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Interactions Between Cyclosporin and Lipid-Lowering Drugs

Implications for Organ Transplant Recipients

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Abstract

Dyslipidaemia is more frequent in solid organ transplant recipients than in the general population, primarily as a result of immunosuppressive drug treatment. Both cyclosporin and corticosteroids are associated with dyslipidaemic adverse effects. In order to reduce the overall cardiovascular risk in these patients, lipid-lowering drugs have become widely used, especially HMG-CoA reductase inhibitors (statins). Cyclosporin, as well as most statins (lovastatin, simvastatin, atorvastatin and pravastatin) are metabolised by cytochrome P450 (CYP)3A4, so a bilateral pharmacokinetic interaction between these drugs is theoretically possible. However, results from several studies show that statins do not induce increased systemic exposure of cyclosporin. A small (but not clinically relevant) reduction in systemic exposure of cyclosporin has actually been shown in many studies. Cyclosporin-treated patients on the other hand show several-fold higher systemic exposure of all statins, both those that are metabolised by CYP3A4 and fluvastatin (metabolised by CYP2C9). Therefore, the mechanism for this interaction does not seem to be solely caused by inhibition of CYP3A4 metabolism, but it is probably also a result of inhibition of statin-transport in the liver, at least in part.

Other lipid-lowering drugs, such as fibric acid derivatives, bile acid sequestrants, probucol, fish oils and orlistat are also used in solid organ transplant recipients. Most of them do not interact with cyclosporin, but there are reports indicating that both probucol and orlistat may reduce cyclosporin bioavailablility to a clinically relevant degree. There is no information on possible interaction effects of cyclosporin on the pharmacokinetics of lipid-lowering drugs other than statins, but it is not likely that any clinical relevant interference exists with fish oil, orlistat, probucol or bile acid sequestrants.

With the use of new and more powerful immunosuppressive drugs acute rejection episodes and early graft survival rates have significantly improved in solid organ transplantation. Other factors, such as chronic rejection and cardiovascular disease, have therefore become dominant factors for overall patient and graft survival.[1] Dyslipidaemia is an independent risk factor for chronic cardiovascular disease in the general population and the incidence of post-transplant dyslipidaemia is higher than in the general population. The use of cyclosporin and corticosteroids, in particular, has led to an increased incidence of post-transplant dyslipidaemia.[2] No large prospective studies ex-

amining the effect of lipid lowering intervention with hard cardiovascular endpoints have yet been performed in solid organ transplanted patients. Even though such hard end-point data do not exist, the use of lipid lowering drugs, especially HMG-CoA reductase inhibitors (statins), has increased in transplant recipients.

The scope of the present review is not the lipid lowering effect of these drugs but their pharmacokinetic interactions with the widely used immunosuppressive drug cyclosporin. This interaction has previously been shown to lead to severe adverse effects, such as muscle toxicity, which in some patients have lead to rhabdomyolysis and renal failure when statins and cyclosporin were combined.[3,4] Although this problem was first recognised with the combination of lovastatin and cyclosporin, all statins (with the exception of fluvastatin) have been reported to induce rhabdomyolysis in cyclosporin-treated patients.[4] From the alternative perspective, alterations in cyclosporin pharmacokinetics may induce under immunosuppression (induction of cyclosporin metabolism) or adverse effects such as nephrotoxicity, hypertension, glucose intolerance and dyslipidaemia (inhibition of cyclosporin metabolism).[5]

Most studies presented in the literature have not been designed to investigate pharmacokinetic interactions, but rather for the lipid-lowering effect and/or safety. Most of these studies do not report the area under the blood concentration versus time curve (AUC) but only trough concentrations of cyclosporin. The pharmacokinetic knowledge obtained from these studies is limited since trough concentrations show high variability, and a poor correlation with AUC and the general efficacy of cyclosporin. It is also important to recognise that transplant recipients generally receive several different drugs and multiple pharmacokinetic interactions are possible. It is therefore difficult to interpret the pharmacokinetic results from these studies for likely responsible mechanisms or the clinical relevance. In this article, the pharmacokinetic interactions between cyclosporin and lipid-lowering drugs are reviewed from all published results, although some studies are not primarily designed for pharmacokinetic interaction investigation.

1. Statins

All statins, with the exception of pravastatin, are almost completely metabolised before elimination. The metabolism of atorvastatin, lovastatin and simvastatin is primarily mediated by cytochrome P450 (CYP)3A4,[6-8] while cerivastatin (now withdrawn from the market) is subjected to metabolism by both CYP3A4 and CYP2C8.[9] Pravastatin is also in part metabolised by CYP3A4 but is mainly subjected to several conjugation reactions[10,11] and about 10% of an oral dose of pravastatin is, unlike the other statins, excreted unchanged via the kidneys.[12] Fluvastatin is also a CYP3A4 substrate but it is primarily metabolised by CYP2C9.[13,14]

Since cyclosporin is also mainly metabolised by CYP3A4, bilateral pharmacokinetic interactions with all statins are theoretically likely to occur. With the recently published studies, data are now available for all statins and their pharmacokinetic interactions with cyclosporin. However, a problem with most of these studies is that an appropriate control group without cyclosporin is lacking and the systemic exposure of statins is instead compared with healthy, often historical, controls.

