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Pharmacokinetics and Pharmacodynamics of Mycophenolate in Patients After Renal Transplantation

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1. Introduction

Mycophenolic-acid (MPA) is a selective, non-competitive inhibitor of Inosine-Monophosphate-Dyhydrogenase (IMPDH) leading to the inhibition of the de-novo synthesis of guanosine-nucleotides. In human lymphocytes inhibition of IMPDH results in altered cellular proliferation with arrest in the S-phase of the cell cycle. Due to the absence of a salvage pathway, proliferating activated t-cells are severely affected by the inhibitory effects of MPA (1-3). For patients after renal transplantation MPA is used either as mycophenolate-mofetil (MMF, Cellcept) or as enteric-coated mycophenolate-Sodium (EC-MPS, Myfortic) in daily doses of 2000 mg respectively 1440 mg per day.

Since its introduction in immunosuppressive therapy more than ten years ago, Mycophenolate-Mofetil (MMF) is an established part of immunosuppressive therapy after renal transplantation. Still in the first publication of the landmark Tricontinental trial because of possibly dose-related side effects of the drug (CMV-infection, gastrointestinal disturbances, and increased cancer risk) the need for individualization depending on clinical course or other factors was mentioned (4).

The usefulness of pharmacokinetic measurements of MMF was shown in early studies stating that the Area-under the curve (AUC) of MMF is predictive of the likelihood of allograft rejection after renal transplantation in patients receiving mycophenolate mofetil (5). To facilitate therapeutic drug monitoring different limited sampling strategies for adult and pediatric patients after renal transplantation were established (6-13).

The two available preparations of MPA (MMF, EC-MPS) showed equivalent drug exposure measured by MPA-AUC when applied to the patients in equimolar doses. Therefore, both preparations are seen as equipotent (14-16).

2. Pharmacokinetics of MPA

MPA trough levels show relevant inter- and intraindividual variability especially in patients with elevated serum creatinine and proteinuria (17-19). Clinically important, low trough

levels are associated with an increased frequency of rejection (20), whereas elevated MPA trough levels are related to an increased risk for infections (21). Nevertheless, relevant correlations between MPA trough levels and MPA-AUC values could not be detected, therefore the usefulness of measuring trough levels in routine care of renal transplant recipients is doubted (22-24).

2.1 Effect of immunosuppressive therapy on MPA pharmacokinetics

Concomitant immunosuppressive therapy has major influence on MPA pharmacokinetics. For patients on Cyclosporine (CsA) therapy lower MPA trough levels are observed (25). In addition, MPA trough levels increased after discontinuation of CsA resulting in almost a doubling of MPA trough concentrations (26). In general, the variability of MPA-AUC in patients with concomitant cyclosporine and steroid therapy seems to be low (27). However, in 154 patients with an immunosuppressive therapy consisting of CsA, prednisone and MMF the mean MPA AUC increased after 21 days although mean MMF dose was reduced (28).

For patients treated with tacrolimus (TAC) increased MPA trough levels are reported (29). Additionally, a randomized trial with 150 participants, patients receiving TAC and MMF displayed significantly higher MPA trough levels and higher MPA exposure measured by MPA-AUC than those receiving CsA and the same dose of MMF. Equivalent MPA levels could only be attained in patients receiving CsA by increasing the MMF dose by 50% (30). Similar results were obtained for pediatric renal transplantation (31). Interestingly, at least in Japanese renal transplant patients, a difference for MPA-AUC in patients with different tacrolimus-trough levels could not be detected (32). At least, for renal transplant recipients limited sample strategies for MPA-AUC with concomitant medication of tacrolimus are established (33).

In patients with Sirolimus (SRL) MPA exposure in the presence of SRL is higher than MPA exposure with CsA. Therefore it was recommended, that the MMF dose should be reduced to 0.75 g twice a day in patients receiving SRL to obtain MPA-AUC levels comparable to that in patients treated with CsA and MMF 1 g twice a day (8). These results were confirmed in a pharmacokinetic study in 31 renal transplant patients (34). It was also shown, that although MPA peak concentration and time to peak concentration was comparable, the MPA-AUC was higher in patients receiving SRL instead of CsA (35).

