Interactions Between Tacrolimus and Antimicrobial Agents

David L. Paterson and Nina Singh

From the Infectious Disease Section, Veterans Affairs Medical Center, Pittsburgh, Pennsylvania

Tacrolimus is being increasingly used as an immunosuppressive agent in transplant recipients. The drug is metabolized by the cytochrome P-450 3A system, thus antimicrobials that inhibit or induce these enzymes can alter levels of tacrolimus in the bloodstream. Tacrolimus is potentially nephrotoxic and neurotoxic; the likelihood of toxicity rises as blood levels of the drug increase. Increased tacrolimus levels and subsequent toxicity have been produced by a number of antimicrobial agents that inhibit the cytochrome P-450 3A system. Conversely, drugs with the potential to induce the cytochrome P-450 3A system can reduce the levels of tacrolimus in the blood, leading to increased risk of acute rejection in transplant recipients. Antimicrobial agents that can have adverse effects on renal function may add to the nephrotoxicity of tacrolimus. The potential for drug interactions should be reviewed before antimicrobial agents are prescribed to patients treated with tacrolimus.

Tacrolimus (previously known as FK 506) is a new immunosuppressive drug that is widely used both as a primary immunosuppressive agent and as rescue therapy in patients undergoing organ transplantation [1]. It is a macrolide produced by Streptomyces tsukubaensis. Multicenter trials in the United States and Europe have demonstrated that the use of tacrolimus in liver transplant recipients has been associated with significantly lower rejection rates than the use of cyclosporine [2, 3]. Patients receiving tacrolimus also have lower requirements for concurrent immunosuppression, e.g., with corticosteroids or OKT3 [2, 3]. Other advantages of tacrolimus over cyclosporine include a lesser likelihood that gingival hyperplasia, hirsutism, coarsening of the facial features, and hypertension will occur.

However, like cyclosporine, tacrolimus is nephrotoxic and neurotoxic and has a narrow therapeutic window. There is a correlation between increased blood levels of tacrolimus and nephrotoxicity [4, 5] and severe neurotoxicity [4, 6]. Hence, the use of tacrolimus requires knowledge of potential drug interactions that may lead to increased blood levels of the drug. Conversely, interactions with other drugs may result in diminished serum concentrations of tacrolimus, thereby increasing the risk of organ rejection [7].

Use of other drugs with adverse effects similar to those of tacrolimus (i.e., nephrotoxicity or neurotoxicity) may lead to additive or even synergistic toxicity when they are used in combination with tacrolimus. This toxicity is not due to a pharmacokinetic interaction but rather to similar effects at the site of the end-organ (brain or kidney).

Recent concern has also been expressed about the possibility of immunologic interactions between tacrolimus and other drugs [8], in that the inhibition of T cell proliferation by tacrolimus may be antagonized or overenhanced by interactions with other drugs.

Infections are the major cause of morbidity and mortality after transplantation, and thus antimicrobial agents are widely used in patients who have received organ transplants. We review the interactions between tacrolimus and the complete range of antimicrobial agents. Interactions between tacrolimus and drugs other than antimicrobial agents will not be discussed herein, as recent reviews of these interactions are available elsewhere [9, 10]. Reviews of interactions between the older immunosuppressive agents and antimicrobial agents are also available elsewhere [9, 11].

Methods

To evaluate drug interactions between tacrolimus and antimicrobial agents, we initially performed a MEDLINE search of the literature published between 1966 and 1997 by using the keywords tacrolimus and drug interactions. In addition, we searched MEDLINE by using the keywords tacrolimus in combination with the individual antimicrobial agents (e.g., clarithromycin). TOXLINE was also searched for drug interactions involving tacrolimus. We reviewed the references cited in the retrieved articles for other relevant articles. Recent issues of journals relevant to infectious diseases and transplantation were manually searched for articles that may not yet have been indexed in MEDLINE or TOXLINE. Proceedings of both infectious diseases and transplantation conferences held between 1990 and 1996 were also searched for relevant articles. The manufacturers of tacrolimus (Fujisawa USA, Deerfield, IL) were contacted for any unpublished reports of relevant interactions. Finally, for completeness, as recommended in a recent review of searching for drug-interaction citations on bibliographic databases [12], we searched EMBASE (Electronic Excerpta Medica, Elsevier, New York) for any potential interactions missed by other search methods.
Results

Clinically observed interactions between tacrolimus and antimicrobial agents are reviewed in Table 1. Interactions between antibiotics, antifungals, antivirals, and antiparasitic agents are reviewed in Tables 2–5.

Interactions with β-Lactam Antibiotics (Penicillins, Cephalosporins, and Penems)

Mechanisms and experimental models. The majority of β-lactam antibiotics undergo little metabolism and are excreted as intact molecules via the kidney [23]. Hence, they are unlikely to interfere with the metabolism of tacrolimus, which is mainly metabolized by the cytochrome P-450 system [24, 25]. The effect of two individual cephalosporins on the metabolism of tacrolimus by the human cytochrome P-450 system has been tested [26]; neither drug had any major effect. Cefixime at concentrations of 10 μmol and 100 μmol inhibited tacrolimus metabolism 4.4% and 10.2%, respectively. Cefotaxime at concentrations of 10 μmol and 100 μmol stimulated tacrolimus metabolism 16.6% and 9.7%, respectively.