There is an overlap for many drugs between the affinity to CYP3A4 and the affinity to P-glycoprotein (P-gp),[15] and many of the drugs metabolised via CYP3A4 are also transported via other molecules such as organic anion transporting polypeptides (OATP).[16] The presence of increased systemic exposure of statins when co-administered with cyclosporin may, therefore, be due to either transport interactions or inhibited CYP3A4 metabolism, or a combination of these mechanisms. In respect to this it should also be mentioned that cyclosporin is highly bound to lipoproteins in plasma and a general lipid-lowering effect will, therefore, possibly alter its free fraction. Akhlaghi et al.[17] have investigated the effect of simvastatin on the free fraction of cyclosporin and found an increase of about one third. Whether this is due to

an interaction with simvastatin or is an effect due to lipid lowering is not known. In addition, García-Sáiz et al.[18] showed a weak association between cyclosporin trough concentration/dose ratio and cholesterol levels in some transplant recipients.

1.1 Lovastatin

Olbricht et al.[19] investigated the bilateral interaction between lovastatin and cyclosporin in 21 renal transplant recipients receiving lovastatin 20 mg/day for 28 days. Cyclosporin $AUC_{0-\infty}$ was unchanged by addition of lovastatin to the treatment regimen; however, lovastatin AUC_{0-24} was 20-fold higher at day 28 compared with healthy historical controls not receiving cyclosporin. Lovastatin also showed an almost 90% increase in $AUC_{0-\infty}$ from day 1 to day 28. This accumulation over time may indicate that lovastatin clearance or distribution volume are significantly affected in cyclosporin-treated patients leading to a half-life closer to the dose administration interval.

In a study including several different control groups, Gullestad et al.[20] investigated lovastatin AUC_{0-8} in both renal and heart transplant recipients. Six heart and five renal transplant recipients on cyclosporin therapy, five renal transplant without cyclosporin therapy, five psoriasis patients treated with cyclosporin and eight non-cyclosporin treated hypercholesterolaemic, but otherwise healthy, controls were included in this study. They all received lovastatin 10 mg/day over 10 days. The three groups of patients treated with cyclosporin showed at least 5-fold higher lovastatin AUC_{0-8} compared with those not treated with cyclosporin, and heart transplant recipients tended to have higher AUC_{0-8} compared with the other cyclosporin-treated patients. There were no available data on cyclosporin concentrations in this study.

Traindl et al.[21] investigated 12 renal transplant recipients who received lovastatin 20 mg/day for 6 months. Serum trough cyclosporin concentrations were stable (numerical increase of about 4%) during the study period; however, there is no information on cyclosporin doses or possible dose adjustments during the investigation period. Lovastatin concentrations were not measured in this study.

1.2 Simvastatin

Arnadottir et al.[22] performed a controlled interaction study in renal transplant recipients, including five cyclosporin recipients and five who did not receive cyclosporin. Simvastatin AUC_{0-24} was approximately 3-fold higher in the cyclosporin-treated patients. Cyclosporin concentrations were not reported in this study, but in another study by the same group[23] there was no indication that simvastatin 20 mg/day interfered with blood cyclosporin concentrations. Campana et al.[24] showed a 6-fold higher systemic exposure of simvastatin in cyclosporin-treated patients when comparing seven cyclosporin-treated heart transplant recipients with seven non-transplanted patients. Trough cyclosporin concentrations increased non-significantly by about 12% in this study.

Rehman et al.[25] treated 20 renal transplant recipients with simvastatin 10 mg/day for 6 months (18 patients completed the trial) and reported that trough cyclosporin concentrations remained in the normal range, although no information regarding dose adjustment was given. In addition, Martinez Hernandez et al.,[26] Capone et al.,[27] Pflugfelder et al.[28] and Vanhaecke et al.[29] did not find any significant changes in trough cyclosporin concentrations in studies of similar design.

Akhlaghi et al.[17] studied 32 heart transplant recipients for a period of at least 6 months who were receiving simvastatin. Both the daily dose and trough concentration of cyclosporin decreased during the investigation period. Therefore, it is difficult to draw any definite conclusions regarding any possible interaction effect of simvastatin on cyclosporin pharmacokinetics. However, in a subpopulation of 12 patients, the same authors measured the free fraction of cyclosporin. Both the unbound fraction of cyclosporin and the apparent clearance of cyclosporin were increased by coadministration of simvastatin.[17] This may indi-

cate that the clinical significance of this interaction is low as long as the efficacy of cyclosporin is proportional to its free concentration, which in this situation would be relatively unchanged. The mechanism responsible for this change in cyclosporin pharmacokinetics could be a decreased plasma lipoprotein binding as a result of the overall lipid-lowering effect of simvastatin in these patients.

Lepre et al.[30] did not find any significant differences in trough cyclosporin concentrations in 51 renal transplant recipients in a double-blind, placebo-controlled trial with simvastatin.

1.3 Pravastatin

Castelao et al.[31] investigated the effect of pravastatin treatment over 12 months in renal transplant recipients. However, the daily dose of cyclosporin was decreased during this period and so trough cyclosporin concentrations were proportionally decreased as well, therefore, no absolute conclusions can be drawn regarding pravastatin interference with cyclosporin pharmacokinetics. Similarly, no significant change in trough cyclosporin concentrations was present in heart transplant recipients.[32] However, in these cyclosporin-treated heart transplant recipients a significantly increased systemic exposure of pravastatin was present with the $AUC_{0-\infty}$ 23-fold higher than in non-transplanted controls. Olbricht et al.[19] and Park et al.[33] also showed a significantly higher systemic exposure of pravastatin in cyclosporin-treated patients (5- and 12-fold, respectively). However, this higher pravastatin exposure was not associated with an accumulation over the month of administration. This may indicate that cyclosporin mainly changes pravastatin pharmacokinetics in such a way that does not influence its half-life to any major degree. Either there is only a change in bioavailability or the change in clearance or distribution volume is not large enough to alter the half-life to a degree required to induce an accumulation. Olbricht et al.[19] reported a non-significant change in cyclosporin $AUC_{0-\infty}$ (numerical decrease of about 4%), while cyclosporin trough levels were significantly decreased by about 15% in the study by Park et al.[33]

