Pharmacokinetics of tacrolimus-based combination therapies

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Abstract
This paper reviews the pharmacokinetics of tacrolimus, with special reference to its combination with adjunctive immunosuppressants. Oral bioavailability of tacrolimus, which is variable between patients, averages \( \sim 25\% \). This is largely due to extrahepatic metabolism of tacrolimus in the gastrointestinal epithelium. Nevertheless, intra-patient variability is low, as evidenced by the small number of dose changes required to maintain patients within the recommended tacrolimus target levels. Tacrolimus is distributed extensively in the body with most partitioned outside the blood compartment. Concentrations of tacrolimus in blood are used as a surrogate marker of clinically relevant concentration of the drug at the site(s) of action. Convenient whole-blood sampling within a \( \pm 2\)-h window around 12 h post-dose (\( C_{\text{min}} \)) is highly predictive of systemic exposure to tacrolimus and is thus used to optimise therapy. Sampling at other time-points offers no advantage over \( C_{\text{min}} \) monitoring. The interactions of tacrolimus with other immunosuppressive agents are well characterized. After cessation of concomitant corticosteroid treatment, exposure to tacrolimus increases by \( \sim 25\% \). In contrast, there is no pharmacokinetic interaction between mycophenolate mofetil (MMF) and tacrolimus. Therefore, systemic exposure to the active metabolite of MMF, mycophenolic acid, is higher with MMF–tacrolimus combination than with MMF–ciclosporin combination. Therefore, 1 g/day MMF may be an adequate maintenance dose in tacrolimus-based regimens. Co-administration of tacrolimus and sirolimus, while having no effect on exposure to sirolimus, results in reduced exposure to tacrolimus at sirolimus doses of 2 mg/day and above. In conclusion, tacrolimus levels should be monitored when sirolimus is co-administered at doses \( \geq 2 \) mg/day and after cessation of corticosteroid treatment.

Keywords: interaction; MMF; MPA; mycophenolate mofetil; sirolimus; tacrolimus

Introduction
The optimal use of immunosuppressive agents when administered as combination therapies is dependent upon their pharmacokinetic characteristics and any potential interactions. In order to explore more fully the use of tacrolimus in combination with corticosteroids, mycophenolate mofetil (MMF) and sirolimus, the pharmacokinetics of tacrolimus and of the concomitant immunosuppressive agents have been reviewed with an emphasis on optimizing dosing schedules.

Pharmacokinetics of tacrolimus
After absorption, tacrolimus binds strongly to both erythrocytes and plasma proteins. Binding to erythrocytes is in the region of 95\%. Of the 5% partitioned into plasma, 99\% is bound to plasma proteins (mainly albumin and \( z_1 \)-acid glycoprotein). Concentrations in blood/plasma, which are composites of both bound and unbound fractions of the drug, are routinely monitored to ensure appropriate exposure to the drug. However, they are only surrogate markers for the concentration of active drug at the site(s) of action [1,2]. The pharmacological activity is considered to be a function of the unbound fraction of tacrolimus (<0.1\%). Tacrolimus is distributed extensively in the body and at steady state the majority of the drug resides outside the blood compartment; that is, in the tissues.

Cytochrome P450 3A4 (CYP3A4) is the principal iso-enzyme responsible for the metabolism of tacrolimus. Extrahepatic metabolism by CYP3A4 in the gastrointestinal epithelium is responsible for pre-systemic elimination of about half of the absorbed dose, whereas first-pass metabolism by CYP3A4 in the liver accounts for an additional 10\% of elimination. The extent of absorption of tacrolimus from the gastrointestinal tract is also influenced by the activity of P-glycoprotein (P-gp) in enterocytes. P-gp is a transmembrane transporter that is closely associated with CYP3A4 and secretes tacrolimus and its metabolites.
back into the lumen of the gut [1]. This extensive pre-
-systemic metabolism limits the oral bioavailability of
tacrolimus to $\sim 25\%$. The activity of the metabolizing
enzyme as well as of the P-gp transporter varies
considerably between individuals and between races,
and this requires the dosage to be individualized to
achieve the desired systemic exposure. Nevertheless,
the intra-patient variability in systemic exposure is
considered to be low. The low intra-patient variability
in the bioavailability of tacrolimus is evidenced by the
small number of dose changes required to maintain
target whole-blood trough concentrations.