Clinical studies. Renal toxicity can occasionally occur with β-lactam antibiotics, particularly the penicillins [27]. This toxicity is usually in the form of interstitial nephritis, as is most often seen with drugs such as methicillin [28]. There have been no published reports describing an increased likelihood of nephrotoxicity when tacrolimus and β-lactam antibiotics are used simultaneously. The results of one study suggest that nafcillin potentiates cyclosporine nephrotoxicity in lung transplant recipients [29]. In this study there was no difference in cyclosporine levels between patients who received nafcillin and those who did not. Although it has been suggested that nafcillin may enhance the hepatic metabolism of cyclosporine [30], there are no data suggesting that such an interaction occurs with tacrolimus. It is of interest that the results of a placebo-controlled, single-blinded study suggested that imipenem/cilastatin may reduce cyclosporine-induced nephrotoxicity [31]. The proposed mechanism was that cilastatin protected renal tubular cells from the potentially damaging effects of cyclosporine. It is presumed that the nephrotoxicity of tacrolimus is due to mechanisms that are similar to those that produced the nephrotoxicity of cyclosporine [6], so it is possible that cilastatin may have a similar protective effect when used with tacrolimus. However, this theory remains untested.

Neurotoxicity can occur with β-lactam antibiotics, particularly when they are used at high doses in patients with impaired renal function [32], or when imipenem is used in patients with CNS abnormalities [33]. A number of reviews of tacrolimus-induced neurotoxicity have been published [34, 35], but none have suggested that neurotoxicity is more common in patients receiving concurrent β-lactams.

Interpretation and recommendations. Gram-positive organisms are emerging as the leading cause of bacterial infection in organ transplant recipients. Staphylococcus aureus and Staphylococcus epidermidis are the foremost causes of bacteremia in organ transplant recipients [36], and enterococci are an increasingly important problem in liver transplant recipients. We recommend that doses of β-lactams be identical to those used to treat infections with such organisms in patients without transplants who have comparable renal function. There is no current indication to avoid the concurrent use of nafcillin and tacrolimus, despite the limited data on an interaction with cyclosporine. Similarly, the data on the nephroprotective effect of cilastatin when used in combination with cyclosporine are too preliminary to extend to tacrolimus, and we do not recommend concurrent use of these drugs solely for a purported nephroprotective effect.

The intravenous formulation of tacrolimus contains alcohol, and there is potential for interaction between cephalosporins containing a methylthiotetrazole group and alcohol, producing a disulfiram-like reaction [37]. This has not been described with intravenous tacrolimus, but physicians need to bear this potential in mind when cefamandole, cefoperazone, cefotetan, moxalactam, cefmetazole, or cefmenoxime are coadministered with intravenous tacrolimus.

Interactions with Glycopeptide Antibiotics (Vancomycin and Teicoplanin)

Mechanisms and experimental models. Vancomycin and teicoplanin undergo minimal metabolism and are eliminated from the body almost exclusively by glomerular filtration. Since these drugs do not interact with the cytochrome P-450 system, there have been no in vitro studies on their effect on tacrolimus metabolism.

Clinical studies. Recent reviews have suggested that current preparations of vancomycin are associated with a considerably lower incidence of nephrotoxicity than was previously appreciated [38]. While combinations of vancomycin and other drugs are associated with a higher rate of nephrotoxicity than

Table 1. Clinically observed and reported interactions between tacrolimus and antimicrobial agents.

<table>
<thead>
<tr>
<th>Antimicrobial agent [reference]</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin [13–15]</td>
<td>Increased tacrolimus levels, with subsequent nephrotoxicity</td>
</tr>
<tr>
<td>Clarithromycin [16]</td>
<td>Increased tacrolimus levels, with subsequent nephrotoxicity</td>
</tr>
<tr>
<td>Clotrimazole [17]</td>
<td>Increased tacrolimus levels, with subsequent nephrotoxicity</td>
</tr>
<tr>
<td>Fluconazole [18–21]</td>
<td>Increased tacrolimus levels, with subsequent nephrotoxicity</td>
</tr>
<tr>
<td>Ketoconazole [18]</td>
<td>Increased tacrolimus levels</td>
</tr>
<tr>
<td>Rifampin [15, 22]</td>
<td>Decreased tacrolimus levels, leading to acute rejection</td>
</tr>
</tbody>
</table>
Table 2. Theoretically significant interactions between tacrolimus and antibiotics.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Potential interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Additive nephrotoxicity</td>
<td>Use aminoglycoside once daily and for a short course to lessen risk of toxicity</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>β-lactamase inhibitor–β-lactam combination</td>
<td>Neurotoxicity of β-lactam</td>
<td>May resemble toxicity of tacrolimus</td>
</tr>
<tr>
<td>Selected cephalosporins</td>
<td>Disulfiram-like reaction with alcohol in iv tacrolimus formulation</td>
<td>Unlikely to be a common, clinically important problem</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Potentially important; tacrolimus dose reduction indicated</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>May inhibit tacrolimus metabolism</td>
<td>Dose change probably not required</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Immunologic effects</td>
<td>Unlikely to be clinically important</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Immunologic effects</td>
<td>Unlikely to be clinically important</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>Renal protective effect of cilastatin</td>
<td>Unproven clinically</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically important interaction; use azithromycin preferentially</td>
</tr>
<tr>
<td>Meropenem</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Disulfiram-like reaction with alcohol in iv tacrolimus formulation</td>
<td>Unlikely to be a common, clinically important problem</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Renal and neurotoxicity</td>
<td>May resemble toxicity of tacrolimus</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Immunologic effects</td>
<td>Unlikely to be clinically important</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Potentially important; tacrolimus dose reduction may be necessary</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Induction of tacrolimus metabolism</td>
<td>Acute rejection has been observed when rifampin and tacrolimus are coadministered</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>None at low doses</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>None suspected</td>
<td>Monitor renal function if high dose given</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Minor inhibition of tacrolimus metabolism</td>
<td>Unlikely to be a clinically important interaction</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Additive nephrotoxicity</td>
<td>Vancomycin is a relatively minor nephrotoxin; need to adjust vancomycin dose interval if renal dysfunction occurs</td>
</tr>
</tbody>
</table>