1.4 Fluvastatin

Although not designed to investigate cyclosporin pharmacokinetics in fluvastatin-treated patients, the study of Schrama et al.[34] showed that five of nine heart transplant recipients and one of ten kidney transplant recipients included in the study reduced their daily cyclosporin doses after introduction of fluvastatin to their drug regimen. In accordance with this reduction of cyclosporin dose, the cyclosporin AUC after 8 weeks of fluvastatin treatment was about 15% (nonsignificant) lower. However, Holdaas et al.[35] did not find indications to adjust the daily dose of cyclosporin in 14 renal transplant recipients treated with fluvastatin 20–40 mg/day over 20 weeks. Trough cyclosporin concentrations actually tended to be lower when combined with fluvastatin treatment. In a study of similar design Martínez-Castelao et al.[36] found that dose adjustment of cyclosporin was necessary in fluvastatin treated patients. In contrast with these findings, neither Li et al.[37] nor Hadjigavriel and Kyriakides[38] found any effect of fluvastatin treatment on trough cyclosporin concentrations in studies on renal transplanted patients.

Goldberg and Roth[39] investigated systemic exposure of fluvastatin in 20 renal transplant recipients. The patients received fluvastatin 20 mg/day for 14 weeks and the AUC of fluvastatin was 200% greater than that of healthy controls. These results are supported by recent results showing 3.1 to 3.5-fold higher AUC_{0-24} of fluvastatin in ten male heart transplant recipients compared with ten healthy male volunteers.[40] The trough cyclosporin concentration was not significantly changed over 4 weeks in these transplant recipients.

1.5 Atorvastatin

Demetriou et al.[41] investigated the effect of atorvastatin 10 mg/day in 24 renal transplant recipients. Neither daily dose nor trough cyclosporin concentrations were changed during this 3-month

study. However, Renders et al.[42] investigated the effect of atorvastatin 10 mg/day over 3 months in ten cyclosporin-treated renal transplant recipients. Four of the ten patients had to reduce their cyclosporin dose because trough cyclosporin concentrations increased by more than 25%. These four patients showed a small increase in trough concentration, although the dose had been reduced by an average of 17%. In the six patients who did not adjust their dose, trough cyclosporin concentrations were 13% higher compared with pre-treatment values. This study indicates that atorvastatin induces a potentially clinical relevant increase in systemic exposure of cyclosporin, at least in some patients.

However, Åsberg et al.[43] showed that the systemic exposure of cyclosporin, measured as AUC_{0-12}, significantly decreased by about 10% in 21 renal transplant recipients after 4 weeks of treatment with atorvastatin 10 mg/day. However, this reduction in cyclosporin AUC is probably not of clinical relevance. In this study the systemic exposure of atorvastatin was also shown to be about 6-fold higher in the cyclosporin-treated patients than in historical controls not receiving cyclosporin.

1.6 Cerivastatin

Cerivastatin has been withdrawn from the market because of a high incidence of adverse effects compared with other statins. Mück et al.[44] investigated the effect of cerivastatin 0.2 mg/day, administered to twelve renal transplant patients receiving cyclosporin and in controls not receiving cyclosporin. The AUC_{0-12} of cyclosporin was not significantly affected by cerivastatin co-administration but showed a numerical decrease of about 10%. The systemic exposure of cerivastatin and metabolites were also measured in this study. Compared with healthy controls, the cyclosporin treated renal transplant recipients had an approximately 4-fold higher cerivastatin AUC. Renders et al.[42] investigated the effect of cerivastatin 0.2 mg/day over 3 months in ten cyclosporin-treated renal transplant recipients, but found no significant change in trough cyclosporin concentrations.

1.7 Statin Effects on Cyclosporin Pharmacokinetics

The overall interpretation of the literature data is that statins, regardless of whether they are primarily metabolised by CYP3A4 or not, do not interact with cyclosporin to a degree that is clinically relevant. However, considering the narrow therapeutic range of cyclosporin and the high inter-individual variability shown in these studies, it could still be advisable to intensify the cyclosporin monitoring at start of statin therapy or during dose adjustments in transplanted patients. The literature does not indicate any difference between different types of solid organ transplantation, at least not between heart and kidney transplant recipients. However, most of the published studies only report trough cyclosporin concentrations and the primary aim in most of these studies has been to investigate the lipid lowering efficacy and/or overall safety. Selection of studies reporting AUC measurements of cyclosporin without significant dose changes during the study (table I)[19,43,44] indicate a numerically small, but probably not clinically relevant, decrease in systemic exposure of cyclosporin.

Table I. Interaction studies presenting effects on AUCs of cyclosporin when co-administrated with different statins. Changes in systemic exposure of the respective statin are also given (clinical exposures of cyclosporin were comparable in all studies)

Study	Statin	Change in AUC_{CsA}	Change in AUC_{statin} (%)	p-Value
Olbricht et al.[19]	Lovastatin (20 mg/day for 28 days)	±	+1900	Not tested
Olbricht et al.[19]	Pravastatin (20 mg/day for 28 days)	±	+400	Not tested
Mück et al.[44]	Cerivastatin (0.2 mg/day for 7 days)	±	+400	NS
Åsberg et al.[43]	Atorvastatin (10 mg/day for 28 days)	–9.5%	+500	0.013

AUC_{CsA} = area under the blood concentrations versus time curve of cyclosporin; **NS** = not significant; **Statin** = HMG-CoA reductase inhibitor; ± indicates no change.