Steroids have been shown to induce the hepatic glucuronyltransferase (GT) expression enhancing the activity of uridine diphosphate-GT, the enzyme responsible for mycophenolic acid (MPA) metabolism. Therefore, also for steroids interactions with MPA are reported. During a steroid tapering and withdrawal phase in 26 patients MPA trough levels progressively increased and plasma MPA clearance declined (36).

2.2 Effect of concomitant therapy on MPA pharmacokinetics

For patients in the maintenance phase after transplantation it is known, that MPA-AUC increases with declining transplant function (37). This effect may be modulated by concomitant medication. Beside immunosuppression, patients after renal transplantation have to use antiviral prophylaxis. At least for Ganciclovir no effect on MPA clearance in kidney transplant recipients was reported (38).

With respect to the use of proton pump inhibitors the published results are unequivocally. In Japanese patients, the peak MPA-concentrations were lower with 30 mg lansoprazole

than with 10 mg rabeprazole or without PPI. For patients with cytochrome (CYP) 2C19, and multidrug resistance (MDR)1 C3435T polymorphisms this was also seen for the MPA-AUC (39).

Patients after heart transplantation with PPI co-medication show significantly lower MPA plasma concentrations resulting in lower drug exposure exposing the patients at a higher risk for acute rejection (40). Also in patients with autoimmune diseases the co-medication of pantoprazole with MMF significantly influences the drug exposure and immunosuppressive potency of MMF (41). In contrast, the recently published sub-analysis of the CLEAR-study reported no difference in MPA-AUC in patients with or without PPI-therapy when a 3g/d loading dose of MMF for 5 days used. However, MPA concentrations 2 h and 12 h after MMF intake were reduced (42).

At least for heart transplant recipients no influence of pantoprazole on EC-MPS pharmacokinetics could be disclosed (43).

Own results in 74 patients in the early and maintenance phase after renal transplantation showed a relevant reduction in normalized MPA-AUC (40,9 +/- 19,7 vs. 26,1 +/- 11,7 mg/l*h; p<0,01) in patients with PPI co-medication. A difference between patients using either omeprazole or pantoprazole in MPA-AUC could not be detected. (Rath et al., Congress of the German Transplantation Society, 2009)

3. Clinical relevance of MPA-AUC

3.1 MPA-AUC and acute rejection

In different clinical trials, MPA drug exposure was correlated with the occurrence of biopsy proven acute rejection (BPAR). In a double blind trial aiming for three predefined target MPA AUC values the incidence of BPAR was lower in patients with MPA AUC values between 30 and 60 $\mu\text{g} \times \text{h}/\text{ml}$ (28). Similar results were reported for a group of 46 stable patients after renal transplantation, with better graft function in patients with a MPA AUC > 40 $\mu\text{g}/\text{ml} \times \text{h}$ and for pediatric renal transplantation (20;44;45).

Three randomized trials, the OPTICEPT study, the APOMYGRE-trial (Adaption de Posologie du MMF en Greffe Renale) and the FDCC study (fixed-dose versus concentration controlled) investigated the benefit of therapeutic drug monitoring for MMF in renal transplant recipients.

The APOMYGRE Trial was a study in 137 allograft recipients treated with basiliximab, cyclosporine A, corticosteroids and MMF. Patients were randomized to receive either concentration-controlled doses or fixed-dose MMF. A novel Bayesian estimator of MPA AUC based on three-point sampling was used to individualize MMF doses. At month 12, the concentration-controlled group had fewer treatment failures and acute rejection episodes. Therefore, the authors conclude, that therapeutic MPA monitoring using a limited sampling strategy can reduce the risk of treatment failure and acute rejection in renal allograft recipients 12 months post-transplant with no increase in adverse events (46).

The FDCC study was a randomized trial in 901 patients after renal transplantation allocating patients to receive MMF either in a fix dose or in a concentration controlled manner aiming at a predefined MPA AUC of 45 $\text{mg} \times \text{h}/\text{L}$. In general, there was no difference in the incidence of primary treatment failure or biopsy proved rejection. However, MPA-AUC levels at day 3 after transplantation predicts the incidence of BPAR in the first year (47).