is vancomycin alone, there have been no studies suggesting that the specific combination of vancomycin and tacrolimus has a particular propensity for causing excessive nephrotoxicity. Teicoplanin is thought to be less nephrotoxic than vancomycin [39]; the combination of teicoplanin/tacrolimus has not been studied.

**Interpretation and recommendations.** As previously stated, serious staphylococcal infections are common in transplant recipients [36]. If vancomycin or teicoplanin are indicated, attention should be paid to using them in dosages appropriate to a patient’s renal function. In particular, if tacrolimus-induced nephrotoxicity occurs, dosage reduction may be required.

**Interactions with Macrolide Antibiotics (Erythromycin, Roxithromycin, Clarithromycin, and Azithromycin)**

**Mechanisms and experimental models.** Several studies have been performed to examine the interaction between macrolides and tacrolimus in vitro or in animal models. Erythromycin, clarithromycin, roxithromycin, dirithromycin, and trioleandomycin share a 14-membered macrolide lactone ring structure. Azithromycin differs in having a 15-membered ring [40]. The 14-membered ring macrolides are known to form inactive complexes with cytochrome P-450 3A isozymes and therefore inhibit the metabolism of other drugs [41]. Tacrolimus is primarily metabolized by this cytochrome P-450 3A system [24, 25]. Several authors have shown that the 14-membered-ring macrolides inhibit the metabolism of tacrolimus by both the hepatic and small intestinal cytochrome P-450 3A subfamily in vitro [26, 42, 43]. For example, erythromycin at a concentration of 100 μmol inhibited the cytochrome P-450 3A–mediated metabolism of tacrolimus by 32.5% [26]. Animal studies have also confirmed this effect on tacrolimus metabolism. Rui et al. [44] showed that acute treatment with oral erythromycin (50 mg/(kg·d)) increased tacrolimus concentrations threefold in male Wistar rats.
Table 3. Theoretically significant interactions between tacrolimus and antifungal agents.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Potential interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Additive nephrotoxicity</td>
<td>Liposomal preparations should be less toxic</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically important, even when used orally</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically important</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>None suspected</td>
<td>Reduce dose if renal impairment develops</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Neurotoxicity</td>
<td>May resemble that of tacrolimus</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically important</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically important</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Not likely to be significant if used topically</td>
</tr>
<tr>
<td>Nystatin</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>None suspected</td>
<td>Do not use if renal function impaired</td>
</tr>
</tbody>
</table>

No studies have been performed on the interaction between the 15-membered ring macrolide, azithromycin, and tacrolimus in vitro. However, it is known that azithromycin does not share the property of formation of complexes with cytochrome P-450 3A isozymes, and hence, seems less likely to interfere with the metabolism of drugs metabolized by this pathway. Amacher et al. [45] showed that, unlike erythromycin, azithromycin did not induce or inactivate the hepatic cytochrome P-450 system in Sprague-Dawley rats.

Erythromycin, like tacrolimus, has a suppressive effect on human lymphocyte proliferation and potentiates the action of tacrolimus in vitro [46]. The clinical relevance of this action is unknown.

Clinical studies. Several case reports on the clinical impact of interaction between 14-membered-ring macrolides, such as erythromycin and clarithromycin, and tacrolimus have appeared [13–16]. In contrast, there are no case reports of such an interaction with azithromycin.

Jensen et al. [13] described a 62-year-old male who had marked deterioration in renal function that coincided with the coadministration of erythromycin and tacrolimus after renal transplantation. Shaeffer et al. [14] described a 39-year-old male who similarly had a rise in plasma tacrolimus levels and deterioration in renal function when given oral erythromycin after liver transplantation. Furlan et al. [15] reported two cases of acute renal impairment associated with the coadministration

Table 4. Theoretically significant interactions between tacrolimus and antiviral agents.