Only one of these studies actually shows a statistically significant reduction of cyclosporin AUC (9.5 ± 18%).[43]

1.8 Cyclosporin Effects on Statin Pharmacokinetics

A review of the literature reveals that the systemic exposure of statins is several-fold higher in cyclosporin-treated patients. The primary metabolic pathway of the different statins does not seem to be relevant for this interaction since all statins have been reported to be subject to this interaction. However, the major drawback with these interaction studies is the lack of appropriate control groups. Only one study[20] actually compared systemic exposure of the statin (lovastatin) in cyclosporin-treated with non-cyclosporin-treated transplant recipients (azathioprine and prednisolone immunosuppression). Although these non-cyclosporin treated renal transplant recipients had a longer post-transplant time, this is the best control group presented so far. This study supports that the increased systemic exposure of statins found in the other studies, although only compared with non-transplanted patients, is most probably caused by an interaction with cyclosporin. Psoriasis patients treated with cyclosporin also showed a comparable increase in lovastatin exposure in this study by Gullestad et al.[20] There was also a tendency for higher exposure of the statin in heart compared with renal transplant patients in this study. The limited number of patients may explain why this difference did not reach statistical significance. There are no other indications from the literature that different types of solid organ transplantation affect statin exposure differently.

Regardless whether a statin is primarily metabolised by CYP3A4, they all show an increased systemic exposure when cyclosporin is co-administered, in non-transplanted as well as transplanted patients. Therefore, it is unlikely that this interaction is due to inhibition of CYP metabolism. However, pravastatin may be less extensively affected by cyclosporin co-administration. Olbricht et al.[19] showed that there was no accumulation of pravastatin over 28 days of drug administration, whereas the lovastatin AUC had almost doubled at day 28 compared with day 1. It is possible that the more flexible elimination of pravastatin, including both CYP metabolism and renal elimination of unchanged and conjugated pravastatin, limits the interaction potential of cyclosporin with pravastatin compared with lovastatin.[19] Smith et al.[45] investigated lovastatin pharmacokinetics in a rat model of cyclosporin-induced cholestasis. The metabolism of cyclosporin was not changed in this study indicating that the altered disposition of lovastatin found was due to an effect on drug transport. An *in vitro* study showed that the lactone forms of atorvastatin, simvastatin and lovastatin, respectively, inhibited P-glycoprotein (P-gp) transport in a concentration-dependent manner.[46] However, neither pravastatin or fluvastatin nor the acidic forms of atorvastatin, simvastatin or lovastatin showed any relevant P-gp inhibition. However, P-gp transport interaction may explain the interaction between cyclosporin and at least atorvastatin, simvastatin and lovastatin as observed in clinical studies. This finding is also in agreement with the findings that pravastatin, and maybe also fluvastatin, may show a different potential for cyclosporin interference. Atorvastatin has also been shown to inhibit P-gp transport in another *in vitro* system.[47] In addition, other transporter molecules may be involved in statin transport in different compartments of the body. For example, most statins have been shown to be transported by the liver specific OAPT2 transporter (Human Hepatic Organic Anion Transporting Polypeptide)[48] and, *in vitro*, atorvastatin has also been shown to be transported by the H^+-monocarboxylic acid co-transporter (MCT) in a CACO-2 cell line.[49]

An interaction with statin transport in the liver may result in two different pharmacokinetic alterations, both of which could explain the increase in systemic exposure seen *in vivo*. First, since statins are mainly distributed to the liver, a restriction of the transport in the liver would give a significant reduction of its distribution volume resulting in an increase in plasma concentration. Alternatively, a

decreased liver transport of statins may induce a decreased intrinsic clearance by reducing availability to the metabolising enzymes and/or inhibiting excretion into the bile.

As discussed earlier by Olbricht et al.,[19] another interesting finding, albeit with historical controls, is that, although the systemic exposure of statins is increased several-fold in cyclosporin-treated transplant recipients, the lipid-lowering effect is the same and out of proportion to the increased systemic exposure. In fact, atorvastatin was not shown to induce any significantly different lipid-lowering effect in renal transplant recipients compared with the historical controls even though the AUC_{0-24} of atorvastatin was 6-fold higher.[43] This is consistent with a proposed transport interaction between cyclosporin and atorvastatin reducing the total distribution volume (and therefore increasing the systemic exposure) by reducing distribution to the liver. Such a restricted availability to the liver may explain a relatively lower lipid-lowering efficacy in this situation.

2. Fibric Acid Derivatives

Fibric acid derivatives (fibrates), such as gemfibrozil, fenofibrate, bezafibrate and ciprofibrate, are generally well absorbed, show high plasma protein (albumin) binding and are primarily metabolised by CYP3A4. The metabolites are primarily excreted by the kidneys. The pharmacokinetic properties of fibric acid derivatives have been reviewed by Miller and Spence.[50] Some report an interaction between cyclosporin and fibric acid derivatives but only trough concentrations have been measured. Pisanti et al.[51] treated 40 renal transplant recipients with gemfibrozil for several months, and neither the dose nor the trough cyclosporin concentrations were changed to any significant degree in these patients. No change in trough cyclosporin concentrations was found in a study of 48 heart transplant recipients treated with gemfibrozil.[28] However, Fehrman-Ekholm et al.[52] have shown cyclosporin concentrations to be lower in renal transplant recipients when combined with gemfibrozil. Significantly lower trough cyclosporin concentrations have also been shown in heart transplanted patients receiving fenofibrate,[53] although another report indicated no change in cyclosporin concentrations during co-administration with fenofibrate in this patient population.[54]

2.1 Effects on Cyclosporin Pharmacokinetics

Because of the lack of appropriate pharmacokinetic investigation of this topic, no clear conclusions can be drawn regarding the interaction between fibric acid derivatives and cyclosporin. Both a lack of interaction as well as decreased cyclosporin concentrations have been reported. The mechanism for a possible reduction of cyclosporin concentrations has not been investigated but could possibly be associated with a general lipid-lowering effect rather than a CYP interaction.