For the purpose of both efficacy and safety, expo-
sure to tacrolimus and other immunosuppressive drugs
must be monitored during use. The area under the
blood-concentration–time curve (AUC) is taken as
being representative of total systemic exposure. It has
been shown [1,2] that tacrolimus AUC values on day 2
after transplantation correlate with clinical outcome;
that is, tacrolimus AUC values were significantly lower
in patients who had experienced acute rejection than in
those who had not ($P = 0.007$). Routine use of AUC
for monitoring would require serial blood samples to
be taken over the interval between doses in order to
define a blood-concentration–time profile. Clinically
this is not practicable. Several clinical studies have
shown a good correlation between AUC and trough
concentration ($C_{\text{min}}$, determined at 12 h post-dose) of
tacrolimus (correlation coefficient $[r^2] = 0.91$) [3].
Therefore, $C_{\text{min}}$ is used as a surrogate marker for
systemic exposure (as reflected in the AUC). In
addition, the whole-blood-concentration–time profile of
tacrolimus is flat at 10–12 h after dosing. Thus,
blood samples for monitoring taken within a $\pm 2$-h
time window are considered to be equally predictive of
exposure. Furthermore, evaluations of tacrolimus
whole-blood concentrations at other time-points
showed no better correlation with the AUC. For
example, the correlation between the 2-h concentration
and AUC was $r = 0.83$ [3].

Drug interactions

The cornerstone immunosuppressant tacrolimus is
most often administered in combination with cortico-
steroids, and MMF or sirolimus. Whether clinically
significant drug interactions are apparent will be
discussed in the following paragraphs.

Corticosteroids

Corticosteroids are inducers of CYP3A4. This was
demonstrated clearly in the recent studies of van
Duijnhoven et al. [4] in patients receiving tacrolimus
at either 5 ($n = 54$) or 10 mg ($n = 30$) prednisolone.
In order to investigate any interaction, the trough
concentrations of tacrolimus were normalized by unit
dose and compared before and after prednisolone
therapy was stopped. It was found that exposure to
tacrolimus increased by $\sim 25\%$ upon withdrawal of
prednisolone ($P = 0.003$ and $P = 0.11$ in the 5 and
10 mg treatment groups, respectively). Mean serum
creatinine levels also increased after cessation of
prednisolone (from 143 to 151 mmol/l, $P = 0.034$),
and this was thought to be due to the increase in
tacrolimus concentrations. However, following reduc-
tion of the tacrolimus dosage, both tacrolimus and
serum creatinine concentrations returned to their
levels prior to steroid withdrawal. The increase in tacrolimus
levels upon withdrawal of steroids was also seen in a
large comparative study recently reported by Squifflet
and colleagues [5].

MMF

MMF is used frequently in combination with
tacrolimus- or ciclosporin-based immunosuppressive
regimens. Interactions between MMF and tacrolimus or
ciclosporin have been reported in a number of studies
[6–9]. The bioavailability of MMF is reported to be
almost 100\%. After absorption, MMF is hydrolysed to
its pharmacologically active form, mycophenolic acid
(MPA). When MMF was co-administered with tacro-
limus, the AUC values for MPA increased with time
(from first dose to month 3) for 1 and 2 g doses of
MMF, such that by 3 months the AUC values were
$\sim 20–30\%$ higher. However, there was considerable
variation between individuals [7]. These studies con-
firmed the earlier report of Zucker et al. [8] that
higher MPA levels were observed when MMF was
co-administered with tacrolimus, compared with its co-
administration at the same dose with ciclosporin. At a
dose of 2 g MMF, the mean trough levels of MPA were
2.8 ng/ml in the tacrolimus group compared with
1.2 ng/ml in the ciclosporin group ($P < 0.05$). The
AUC values (0–12 h) were also significantly higher:
50.2 ng.h/ml with tacrolimus co-administration com-
pared with 32.1 ng.h/ml with ciclosporin ($P < 0.05$).
The mean trough levels and AUC values of MPA
achieved with a 2 g dose of MMF in combination
with tacrolimus were similar to those for a 3 g dose of
MMF in combination with ciclosporin. Gregoor et al.
[9] investigated the effect of ciclosporin on MPA
trough levels in kidney transplant patients and
demonstrated a significant increase (almost 50\%,
$P = 0.002$) after discontinuation of ciclosporin. This
suggests that co-administration of ciclosporin reduces
the systemic exposure to MPA.