<table>
<thead>
<tr>
<th>Antiviral agent</th>
<th>Potential interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Neurotoxicity</td>
<td>May resemble that of tacrolimus</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Neurotoxicity</td>
<td>May resemble that of tacrolimus</td>
</tr>
<tr>
<td>Didanosine</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Additive nephrotoxicity</td>
<td>Watch renal function closely</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Effect expected to be less than that of ritonavir</td>
</tr>
<tr>
<td>IFN-α</td>
<td>May inhibit tacrolimus metabolism</td>
<td>Clinical relevance unknown</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Effect expected to be less than that of ritonavir</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Induction of tacrolimus metabolism</td>
<td>Avoid using nevirapine</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>None suspected</td>
<td>No interaction expected with inhaled drug</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Clinically significant</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Inhibition of tacrolimus metabolism</td>
<td>Effect expected to be less than that of ritonavir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Vaccines (live)</td>
<td>Disseminated infection</td>
<td>Avoid in transplant patients</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>None suspected</td>
<td>Avoid in immunosuppressed patients pending further data</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>None suspected</td>
<td>Reduce dose if impairment of renal function develops</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>None suspected</td>
<td>Reduce dose if dialysis required</td>
</tr>
</tbody>
</table>
Table 5. Theoretically significant interactions between tacrolimus and antiparasitic agents.

<table>
<thead>
<tr>
<th>Antiparasitic agent</th>
<th>Potential interaction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atovaquone</td>
<td>None suspected</td>
<td>Should be safe</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>May inhibit tacrolimus metabolism</td>
<td>Look for impact on tacrolimus levels before travel to malarious area</td>
</tr>
<tr>
<td>Dapsone</td>
<td>May inhibit tacrolimus metabolism</td>
<td>Clinical effect probably minor</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>May inhibit tacrolimus metabolism</td>
<td>Look for impact on tacrolimus levels before travel to malarious area</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Disulfiram-like reaction with alcohol in iv tacrolimus formulation</td>
<td>Unlikely to be a common, clinically important problem</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Inhibits tacrolimus metabolism</td>
<td>Watch tacrolimus levels daily during antimalarial treatment</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Additive nephrotoxicity</td>
<td>Interaction unlikely with nebulized drug</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>None at prophylactic doses</td>
<td>Watch renal function if high dose given</td>
</tr>
</tbody>
</table>

of erythromycin in children who had received liver transplants. Wolter et al. [16] described an interaction between tacrolimus and clarithromycin in a 45-year-old female renal transplant recipient.

Interpretation and recommendations. Macrolide antibiotics are particularly useful in the treatment of respiratory tract infections, especially those due to organisms such as *Mycoplasma pneumoniae* and *Legionella* species. Transplant recipients appear to be at high risk for legionellosis [47]. However, since the 14-membered ring macrolides have such marked interactions with tacrolimus, this group of drugs should probably be avoided in a patient receiving tacrolimus. As the 15-membered ring macrolide, azithromycin, does not interact with the cytochrome P-450 3A system in vitro, we hypothesize that this drug may not have a significant interaction with tacrolimus. We would therefore prefer its use to other macrolides for the empirical treatment of community-acquired pneumonia. However, despite anecdotal experience that the combination is safe, the interaction between tacrolimus and azithromycin has not been formally tested in vitro.

It should be noted that despite similar reasoning and anecdotal experience with the azithromycin-cyclosporine combination, a dramatic elevation in cyclosporine blood concentrations has been described in one patient [48]. While azithromycin may be the macrolide of choice for patients receiving tacrolimus, until more data are available, we would advise close monitoring of tacrolimus levels and renal function when the two drugs are given in combination. Quinolones are active in vitro against *Legionella* species [49], lack significant interaction with tacrolimus, and may therefore be more suitable agents than macrolides for the treatment of legionellosis and other atypical pneumonias in transplant recipients [47].

Interactions with Aminoglycosides (Gentamicin, Tobramycin, Amikacin, Netilmicin, Kanamycin, and Streptomycin)

Mechanisms and experimental models. Aminoglycosides are excreted through the kidneys and are unlikely to interfere with the metabolism of tacrolimus. This lack of interference was demonstrated in vitro by Iwasaki et al. [26], who showed that the aminoglycoside, kanamycin, had a negligible effect on tacrolimus metabolism. Concentrations of 10 μmol and 100 μmol resulted in inhibition of tacrolimus metabolism by 5.6% and 8.8%, respectively.

However, both tacrolimus and aminoglycosides are known to produce nephrotoxicity. Aminoglycosides are known to produce damage to the proximal tubular cells, although the precise mechanism by which this leads to a decrease in the glomerular filtration rate is unknown [50]. Tacrolimus can also produce degenerative changes in the proximal tubular epithelium [51], although decreased renal blood flow due to constriction of preglomerular vessels may also be important in the pathogenesis of nephrotoxicity [52, 53]. It is not known whether there is synergistic action between tacrolimus and aminoglycosides in the proximal tubular cells, which could lead to a greater than additive nephrotoxic effect.

Clinical studies. No clinical studies in which assessment could be made of interactions between aminoglycosides and tacrolimus have been performed.

Interpretation and recommendations. There is no doubt that aminoglycosides and tacrolimus are nephrotoxic agents. It is not known whether the combination of the two is likely to cause greater impairment of renal function than the use of either drug alone. Despite their potential for toxicity, aminoglycosides may remain useful agents in the management of serious pseudomonal infections in transplant recipients. The nephrotoxicity of aminoglycosides can be minimized by giving them once daily rather than in multiple daily doses [54] and by restricting the duration of treatment to 5 or 7 days at most [55]. However, serious enterococcal infections should continue to be treated with multiple daily doses of an aminoglycoside (in combination with an appropriate cell-wall-active antibiotic). We would recommend daily monitoring of serum creatinine levels and frequent monitoring of aminoglycoside levels while tacrolimus and aminoglycosides are used together, with dose or dose frequency reduced if significant renal impairment develops.
Interactions with Quinolone Antibiotics (Ciprofloxacin, Ofloxacin, Norfloxacin, and Enoxacin)

Mechanisms and experimental models. The metabolism of quinolones varies according to the individual drug, but some have been known to inhibit microsomal cytochrome P-450 enzymes [49]. However, enoxacin, the quinolone with greatest effect on the cytochrome P-450 system [49], was found to have virtually no in vitro effect on tacrolimus metabolism by cytochrome P-450 3A [26].