3. Bile Acid Sequestrants

Bile acid sequestrants (resins) are highly charged quaternary ammonium salts, which may interfere with drug absorption as a result of non-specific binding in the gastrointestinal tract. On the basis of the chemical properties of cyclosporin no significant direct interaction is expected and some studies support this. Jensen et al.[55] investigated the effect of cholestyramine 4g, given as a single dose at noon, on cyclosporin concentrations in six renal transplant recipients. Neither the trough concentrations nor the AUC of cyclosporin was significantly affected; however, the AUC was numerically increased by about 10%. In the studies by Pflugfelder et al.[28] and Keogh et al.[56] no significant changes in cyclosporin concentrations were found when given concomitantly with a bile acid sequestrant.

4. Probucol

Probucol is a highly lipid soluble antioxidative compound with poor absorption characteristics. It is mainly eliminated through the bile and faeces. There are indications from the literature that probucol inhibits cyclosporin absorption but the

mechanism is not clear. Gallego et al.[57] performed a withdrawal study in ten renal transplant recipients. After a 5-week period on stable therapy, probucol was withdrawn for another 5 weeks. Trough cyclosporin concentrations were significantly lower during probucol treatment. In agreement with this, Wakasugi et al.[58] have reported several cases with lower blood cyclosporin concentrations (about half) when probucol and cyclosporin were co-administered. A study in a rat model supports these findings and it seems that such an interaction may be caused by interference with cyclosporin absorption.[59] In this *in vitro* study, probucol induced a 30% reduction in cyclosporin AUC when cyclosporin was given orally but no effect on cyclosporin concentrations was seen when cyclosporin was administered intravenously. No change in elimination half-life or distribution volume was found in this study.

5. Fish Oils

Oil from cold-water fish show a high content of polyunsaturated fatty acids. In particular, the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in such fish oil extracts have been shown to reduce very low-density lipoprotein cholesterol and triglyceride levels.[60] Since cyclosporin is highly lipophilic, an absorption interaction with fish oil is theoretically possible. One group has conducted several studies with fish oil in renal transplant recipients and primarily found that fish oil does not affect cyclosporin concentration differently from coconut oil.[61,62] However, in one study they showed significantly higher trough cyclosporin concentrations in renal transplant patients receiving fish oil.[63] However, these studies were all performed with the old formulation of cyclosporin (Sandimmun®[1]), and since the new microemulsion preconcentrate formulation (Neoral®) is less dependent on dietary fat and bile acids for absorption,[64] the effect of fish oil is probably less, if present at all, with Neoral®.

6. Orlistat

Although it can be disputed whether or not orlistat really is a lipid- and/or cholesterol-lowering drug it reduced low-density lipoprotein (LDL) cholesterol significantly more than in a control population (not transplanted patients) and the effect on LDL-cholesterol seems to be independent of overall bodyweight reduction.[65] Orlistat decreases the absorption of fat by inhibiting gastrointestinal lipases and has a low bioavailability (3%). Therefore, an absorption interaction with cyclosporin is possible since cyclosporin is dependent on lipid absorption, especially the Sandimmun® formulation.

Six case reports have been published so far, both in heart and kidney transplant recipients. Nägele et al.[66] showed a marked reduction in cyclosporin AUC (cyclosporin administered as Sandimmun®), from 2832 to 700 μg • h/L when co-administered with orlistat. Moreover, le Beller et al.[67] showed similar effects with cyclosporin administered as Sandimmun® and trough cyclosporin concentrations were more than halved during orlistat treatment. This patient was switched to the Neoral® formulation and apparently the effect of orlistat was ameliorated. However, Schnetzler et al.[68] reported a case of clinically relevant orlistat interaction with cyclosporin administered as Neoral®. Trough cyclosporin concentration was more than halved in this patient. Errasti et al.[69] describes two cases where the trough cyclosporin concentrations (Neoral®) were almost halved in renal transplant recipients during coadministration with orlistat. One of these patients showed a reduced renal function after the incident, and the authors speculate that this might be connected to the transient under immunosuppression. In another renal transplant recipient, orlistat has also been shown to decrease trough cyclosporin concentrations even though the administration of the two drugs were separated by 2 hours.[70]

1 The use of tradenames is for identification purposes only and does not imply endorsement.

These six case reports indicate that orlistat may interact with cyclosporin absorption in a clinically relevant manner. A randomised, crossover designed study in 30 healthy volunteers supports the hypothesis of an absorption interaction between orlistat and cyclosporin.[71] All but one participant showed a decrease in steady state cyclosporin concentrations with concomitant orlistat administration. Both AUC_{0-12} and C_{max} were significantly reduced by an average of 30 and 24%, respectively. Separating the dose of cyclosporin and orlistat by 3 hours did not alter the results. For the safety of the healthy volunteers, the dose of cyclosporin was only 50 mg/day in this study and this yielded trough concentrations of 10–20 μg/L. However, this is not supposed to influence the overall interpretation of the results.