It has been speculated that the lower MPA levels in
the presence of ciclosporin are a result of inhibition of
the enterohepatic recirculation. The main metabolite
of MPA is glucuronidated MPA (MPAG), which is
excreted into bile and undergoes enterohepatic recir-
culation. In a rat heart transplant system, a second
peak in the MPA pharmacokinetic profile was seen
with MMF plus tacrolimus or MMF plus placebo,
consistent with enterohepatic recirculation. This
second peak, however, was not seen with a combina-
tion of MMF and ciclosporin [10], suggesting that the
increases in MPA levels that are observed after
conversion from ciclosporin to tacrolimus might result from restored enterohepatic recirculation.

The pharmacokinetics of tacrolimus are unchanged in the presence of MMF [7]. The observed increase in the AUC of MPA suggests that the dose of MMF, when co-administered with tacrolimus, may need to be decreased with time in order to maintain stable systemic exposure to MPA. Moreover, the higher AUC values of MPA in combination with tacrolimus suggest that during maintenance 1 g MMF dosage may provide adequate immunosuppression in a tacrolimus-based regimen.

**Sirolimus**

The novel immunosuppressive mechanism of action of sirolimus is synergistic with that of the calcineurin-inhibiting agents. The pharmacokinetics of tacrolimus in combination with sirolimus, have been evaluated in stable as well as de novo transplant recipients. In stable kidney transplant patients receiving tacrolimus therapy, pharmacokinetics were determined following co-administration of sirolimus at doses of 1, 2 and 5 mg/day [11] (Figure 1). After 14 days of dosing, there was a significant reduction in tacrolimus AUC in the 2 and 5 mg sirolimus dose groups ($P < 0.05$).

In our own study in de novo renal transplant recipients [12], sirolimus was administered at 0.5, 1.0 and 2.0 mg/day, and the pharmacokinetics were determined after the first dose of sirolimus (loading doses of 1.5, 3.0 and 6.0 mg, respectively), at week 2 and at month 3 post-transplantation. The AUC values for tacrolimus, normalized to a 0.1 mg/kg dose, are shown in Figure 2. For all dose levels of sirolimus, a reduction in tacrolimus AUC values compared with the no-sirolimus control was observed with the first dose. Subsequently, the tacrolimus levels recovered, but there was an overall trend for reduced exposure to tacrolimus with increasing doses of sirolimus.

In both of these studies, the plasma levels of sirolimus at doses of 1 and 2 mg/day were similar to those observed in patients receiving sirolimus therapy without tacrolimus [11,12]. This indicates that tacrolimus has no effect on the pharmacokinetics of sirolimus. In contrast, an increase in sirolimus levels has been observed when ciclosporin and sirolimus are co-administered [13].

**Conclusion**

The overall bioavailability of tacrolimus is affected by pre-systemic metabolism resulting in marked inter-patient variation. Nonetheless, intra-patient variability of tacrolimus pharmacokinetics is low; as such, patient management does not require frequent dose changes. Optimal monitoring of tacrolimus is based on convenient whole-blood trough levels, with analysis at other time-points offering no advantage.

Tacrolimus can be safely combined with MMF or sirolimus. In a tacrolimus plus MMF combination regimen, MPA exposure is higher than with a similar dose of MMF in combination with ciclosporin. Concentrations of tacrolimus are decreased by concomitant therapy with prednisolone or with sirolimus at doses of 2 mg/day or higher. Thus, tacrolimus concentrations should be monitored after cessation of prednisolone or sirolimus treatment to ensure that exposure to tacrolimus does not fall outside target limits.

**References**


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**Fig. 1.** The effect of sirolimus on the pharmacokinetics of tacrolimus in stable renal transplant recipients ($n=22$) [11]. $*P < 0.05$, 14 days after starting sirolimus compared with pre-sirolimus.

**Fig. 2.** The effect of sirolimus on the pharmacokinetics of tacrolimus in de novo renal transplant recipients ($n=28$). Bars represent mean ($\pm$ SD) AUC$_{0-12}$ for tacrolimus, normalized to 0.1 mg/kg dose.

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