Concern has been expressed that there may be an immunologic interaction between ciprofloxacin and immunosuppressive drugs [8]. Ciprofloxacin has been shown to induce hyperproduction of IL-2 by human peripheral blood lymphocytes in vitro [56]. Tacrolimus exerts its clinical effect by ultimately causing an inhibition of T cell proliferation due to an inhibition in IL-2 production by T cells [57]. Kelly et al. [58] addressed this finding by incubating peripheral blood lymphocytes with 1% phytohemagglutinin in the presence of ciprofloxacin, with and without tacrolimus. Ciprofloxacin alone, at a high concentration (20–80 mg/L), did produce a marked increase in IL-2 production. The addition of tacrolimus led to a reduction in IL-2 production.

Despite this increase in IL-2 induced by ciprofloxacin, ciprofloxacin in high concentrations actually produced a decrease in peripheral blood lymphocyte proliferation [58]. This antiproliferative effect was even greater when tacrolimus and ciprofloxacin were incubated together. However, it was concluded [58] that these in vitro effects are observed at very high, therapeutically irrelevant ciprofloxacin concentrations (e.g., 80 mg/L), whereas in vivo peak concentrations of ciprofloxacin given every 12 hours orally for 5 days are far lower (~2.5 mg/L) [59]. Kelly et al. [58] believe that it is unlikely that at clinically achievable concentrations, ciprofloxacin will enhance or counteract the tacrolimus-induced immunologic changes.

Clinical studies. There have been no clinical studies describing an interaction between tacrolimus and quinolones.

Interpretation and recommendations. There are few data suggesting a high likelihood of interaction between quinolones and tacrolimus in transplant recipients. However, despite the fact that there had been a similar lack of theoretical basis for interaction between quinolones and cyclosporine, three case reports appeared that described increases in cyclosporine concentrations, with subsequent nephrotoxicity [60–62]. We would recommend routine dosing of quinolones in the transplant recipient receiving tacrolimus, although the dose or dosing frequency must be reduced for ciprofloxacin, norfloxacin, ofloxacin, enoxacin, or lomefloxacin when a patient’s creatinine clearance decreases to <30 mL/min. Finally, quinolones, like tacrolimus, can sometimes be neurotoxic [49]. When the symptoms of neurotoxicity fail to abate in response to a reduction in the dose of tacrolimus, they may be managed by cessation of the concomitant administration of quinolones.

Interactions with the Rifamycins (Rifampin and Rifabutin) and Other Antimycobacterial Drugs

Mechanisms and experimental models. Rifampin is a well-documented, strong inducer of the cytochrome P-450 isoenzymes [63]. Recent data suggest that while rifampin causes a significant increase in cytochrome P-450 3A activity, rifabutin may not have this effect [64]. Since tacrolimus is metabolized by the cytochrome P-450 3A system, it would therefore be expected that coadministration of rifampin, but to a lesser extent rifabutin, would result in diminished tacrolimus levels. This has been shown experimentally in rats [65]. The administration of pyrazinamide, ethambutol, and isoniazid would not be expected to have significant effect on the cytochrome P-450 3A system.

Clinical studies. Furlan et al. [15] described a 10-year-old boy in whom the coadministration of rifampin and tacrolimus after liver transplantation resulted in a decrease in the tacrolimus level below the limit of quantitation within 2 days. The tacrolimus dose needed to be doubled to maintain detectable whole-blood levels. Kiuchi et al. [22] described a 10-month-old girl who received a living-related liver transplant and developed a liver abscess due to Mycobacterium tuberculosis. Treatment with isoniazid, rifampin, ethambutol, and streptomycin were started. She developed severe graft rejection and the vanishing bile duct syndrome. The tacrolimus levels decreased to approximately one-tenth of baseline levels.

Interpretation and recommendations. As a consequence of the use of immunosuppressive agents such as tacrolimus, recipients of organ transplants are at increased risk of infection with Mycobacterium tuberculosis, and possibly, nontuberculous mycobacteria [66–68]. Coadministration of rifamycins and tacrolimus may be difficult, since enzyme induction with marked reduction in tacrolimus levels may result. While the subsequent reduction in immunosuppression may be beneficial in terms of treating the mycobacterial infection, this benefit may be offset by the increased risk of acute rejection [7, 22].

The dosage of ethambutol needs to be reduced if renal impairment due to tacrolimus therapy or other causes occurs. Treatment of drug-resistant tuberculosis or infections caused by atypical mycobacteria is difficult in the patient receiving tacrolimus. Drugs that are unlikely to have significant interactions and that can be considered options include pyrazinamide, streptomycin, amikacin, ofloxacin, and ciprofloxacin.