7. Conclusion

Since cyclosporin has a narrow therapeutic index in solid organ transplant recipients it is important to be aware of all potential pharmacokinetic interactions that may alter its systemic exposure. Statins are the most widely used lipid-lowering drugs and interaction studies have been performed with all the different statins without showing any clinically relevant changes in blood cyclosporin concentrations. On the basis of studies measuring trough cyclosporin concentrations it seems like probucol almost halves the exposure of cyclosporin when co-administrated. This is also supported by an experimental rat study. In addition, orlistat has been shown to reduce the systemic exposure of cyclosporin by more than 50% in several case reports and by 30% in a crossover study in healthy volunteers. The literature is conflicting regarding the effects of fibric acid derivatives on cyclosporin pharmacokinetics and both unaltered as well as significantly reduced cyclosporin concentrations have been reported. However, this interaction has only been investigated using trough cyclosporin concentrations, therefore, no clear conclusions can be drawn from these results. Because of the chemical properties of bile acid sequestrants, no interaction with cyclosporin is anticipated and the literature supports this hypothesis. Fish oils also seem to be without clinically relevant interactions with cyclosporin in the old formulation of cyclosporin (Sandimmun®).

Only statins have been investigated for the reverse interactions, that is cyclosporin interacting with the pharmacokinetics of lipid-lowering drugs. Since most statins as well as cyclosporin are metabolised by CYP3A4 this is a possible interaction mechanism between these drugs. All statins have been investigated for this interaction and all statins show significantly increased systemic exposure in cyclosporin-treated patients, including fluvastatin, pravastatin and cerivastatin, which have alternative elimination routes to CYP3A4. The interaction of cyclosporin with statin pharmacokinetics is, therefore, apparently not solely caused by inhibition of CYP3A4. Experimental and *in vitro* studies may indicate that this interaction is due to, at least in part, a transport interaction in the liver. Both these interactions are possible but the relative contribution to the overall interaction may differ between statins.

In summary, the literature on the interaction of lipid-lowering drugs with cyclosporin is generally insufficient for definite conclusions to be made. In the main, only trough cyclosporin concentrations have been measured and since these are poorly correlated to the systemic exposure, which does correlate with cyclosporin efficacy, it is not possible to draw clinically relevant conclusions from these studies. With these limitations in mind, only probucol and orlistat seem to interact with cyclosporin to a significant degree that may be of clinical relevance.

The effect of cyclosporin on lipid-lowering drugs has only been investigated for statins. All statins show a several-fold increase in the systemic exposure in solid organ transplant recipients receiving cyclosporin as part of their immunosuppressive therapy. However, the controls in these studies have not been optimal since it is difficult to find transplant recipients not using cyclosporin or another calcineurin inhibitor. This limits the conclusions that can be made from these studies

but it seems that cyclosporin-treated transplant recipients should receive dosages of statins in the lower dosage range. Several case reports reporting rhabdomyolysis when using 'normal' dosages of statins in cyclosporin-treated transplant recipients supports this.