The OPTICEPT study was a 2-year, open-label, randomized, multicenter trial comparing the efficacy and safety of concentration-controlled MMF dosing with a fixed-dose regimen in 720 kidney recipients. In patients with Tacrolimus, those with higher MMF exposure had less rejection episodes (48).

Similarly, a recently published substudy of the FDCC-trial in patients with delayed graft function disclosed significantly lower dose-corrected MPA AUC on Day 3 and Day 10 in this patient group (49).

3.2 MPA-pharmacokinetics and gastro-intestinal side effects

It is known, that side effects of MMF are causing dose reductions in approximately 60% of the patients leading to a cumulative and increasing risk for acute rejection (50). In addition, gastrointestinal (GIT) side effects affect medical adherence of the patients with consecutive risk for graft failure (51). In addition, dose reductions of MMF are related to increased costs, mainly due to frequent hospitalization of the patients (52).

USRDS data of 3589 patients with MMF prescription and GIT complaints revealed that dosage reduction or discontinuation of mycophenolate mofetil in the first 6 months after diagnosis of GI complications was associated with significantly increased risk of graft failure and increased healthcare costs in adult renal transplant recipients (53). Another report from USRDS data of 3675 patients with gastrointestinal complications under MMF and subsequent dose reduction also disclosed an increased risk for graft loss after dose reduction or discontinuation of MMF (54).

The enteric coated preparation of mycophenolate (EC-MPS) is attributed to a lower rate of gastrointestinal side effects, but in a prospective study based on patient questionnaires the rate of gastrointestinal side effects was nearly identical between the two formulations (55). In addition, a double-blind study comparing MMF and the newly developed enteric-coated formulation of MPA (EC-MPS) showed no advantage for either of the drugs (56). In contrast, a large, prospective study in more than 700 renal transplant recipients disclosed a significant improvement in gastrointestinal adverse events after conversion from MMF to EC-MPS (57). A study in patients with GIT complaints under MMF switching to EC-MPS indicates that converting patients with mild, moderate or severe GI complaints from MMF to EC-MPS significantly reduces GI-related symptom burden and improves patient functioning and well-being (58).

Also in liver transplant patients results are reported that converting patients with gastrointestinal complaints from MMF to equimolar doses of EC-MMF leads to a reduction of gastrointestinal-related symptom burden and frequency of stools (59).

There is some evidence from pharmacokinetic studies that elevated MPA exposure correlates with the occurrence of gastrointestinal side effects. Some authors suggest that gastrointestinal side effects are related to exposure of the active substance MPA (60). Others report, that the occurrence of possibly MMF-related side effects corresponds with MPA-AUC and MPA concentration 30 minutes after oral dose of 1000 mg (61). Also, a longitudinal study in 37 patients with 357 MPA measurements revealed higher trough levels in patients with MMF associated side effects (62). It is known that MPA trough levels >3 mg/l, peak levels >8.09 mg/l and MPA-AUC >37.6 mg \cdot h/l may lead to adverse effects (63). Also in 31 patients after renal transplantation higher MPA-AUC (>60 mg \cdot h/l) was

associated with side effects (64). Nevertheless, in a small pharmacokinetic study with 11 hispanic renal transplant patients treated with EC-MPS the MPA-AUC does not correlate with overall Gastrointestinal Symptom Rating Scale scores or subscale scores (65).

Also, a 5-year clinical follow-up study in 100 renal allograft recipients in whom MPA exposure was measured at 7 days, 6 weeks, 3 months, 1, 3, and 5 years post transplantation using abbreviated AUC measurements reported more episodes of leucopenia and anemia with MPA AUC(0-12h) ranges $>60 \text{ mg/L} \times \text{h}(-1)$. However, no association between incident episodes of diarrhea or infection and target MPA AUC (0-12 h) ranges (66).