Interactions with Miscellaneous Antibiotics

There are few in vitro studies and no clinical studies detailing the experience with other antibiotics and tacrolimus. However, some generalizations can be made.

Quinupristin/dalfopristin, an antibiotic combination frequently active against vancomycin-resistant enterococci (VREF), is structurally similar to macrolide antibiotics [69]. However, despite the frequent use of this combination in liver transplant centers where VREF is a problem, to our knowledge, there
have been no published reports of interactions with tacrolimus. Quinupristin/dalfopristin is a potent inhibitor of the cytochrome P-450 3A isoenzymes [70], and hence, tacrolimus levels would be expected to rise with concomitant use of this combination. We advise daily measurement of serum creatinine and tacrolimus levels for patients receiving these agents.

Trimethoprim-sulfamethoxazole (TMP-SMZ), in doses used as prophylaxis for Pneumocystis carinii pneumonia, has not been shown to interact with tacrolimus. High-dose TMP-SMZ is not known to interfere with the metabolism of tacrolimus but may cause renal impairment due to a number of mechanisms, including interstitial nephritis. In addition, a reduction in the dose of TMP/SMZ is required if a patient’s creatinine clearance decreases to <30 mL/min.

Minocycline has been shown to have a trivial effect on tacrolimus metabolism by the cytochrome P-450 3A isoenzymes [26]. The effects of tetracycline and doxycycline on the metabolism of tacrolimus by the cytochrome P-450 3A isoenzymes have not been studied. The doses of tetracycline and minocycline need to be reduced, or the drugs need to be discontinued, in patients with renal impairment. The doses of doxycycline do not need adjustment in patients with renal dysfunction.

Lincomycin had approximately half as much inhibitory effect on tacrolimus metabolism as erythromycin (15.1% inhibition with lincomycin vs. 32.5% with erythromycin) [26]. An interaction between clindamycin and tacrolimus has not been studied or observed. We use routine doses of clindamycin or lincomycin in transplant recipients but observe renal function and tacrolimus levels closely.

Metronidazole has no known metabolic interactions with tacrolimus. The intravenous formulation of metronidazole contains dehydrated alcohol, and hence, a disulfiram-like reaction is theoretically possible when the two drugs are coadministered, although this has not been described. Fosfomycin has been shown to have a minimal effect on tacrolimus metabolism by the cytochrome P-450 system [26]. However, an immunologic interaction has been observed in vitro [71]. Combined treatment with fosfomycin and tacrolimus produced at least additive suppression of T cell proliferation.

Fusidic acid, an antistaphylococcal antibiotic, has some immunosuppressive properties; the presence of fusidic acid has been shown to result in a decrease in production of IL-1 and IL-2 from activated blood mononuclear cells [72]. The clinical significance of this effect is uncertain but is unlikely to be a concern if the drug is used topically.

Mupirocin, used topically, is not expected to have any interaction with tacrolimus. Chloramphenicol is metabolized by the cytochrome P-450 system and hence has potential for interaction with tacrolimus. In one study, the administration of chloramphenicol increased the blood concentration of tacrolimus in transplant recipients [65], although the extent of this increase was not reported. We recommend close observation of tacrolimus levels and the serum creatine level if the two drugs are coadministered.

Nitrofurantoin is not expected to have an interaction with tacrolimus. This antibiotic should not be used in a patient with a creatinine clearance of <40 mL/min.

**Interactions with Azole Antifungals (Clotrimazole, Miconazole, Ketoconazole, Fluconazole, and Itraconazole)**

**Mechanisms and experimental models.** In vitro and animal studies have indicated that tacrolimus actually possesses direct antifungal activity [73–75]. However, the overwhelming effect of immunosuppression leads to fungal proliferation at higher doses and thus outweighs the antifungal activity of the drug. It is not known whether any synergy, in terms of antifungal effect, exists between tacrolimus and azole drugs.

It is well known that pharmacokinetic interactions occur between tacrolimus and the azoles. Miconazole, ketoconazole, fluconazole, and itraconazole have been reported to inhibit both liver and the small intestine microsomes that metabolize tacrolimus [26, 42, 43, 76]. Ketoconazole is the most potent inhibitor of tacrolimus metabolism in vitro [76]. However, in a study of rats, acute treatment with fluconazole increased tacrolimus concentrations by fourfold, whereas treatment with ketoconazole increased tacrolimus concentrations by only twofold [44].

**Clinical studies.** Mieses et al. [17] reported a significant interaction between clotrimazole troches and tacrolimus, which resulted in acute renal impairment in a 55-year-old man after liver transplantation. Because clotrimazole is poorly absorbed, the authors explained this interaction as being due to interaction with cytochrome P-450 enzymes in the enterocytes of the patient’s jejunal mucosa.

Assan et al. [18] described a clinically important interaction between fluconazole and tacrolimus after liver transplantation in a 57-year-old female; the tacrolimus levels were elevated, and acute renal impairment occurred. The same patient was challenged with ketoconazole 1 year later when she was in a stable clinical condition, and the tacrolimus levels were again found to be elevated. Vincent et al. [19] described two children who developed nephrotoxicity after liver transplantation when they were given intravenous fluconazole and tacrolimus. Manéz et al. [20] described 20 transplant patients who were given fluconazole and tacrolimus; these investigators showed that the effect of fluconazole on tacrolimus levels was dose dependent. These authors used a median dosage reduction of 56% (range, 0–88%) to keep trough plasma tacrolimus concentrations below 2 ng/mL. Osowski et al. [21] described 15 patients who received intravenous fluconazole (400 mg/d) in combination with intravenous tacrolimus. Mean baseline whole-blood levels of tacrolimus rose 16%, and two patients developed an increase in serum creatinine greater than twice baseline.

