor, headache and hyperkalaemia. A systematic review of 54 studies evaluated the reported incidence of new-onset diabetes mellitus in adult solid-organ transplant recipients receiving treatment with calcineurin inhibitors (tacrolimus and ciclosporin) (30). Overall, new-onset diabetes mellitus was reported in 13.4% of transplant recipients, with a higher incidence occurring in patients receiving tacrolimus than ciclosporin (16.6% versus 9.8%). The trend was observed across all transplant groups studied. The results of a meta-analysis of 16 studies found the frequency of insulin-dependent diabetes mellitus to be significantly higher in patients treated with tacrolimus (10.4% versus 4.5%; $P < 0.001$). A systematic review of 10 studies (2357 participants) found that sirolimus combined with tacrolimus may lead to higher rates of diabetes, hyperlipidaemia and lymphocele compared with a combination of tacrolimus and mycophenolate mofetil (16). This is in line with the results of a three-arm, multicentre randomized controlled trial that showed a trend toward less diabetes in the steroid-free group containing daclizumab induction, tacrolimus and mycophenolate mofetil (31). When treatment based on ciclosporin plus azathioprine was compared with tacrolimus plus mycophenolate mofetil, no significant difference was seen in the incidence of diabetes after transplantation (32). Tacrolimus in combination with 2 g/day mycophenolate mofetil showed the lowest incidence of new diabetes mellitus compared with tacrolimus and azathioprine or 1 mg/day mycophenolate mofetil (33). Similar results were found in a randomized trial of 538 adult renal transplant patients which reported a significantly lower incidence of insulin-dependent diabetes if treatment was based on the combination of daclizumab, tacrolimus and mycophenolate mofetil (5.4% versus 0.4%; $P = 0.003$) (34). Gastrointestinal complications were more likely in patients treated with tacrolimus than those treated with ciclosporin; however, patients given tacrolimus were less likely to experience viral infections and hypertension (35). No differences have been seen between tacrolimus and ciclosporin for kidney dysfunction (RR 1.41, 95% CI 0.93 to 2.14), kidney failure (RR 1.57, 95% CI 0.28 to 8.94) or kidney failure requiring haemodialysis (RR 1.45; 95% CI 0.50–4.26) (26,28) . However, a study that monitored mean creatinine levels at 5 years showed preserved renal function in patients given sirolimus and mycophenolate mofetil versus the tacrolimus and mycophenolate mofetil treatment (36). There is consistent evidence of no difference in neurotoxicity between tacrolimus and ciclosporin, as well as no difference in the rates of stroke (28).No difference was observed in the frequency and type of infections between tacrolimus and ciclosporin (28) . When sirolimus is combined with tacrolimus, higher rates of infectious complications have been found, however they were not statistically significant (16). In general, there was no difference in the malignancy rates in patients treated with tacrolimus compared with ciclosporin, with one study showing a trend toward lower risk of malignancy in patients treated with tacrolimus (21). The incidence of malignancies and opportunistic infections was low and similar for both tacrolimus and ciclosporin (27). A systematic review of five studies (923 participants) compared the effects of tacrolimus and ciclosporin on metabolic syndrome and cardiovascular risk factors after renal transplantation in adults (37). Compared to ciclosporin, tacrolimus treatment was associated with a lower incidence of hyperlipidaemia (RR 0.50, 95% CI 0.39 to 0.64) and hypertension (RR 0.91, 95% CI 0.83 to 1.00); the difference for hypertension was not significant.

Rapport coût/efficacité

Immediate-release tacrolimus is considered a cost-effective and clinically effective option for preventing organ rejection in children, young people and adults having a kidney transplant (38,39). Based on a health technology assessment report of 16 tacrolimus combinations, the only cost-effective combination was basiliximab induction followed by maintenance with immediate-release tacrolimus and mycophenolate mofetil at an incremental cost of £ 20 000–30 000 per quality-adjusted life year (50). Mycophenolate mofetil used together with tacrolimus is a cost-effective use of resources for preventing organ rejection in children and young people having a kidney

transplant (39). Twice daily tacrolimus with mycophenolate mofetil and corticosteroids were found to be more cost-effective than belatacept in terms of acute rejection outcomes in adult kidney transplant patients (17). A study comparing the costs of tacrolimus versus ciclosporin treatment (resource-use quantities, cost of drugs, concomitant medications, hospitalization, dialysis and rejection episodes) in 50 centres in western European countries found that per-patient savings with tacrolimus ranged from € 524 to € 1776. Most of the savings were due to shorter initial hospital stay, fewer rehospitalizations, lower cost of immunosuppressive drugs for graft rejection and lower incidence of dialysis (51). Compared to sirolimus, tacrolimus was found to be a more-cost effective treatment for preventing adverse events after renal transplantation because it reduces the incidence of graft rejection and the cost of treatment with steroids and antibody therapy (52). Prolonged-release tacrolimus administered orally as one capsule a day was not found to be cost-effective (39,50).

Directives de l'OMS

WHO guidelines for the prevention and management of organ transplant rejection are not currently available. The use of tacrolimus for induction and maintenance of immunosuppression following solid organ transplant is recommended in the following national and international guidelines. • Immunosuppressive therapy for kidney transplant in adults (38). Immunosuppressive therapy for kidney transplant in children and young people (39). National Institute for Health and Care Excellence (NICE) (2017) • Renal Association. Clinical practice guidelines – standardisation of immunosuppressive and anti-infective drug regimens in UK paediatric renal transplantation: the harmonisation programme (2020) (40) • European Association of Urology. EAU guidelines on renal transplantation (2018) (41) • Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients (2010) (42) • Renal Association clinical practice guideline in post-operative care in the kidney transplant recipient (2017) (43) • Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care (2020) (44) • Antibody-mediated rejection in cardiac transplantation: emerging knowledge in diagnosis and management: a scientific statement from the American Heart Association (2015) (45) • Monitoring of nonsteroidal immunosuppressive drugs in patients with lung disease and lung transplant recipients: American College of Chest Physicians evidence-based clinical practice guidelines (2012) (46) • Adult liver transplantation: UK clinical guideline – part 2: surgery and post-operation (2020) (47) • European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation (2016) (48) • Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation (49)

Disponibilité

Immediate-release tacrolimus is available globally as originator and generic products.

Autres considérations

Evidence on bioequivalence of generic and brand-name tacrolimus is limited and is not consistent across various studies. Data from observational studies involving kidney transplant patients who were switched from immediate-release originator tacrolimus to a generic tacrolimus suggested this switch was feasible and appeared to be safe, but required careful monitoring of patient trough concentrations for tacrolimus, plasma creatinine levels and overall patient status (53,54). The change resulted in cost savings, despite the cost of extra monitoring (54). Similar results were found in another study of stable liver transplant patients who were switched to generic tacrolimus and followed for 6 months: the generic medicine was is effective and seemed to be safe and cost-efficient (55). A systematic review, mostly based on observational data and studies with some risk of bias, concluded that there was no significant difference in biopsy-proven acute rejection rates between generic and brand-name tacrolimus and even found some evidence suggesting a lower risk of biopsy-proven acute rejection with generic tacrolimus (56). However, unlike evidence from observational studies, a randomized cross-over trial involving stable elderly kidney transplant patients found that generic and originator immediate-release tacrolimus were not bioequivalent. Patients on generic tacrolimus had significantly higher levels of systemic drug exposure, which may increase the likelihood of nephrotoxicity and other adverse effects (57).

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