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References

1. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000; 57 (1): 307-13
2. Wierzbicki AS. The role of lipid lowering in transplantation. Int J Clin Pract 1999; 53 (1): 54-9
3. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacother 2001; 35 (9): 1096-107
4. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacother 2002; 36 (2): 288-95
5. Jardine A. Assessing cardiovascular risk profile of immunosuppressive agents. Transplantation 2001; 72 (12 Suppl.): S81-S8
6. Christians U, Jacobsen W, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? Pharmacol Ther 1998; 80 (1): 1-34
7. Prueksaritanont T, Gorham LM, Ma B, et al. In vitro metabolism of simvastatin in humans [SBT] identification of metabolizing enzymes and effect of the drug on hepatic P450s. Drug Metab Dispos 1997; 25 (10): 1191-9
8. Malinowski JM. Atorvastatin: a hydroxymethylglutaryl-coenzyme A reductase inhibitor. Am J Health Syst Pharm 1998; 55 (21): 2253-67
9. Mück W. Rational assessment of the interaction profile of cerivastatin supports its low propensity for drug interactions. Drugs 1998; 56 Suppl. 1: 15-23
10. Jacobsen W, Kirchner G, Hallensleben K, et al. Comparison of cytochrome P-450-dependent metabolism and drug interactions of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors lovastatin and pravastatin in the liver. Drug Metab Dispos 1999; 27 (2): 173-9
11. Jacobsen W, Kirchner G, Hallensleben K, et al. Small intestinal metabolism of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor lovastatin and comparison with pravastatin. J Pharmacol Exp Ther 1999; 291 (1): 131-9
12. Singhvi SM, Pan HY, Morrison RA, et al. Disposition of pravastatin sodium, a tissue-selective HMG-CoA reductase inhibitor, in healthy subjects. Br J Clin Pharmacol 1990; 29 (2): 239-43
13. Fischer V, Johanson L, Heitz F, et al. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions. Drug Metab Dispos 1999; 27 (3): 410-6
14. Scripture CD, Pieper JA. Clinical pharmacokinetics of fluvastatin. Clin Pharmacokinet 2001; 40 (4): 263-81
15. Zhang Y, Benet LZ. The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein. Clin Pharmacokinet 2001; 40 (3): 159-68
16. Bramow S, Ott P, Thomsen Nielsen F, et al. Cholestasis and regulation of genes related to drug metabolism and biliary transport in rat liver following treatment with cyclosporine A and sirolimus (Rapamycin). Pharmacol Toxicol 2001; 89 (3): 133-9
17. Akhlaghi F, McLachlan AJ, Keogh AM, et al. Effect of simvastatin on cyclosporine unbound fraction and apparent blood clearance in heart transplant recipients. Br J Clin Pharmacol 1997; 44 (6): 537-42
18. Garcia-Saiz M, Lopez-Gil A, Alfonso I, et al. Factors influencing cyclosporine blood concentration-dose ratio. Ann Pharmacother 2002; 36 (2): 193-9
19. Olbricht C, Wanner C, Eisenhauer T, et al. Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. Clin Pharmacol Ther 1997; 62 (3): 311-21
20. Gullestad L, Nordal KP, Berg KJ, et al. Interaction between lovastatin and cyclosporine A after heart and kidney transplantation. Transplant Proc 1999; 31 (5): 2163-5
21. Traindl O, Reading S, Franz M, et al. Low-dose lovastatin in hyperlipidemic kidney graft recipients with cyclosporine A. Transplant Proc 1992; 24 (6): 2745-7
22. Arnadottir M, Eriksson LO, Thysell H, et al. Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. Nephron 1993; 65 (3): 410-3
23. Arnadottir M, Eriksson LO, Germershausen JI, et al. Low-dose simvastatin is a well-tolerated and efficacious cholesterol-lowering agent in ciclosporin-treated kidney transplant recipients: double-blind, randomized, placebo-controlled study in 40 patients. Nephron 1994; 68 (1): 57-62
24. Campana C, Iacona I, Regazzi MB, et al. Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. Ann Pharmacother 1995; 29 (3): 235-9
25. Rehman MA, al-Sulaiman MH, Mousa DH, et al. Effects of simvastatin in hyperlipidemic renal transplant patients receiving cyclosporine. Transplantation 1995; 60 (4): 397-9
26. Martinez Hernandez BE, Persaud JW, Varghese Z, et al. Low-dose simvastatin is safe in hyperlipidaemic renal transplant patients. Nephrol Dial Transplant 1993; 8 (7): 637-41
27. Capone D, Stanziale P, Gentile A, et al. Effects of simvastatin and pravastatin on hyperlipidemia and cyclosporin blood levels in renal transplant recipients. Am J Nephrol 1999; 19 (3): 411-5
28. Pflugfelder PW, Huff M, Oskalns R, et al. Cholesterol-lowering therapy after heart transplantation: a 12-month randomized trial. J Heart Lung Transplant 1995; 14 (4): 613-22
29. Vanhaecke J, Van Cleemput J, Van Lierde J, et al. Safety and efficacy of low dose simvastatin in cardiac transplant recipients treated with cyclosporine. Transplantation 1994; 58 (1): 42-5
30. Lepre F, Rigby R, Hawley C, et al. A double-blind placebo controlled trial of simvastatin for the treatment of dyslipidaemia in renal allograft recipients. Clin Transplant 1999; 13 (6): 520-5