4. Pharmacodynamics of MPA

4.1 Inhibition of IMPDH-activity

Recently, pharmacodynamic measurement of MPA was introduced into clinical practice. Especially with the use of reversed-phase HPLC, it is possible to monitor the immunosuppressive effect of MPA in its target cell population by quantifying the activity of IMPDH. This nonradioactive method for specific measurement of IMPDH activity in isolated peripheral mononuclear cells was developed by direct chromatographic determination of produced xanthosine 5'-monophosphate (XMP). In the canine model MPA in therapeutic doses leads to an 50% inhibition of IMPDH-activity (67). Application of a single dose of 1 g MMF in dialysis patients resulted in a significant inhibition of IMPDH activity in lysed mononuclear cells. IMPDH activity is inversely correlated to MPA blood concentrations and the IC (50) for in vitro inhibition of IMPDH activity was about 2 to 3 $\mu\text{g/l}$. (68). In addition, others report, that IMPDH-activity on peak concentration of MPA is approximately 40% and could be suppressed for 8 hours (69). In general, it is assumed, that IMPDH activity has a substantial interindividual, but low intraindividual variability (70). This was also shown in pediatric patients (71).

In addition, in renal allograft recipients an inverse relationship between plasma MPA and IMPDH activity within the dose interval was demonstrated and minimum IMPDH activity was a median 8 % of values pre-MMF dose, coinciding with the MPA peak. Six hours post-dose, IMPDH activity had returned to pre-dose values. Patients receiving MMF had a 4.5-fold higher pre-dose enzyme activity than transplanted patients without MMF (72). Long-term treatment with mycophenolate was associated with an induction of IMPDH activity (73). Also a study with 12 patients over two years showed an increase of type 1 IMPDH mRNA during the first 3 months following transplantation and reaching its maximal level during acute rejection episodes, whereas type2 IMPDH mRNA was stable (74). Interestingly, in 30 patients transplantation and the initiation of immunosuppressive therapy was associated with increased IMPDH1 and decreased IMPDH2 expression. In addition, patients with acute rejection during follow-up demonstrated higher IMPDH2 expression in pretransplant CD4+ cells than nonrejecting patients (75). Later, the same group described in detail the MMF concentration dependent modulation of IMPDH1 expression in renal allograft recipients (76).

4.2 IMPDH-activity and acute rejection

Measurement of IMPDH activity may be useful in estimating the degree of immunosuppression in individual patients in addition to applied MMF dose. When

comparing three patients groups with MMF doses of 1.0, 1.5 and 2.0 g/d there was no correlation between MPA-AUC (0-12) values and MMF dose detectable. Also, the degree of inhibition of IMPDH activity was comparable in the three groups, indicating considerable interindividual pharmacodynamic variability (77). In a cross-sectional analysis patients experiencing acute rejection episodes had increased IMPDH activity during rejection episodes (78). Additional information was gained in a genotyping study in 191 kidney transplant patients. There, seventeen genetic variants were identified in the IMPDH1 gene with allele frequencies ranging from 0.2 to 42.7%. Two single-nucleotide polymorphisms, rs2278293 and rs2278294, were significantly associated with the incidence of biopsy-proven acute rejection in the first year post-transplantation (79). A similar study in 82 Japanese transplant recipients found no difference in the incidence of subclinical acute rejection between IMPDH1 rs2278293 or rs2278294 polymorphisms ($p = 0.243$ and 0.735 , respectively). However, the authors report that the risk of subclinical acute rejection for recipients who cannot adapt in therapeutic drug monitoring (TDM) of MPA seems to be influenced by IMPDH1 rs2278293 polymorphism (80). Also, in patients after renal transplantation high pre-transplant IMPDH-activity predisposes to subsequent MPA dose-reductions and increases the risk for acute rejection (81).

4.3 IMPDH activity and MMF or EC-MPS

There is some discussion about the degree of IMPDH suppression with either MMF or EC-MPS. In a single-center, crossover study in patients treated with MMF and EC-MPS IMPDH activity inversely followed MPA concentrations and was inhibited to a similar degree (approximately 85%) by both formulations. In addition, the calculated value for 50% IMPDH inhibition was identical for both drugs (16). However, when comparing the pharmacodynamic activity of MMF and EC-MPS a series of 260 measurements in 110 patients disclosed lower median IMPDH activity in the EC-MPS patients than in the MMF patients. This was especially pronounced in patients on 1440 mg/d EC-MPS compared with 2000 mg/d MMF (82).