**Interpretation and recommendations.** Fungal infections are an important cause of morbidity and mortality in transplant recipients. We urge caution when the azoles and tacrolimus are administered together. The dose of tacrolimus should be halved when an azole is coadministered [20]. Serum creatinine
Interactions with Other Antifungal Drugs (Amphotericin B, 5-Flucytosine, and Nystatin)

Amphotericin B has been shown to have an insignificant effect on the metabolism of tacrolimus [26]. However, amphotericin B is well known to be nephrotoxic. Vincent et al. [19] described two children who developed severe acute renal impairment (creatinine clearance decreased to 20 mL/min) when they received intravenous amphotericin B and tacrolimus after liver transplantation. In these cases, renal function returned to normal within days of stopping the antifungal therapy. It is not known whether there is a more than additive effect when tacrolimus and amphotericin B are used together. Daily monitoring of serum creatinine is probably warranted for patients receiving both drugs.

Liposomal preparations of amphotericin B are less nephrotoxic than the conventional formulation, although no survival benefit has been demonstrated with these agents [77]. Vincent et al. [19] observed a child after liver transplantation who received a long course of liposomal amphotericin B and did not develop renal impairment. White et al. [77] reported a double-blind, randomized trial comparing amphotericin B colloidal dispersion (ABCD) with the conventional formulation in 77 neutropenic adult patients who received either tacrolimus or cyclosporine. The rate of renal toxicity was 27.8% among patients treated with ABCD, as compared with 67.6% among patients given the conventional preparation. Mortality did not differ in the two treatment groups.

Flucytosine is not known to interact with tacrolimus. The dosage of flucytosine should be reduced if tacrolimus-induced renal impairment occurs.

Nystatin, applied topically or as a swish-and-swallow regimen, would not be expected to interact with tacrolimus.

Grisofulvin can frequently produce headaches, which may be confused with tacrolimus-induced neurotoxicity. The effects of alcohol (which is contained in the intravenous formulation of tacrolimus) may be potentiated by griseofulvin. No clinically significant interactions have been reported.

Terbinafine is unlikely to produce changes in tacrolimus metabolism. The use of terbinafine in patients whose creatinine clearance is <50 mL/min is not recommended.

Interactions with Antiretroviral Agents

Mechanisms and experimental models. The protease inhibitors (ritonavir, indinavir, saquinavir, and nefilavir) are metabolized in the liver by the cytochrome P-450 3A4 isoenzyme. In addition, they can act as inhibitors of cytochrome P-450-mediated drug metabolism [78]. They differ in their potencies as inhibitors of cytochrome P-450: ritonavir is significantly more potent than the other protease inhibitors [78]. Hence, although no in vitro studies or animal studies have been performed to examine specific interactions between antiretroviral drugs and tacrolimus, it would be expected that the use of ritonavir may lead to increased serum tacrolimus levels. Conversely, the nonnucleoside reverse transcriptase inhibitor nevirapine may induce hepatic cytochrome P-450 enzymes [79], and reduced serum tacrolimus levels would be expected.

Clinical studies. No clinical studies reporting an interaction between tacrolimus and antiretroviral drugs have been performed.

Interpretation and recommendations. The possible interaction between tacrolimus and antiretroviral drugs is relevant, since a number of organ transplant recipients have been found to be infected with HIV [80]. If antiretroviral therapy is given, ritonavir and nevirapine should probably be avoided if possible. Combination therapy with a regimen such as zidovudine, lamivudine, and indinavir would appear relatively safe and free from major effects on tacrolimus levels. However, as published experience with the use of antiretroviral drugs and tacrolimus is nonexistent, we recommend close monitoring of tacrolimus levels and serum creatinine on initiation of such therapy, or at any time therapy is changed. An issue of lesser concern is the suggestion that tacrolimus may itself be an inhibitor of cytochrome P-450 3A4 isoenzymes [81]. Because the protease inhibitors are metabolized by this enzyme system, the serum levels of these drugs may be increased when tacrolimus is administered. It is not known whether this increase would necessitate reduction in the dose of the protease inhibitor. At this stage, we favor use of standard dosage regimens, with close observation for toxicity from the protease inhibitor.

Zidovudine, didanosine, zalcitabine, stavudine, and lamivudine are predominantly excreted through the kidneys. Adjustment in the dosages of these drugs is required if tacrolimus-induced nephrotoxicity occurs. The dosages of lamivudine, zalcitabine, stavudine, and didanosine should be reduced when a patient’s creatinine clearance decreases to <40–50 mL/min, whereas adjustment in the dosage of zidovudine is required only if dialysis is needed.

Interactions with Other Antiviral Agents

Acyclovir has a minimal effect on the metabolism of tacrolimus in vitro [26]. Dosage reductions of acyclovir are indicated if tacrolimus-induced renal impairment (creatinine clearance, <50 mL/min) occurs. Neurotoxicity, resembling that produced by tacrolimus, can occur if this dosage reduction is not performed.