31. Castelao AM, Grinyo JM, Castineiras MJ, et al. Effect of pravastatin in the treatment of hypercholesterolemia after renal transplantation under cyclosporine and prednisone. Transplant Proc 1995; 27 (4): 2217-20
32. Regazzi MB, Iacona I, Campana C, et al. Clinical efficacy and pharmacokinetics of HMG-CoA reductase inhibitors in heart transplant patients treated with cyclosporin A. Transplant Proc 1994; 26 (5): 2644-5
33. Park JW, Siekmeier R, Merz M, et al. Pharmacokinetics of pravastatin in heart-transplant patients taking cyclosporin A. Int J Clin Pharmacol Ther 2002; 10 (10): 439-50
34. Schrama YC, Hene RJ, de Jonge N, et al. Efficacy and muscle safety of fluvastatin in cyclosporine-treated cardiac and renal transplant recipients: an exercise provocation test. Transplantation 1998; 66 (9): 1175-81
35. Holdaas H, Hartmann A, Stenstrøm J, et al. Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporine. Am J Cardiol 1995; 76 (2): 102A-6A
36. Martínez-Castelao A, Grinyo JM, Fiol C, et al. Fluvastatin and low-density lipoprotein oxidation in hypercholesterolemic renal transplant patients. Kidney Int Suppl 1999; 71: S231-4
37. Li PK, Mak TW, Wang AY, et al. The interaction of fluvastatin and cyclosporin A in renal transplant patients. Int J Clin Pharmacol Ther 1995; 33 (4): 246-8
38. Hadjigavriel M, Kyriakides G. Fluvastatin in renal transplantation. Transplant Proc 1997; 29 (7): 3050
39. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. Transplantation 1996; 62 (11): 1559-64
40. Park JW, Siekmeier R, Lattke P, et al. Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. J Cardiovasc Pharmacol Ther 2001; 6 (4): 351-61
41. Demetriou D, Shabpar A, Bohmig G, et al. Beneficial effects of atorvastatin in the treatment of hyperlipidemia after renal transplantation. Wien Klin Wochenschr 2000; 112 (8): 358-61
42. Renders L, Mayer-Kadner I, Koch C, et al. Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. Nephrol Dial Transplant 2001; 16: 141-6
43. Åsberg A, Hartmann A, Fjeldså E, et al. Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. Am J Transplant 2001; 1 (4): 382-6
44. Mück W, Mai I, Fritsche L, et al. Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. Clin Pharmacol Ther 1999; 65 (3): 251-61
45. Smith PF, Eydelloth RS, Grossman SJ, et al. HMG-CoA reductase inhibitor-induced myopathy in the rat: cyclosporine A interaction and mechanism studies. J Pharmacol Exp Ther 1991; 257 (3): 1225-35
46. Bogman K, Peyer AK, Torok M, et al. HMG-CoA reductase inhibitors and P-glycoprotein modulation. Br J Pharmacol 2001; 132 (6): 1183-92
47. Boyd RA, Stern RH, Stewart BH, et al. Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. J Clin Pharmacol 2000; 40 (1): 91-8
48. Hsiang B, Zhu Y, Wang Z, et al. A novel human hepatic organic anion transporting polypeptide (OATP2): identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. J Biol Chem 1999; 274 (52): 37161-8
49. Wu X, Whitfield LR, Stewart BH. Atorvastatin transport in the Caco-2 cell model: contributions of P-glycoprotein and the proton-monocarboxylic acid co-transporter. Pharm Res 2000; 17 (2): 209-15
50. Miller DB, Spence JD. Clinical pharmacokinetics of fibric acid derivatives (fibrates). Clin Pharmacokinet 1998; 34 (2): 155-62
51. Pisanti N, Stanziale P, Imperatore P, et al. Lack of effect of gemfibrozil on cyclosporine blood concentrations in kidney-transplanted patients. Am J Nephrol 1998; 18 (3): 199-203
52. Fehrman-Ekholm I, Jogestrand T, Angelin B. Decreased cyclosporine levels during gemfibrozil treatment of hyperlipidemia after kidney transplantation. Nephron 1996; 72 (3): 483
53. Boissonnat P, Salen P, Guidollet J, et al. The long-term effects of the lipid-lowering agent fenofibrate in hyperlipidemic heart transplant recipients. Transplantation 1994; 58 (2): 245-7
54. deLorgeril M, Boissonnat P, Bizollon CA, et al. Pharmacokinetics of cyclosporine in hyperlipidaemic long-term survivors of heart transplantation: lack of interaction with the lipid-lowering agent, fenofibrate. Eur J Clin Pharmacol 1992; 43 (2): 161-5
55. Jensen RA, Lal SM, Diaz-Arias A, et al. Does cholestyramine interfere with cyclosporine absorption? A prospective study in renal transplant patients. ASAIO J 1995; 41 (3): M704-6
56. Keogh A, Day R, Critchley L, et al. The effect of food and cholestyramine on the absorption of cyclosporine in cardiac transplant recipients. Transplant Proc 1988; 20 (1): 27-30
57. Gallego C, Sanchez P, Planells C, et al. Interaction between probucol and cyclosporine in renal transplant patients. Ann Pharmacother 1994; 28 (7-8): 940-3
58. Wakasugi H, Yoshimoto M, Aoki M, et al. Effect of probucol on the concentration of cyclosporin A in patients with nephrotic syndrome. Nippon Jinzo Gakkai Shi 2001; 43 (7): 595-9
59. Sugimoto K, Sakamoto K, Fujimura A. Decrease in oral bioavailability of cyclosporin A by coadministration of probucol in rats. Life Sci 1997; 60 (3): 173-9
60. Bays HE, Dujovne CA. Drugs for treatment of patients with high cholesterol blood levels and other dyslipidemias. Prog Drug Res 1994; 43: 9-41
61. Homan van der Heide JJ, Bilo HJ, Donker JM, et al. Effect of dietary fish oil on renal function and rejection in cyclosporine-treated recipients of renal transplants. N Engl J Med 1993; 329 (11): 769-73
62. Homan van der Heide JJ, Bilo HJ, Donker AJ, et al. Dietary supplementation with fish oil modifies renal reserve filtration capacity in postoperative, cyclosporin A-treated renal transplant recipients. Transpl Int 1990; 3 (3): 171-5
63. Homan van der Heide JJ, Bilo HJ, Donker AJ, et al. The effects of dietary supplementation with fish oil on renal function and the course of early postoperative rejection episodes in cyclosporine-treated renal transplant recipients. Transplantation 1992; 54 (2): 257-63
64. Kovarik JM, Mueller EA, van Bree JB, et al. Cyclosporine pharmacokinetics and variability from a microemulsion formulation: a multicenter investigation in kidney transplant patients. Transplantation 1994; 58 (6): 658-63
65. Muls E, Kolanowski J, Scheen A, et al. The effects of orlistat on weight and on serum lipids in obese patients with hypercholesterolemia: a randomized, double-blind, placebo-controlled, multicentre study. Int J Obes Relat Metab Disord 2001; 25 (11): 1713-21

66. Nägele H, Petersen B, Bonacker U, et al. Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. Eur J Clin Pharmacol 1999; 55 (9): 667-9
67. le Beller C, Bezie Y, Chabatte C, et al. Co-administration of orlistat and cyclosporine in a heart transplant recipient. Transplantation 2000; 70 (10): 1541-2
68. Schnetzler B, Kondo-Oestreicher M, Vala D, et al. Orlistat decreases the plasma level of cyclosporine and may be responsible for the development of acute rejection episodes. Transplantation 2000; 70 (10): 1540-1
69. Errasti P, Garcia I, Lavilla J, et al. Reduction in blood cyclosporine concentration by orlistat in two renal transplant patients. Transplant Proc 2002; 34 (1): 137
70. Barbaro D, Orsini P, Pallini S, et al. Obesity in transplant patients: case report showing interference of orlistat with absorption of cyclosporine and review of literature. Endocr Pract 2002; 8 (2): 124
71. Zhi J, Moore R, Kanitra L, et al. Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. J Clin Pharmacol 2002; 42 (9): 1011

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