Valaciclovir, the prodrug of acyclovir, would not be expected to have an effect on the metabolism of tacrolimus. There are no specific recommendations for the dosing of valaciclovir in...
organ transplant recipients because drug trials in this patient population have not been completed.

Famciclovir is not metabolized by the cytochrome P-450 system and is not expected to interact with tacrolimus. Dosage adjustment should be performed when a patient’s creatinine clearance is <60 mL/min.

Ganciclovir is widely used in transplant recipients, but no formal drug interaction studies with tacrolimus have been performed. No pharmaco-kinetic interaction would be expected. Ganciclovir dose should be reduced if tacrolimus-induced renal impairment occurs.

Foscarnet is a nephrotoxic drug; however, it is not known whether tacrolimus nephrotoxicity is potentiated when the two agents are used together.

Inhaled ribavirin should not have an interaction with the metabolism of tacrolimus.

Amantadine does not have a known interaction with tacrolimus but can produce CNS effects similar to those of tacrolimus neurotoxicity. In addition, dosage reduction is necessary if a patient’s creatinine clearance is <50 mL/min.

IFN-α can interfere with the metabolism of some drugs by reducing the activity of hepatic cytochrome P-450 enzymes. However, the relevance of this action to the metabolism of tacrolimus has never been studied. IFN-α can also affect the CNS in ways similar to those observed with tacrolimus.

**Interactions with Antiparasitic Agents**

Dapsone is a substrate for the cytochrome P-450 3A isoenzyme, as is tacrolimus. Dapsone inhibits the metabolism of tacrolimus to a moderate degree [76], although the extent may not be sufficient to have clinical impact.

Pentamidine, when given as an aerosol, is unlikely to have an interaction with tacrolimus. Renal failure occurs frequently when intravenous pentamidine is administered, and close monitoring for an enhancement of this effect by tacrolimus should be performed.

Atovaquone has little potential for interaction with tacrolimus, as atovaquone has no impact on the cytochrome P-450 system.

Chloroquine, quinidine, and mefloquine are substrates for the cytochrome P-450 3A system. Quinidine has been shown to moderately inhibit tacrolimus metabolism in vitro [76]. However, no clinical interactions have been reported between any of these antimalarials and tacrolimus. We recommend the usual dosages of antimalarials for prophylaxis or treatment of malaria, but we advise monitoring of tacrolimus levels before travel to a malarious region.

**Interactions with Vaccines**

The use of live vaccines is contraindicated in patients receiving tacrolimus. These live vaccines include typhoid vaccine, oral live trivalent poliovirus vaccine, BCG (bacille Calmette-Guérin) vaccine, yellow fever vaccine, and measles, mumps, and rubella virus vaccine.

**Discussion**

The use of tacrolimus is increasing, and infectious diseases physicians need to be aware of its potential interaction with antimicrobial agents. Most interactions are based on alteration in the metabolism of tacrolimus by the cytochrome P-450 3A system. Macrolides (with the possible exception of azithromycin), azoles, chloramphenicol, quinupristin/dalfopristin, and protease inhibitors may form inactive complexes with cytochrome P-450 3A enzymes and therefore inhibit the metabolism of tacrolimus. As a result, serum tacrolimus levels may rise, increasing the risk of nephrotoxicity or neurotoxicity. Conversely, rifampin and nevirapine may induce the cytochrome P-450 3A system, leading to reduction in serum tacrolimus levels. This reduction may increase the risk of organ rejection.

In view of the interactions described above, treatment of pneumonia, tuberculosis, HIV infection, and infections with vancomycin-resistant enterococci or with fungi is more difficult in the transplant recipient. One management option is to prescribe an antimicrobial agent of a different class (e.g., a quinolone instead of a macrolide for treatment of suspected legionella pneumonia). Alternative strategies include reduction in dosage of the antimicrobial agent (or tacrolimus) or close monitoring of serum tacrolimus levels. We have found that knowledge of likely interactions can allow anticipatory changes in dosing or in the frequency of serum monitoring for tacrolimus levels. For example, a transplant recipient treated for tuberculosis with a rifampin-containing regimen may need a larger dosage of tacrolimus to prevent organ rejection than would a transplant recipient who is not receiving an antituberculous regimen.

The potential for tacrolimus toxicities to resemble those produced by a variety of antimicrobial agents (and vice versa) also needs to be considered. Nephrotoxicity and neurotoxicity are the major considerations. The neurotoxicity associated with tacrolimus may resemble that seen with high doses of β-lactams, quinolones, or amantadine. Although potentiation of toxicity has not been studied with respect to most drugs, we consider potentiation of nephrotoxicity a possible risk when amphotericin B, aminoglycosides, or foscarnet are used in patients receiving tacrolimus. Finally, reduction of the dosages of many antimicrobial agents is necessary when tacrolimus-induced renal dysfunction occurs.

Iatrogenically immunosuppressed patients are likely to receive a variety of antimicrobial agents in the posttransplantation period. Like cyclosporine, tacrolimus has the potential to interact with many of these drugs. However, since the majority of these interactions are predictable, adverse effects from such interactions should usually be avoidable. As new antimicrobial agents become available, studies on their potential for interaction with tacrolimus should be performed.
References