Nevertheless, for EC-MPS a recently published pharmacokinetic study in 75 de-novo kidney transplant recipients randomly assigning the patients either to receive EC-MPS as standard dose or as intensified dose revealed in an exploratory analysis of IMPDH activity that the intensified regimen resulted in significantly lower IMPDH activity on day 3 after transplantation (83).

There is ongoing discussion about the effect of PPI therapy on pharmacokinetics of MMF and EC-MPS. In a cross-sectional analysis in 153 renal transplant recipients, we measured IMPDH-activity before the first daily dose of MMF or EC-MPS. We could not detect any statistical with respect to PPI intake, type or dosing of either MMF or EC-MPS (Congress of the German Transplant Society, 2009).

5. Measuring IMPDH-activity

5.1 Sample preparation

Peripheral blood is collected in 5ml tubes with Li-heparin as anti-coagulant and stored at room temperature. Heparin is superior to EDTA as anti-coagulant since it maintains cell viability for longer time. Within four hours after arrival of the sample to the lab, and within

no more than two days of collection, the peripheral mononuclear cell fraction is isolated by density centrifugation according to a modified protocol from Glander et al. (2001). Li-heparinized blood (2.5ml) is mixed with an equal volume of phosphate-buffered saline (PBS), carefully layered on 4ml Lymphodex (InnoTrain, Germany) density gradient centrifugation medium in a 15ml screw-cap polypropylene tube, and centrifuged at $1200 \times g$ for 15 min without brake at room temperature.

The mononuclear cell fraction is collected from the interphase and transferred into a fresh 15ml screw-cap tube with 5ml PBS for washing. The cells are washed only once with PBS since repeated washing steps might cause diffusion of mycophenolate from the cells, resulting in over-estimation of the residual IMPDH activity. After centrifugation at $1200 \times g$ for 10 min at room temperature, the supernatant is removed quantitatively. This step is crucial with respect to the assay validity, since only a minute fraction of the total mycophenolate is contained within the cells, while the vast majority (estimated 99%) is present in the plasma. Any trace of the supernatant might therefore still contain considerable amounts of mycophenolate, hence leading to a vast underestimation of the residual IMPDH activity. The cell pellet is resuspended in 250 μ l ice-cold HPLC-grade water, and 125 μ l of the sample are transferred into each of two 2ml screw-cap vials, one designated as working sample, the second as back-up. The vials are deep frozen at -80°C until assayed. In the same way, control cells from healthy probands are prepared; these cells will be included in each assay as an incubation control.

5.2 IMPDH activity assay

The residual IMPDH activity is assayed in a cell-free system. The patient samples and control cells are thawed at room temperature and vigorously vortexed for 30 seconds to support cell lysis; insoluble cell fragments are removed by centrifugation at $4000 \times g$ for 5 min at room temperature in a desktop centrifuge. Cell lysate (50 μ l) is added to 100 μ l incubation buffer containing 1 mmol/L inosine-monophosphate (IMP) as substrate, 0.5 mmol/L NAD as co-substrate, 72 mmol/L sodium dihydrogen-phosphate, and 180 mmol/L potassium chloride (pH = 7.5). After adjusting the volume to 180 μ l with distilled water, the samples are incubated at 37°C in a heating block. In presence of NAD, IMPDH converts inosine-monophosphate to xanthine 5'-mono-phosphate. In the subsequent high-performance liquid chromatography (HPLC) assay, the amount of synthesized xanthine 5'-monophosphate is determined together with the amount of AMP, which serves as an internal standard for normalization to the cell count.

After exactly 2.5 hours of incubation, the reaction is stopped by adding 20 μ l ice-cold 4mol/L perchloric acid. Precipitation of denatured protein is enhanced by incubating the samples at -20°C for 10 min. After centrifugation at 13000 rpm for 2 min in a desktop centrifuge, 170 μ l supernatant are transferred to a test tube containing 14 μ l 2.5 mol/L potassium carbonate solution for neutralization. The exact volume of potassium carbonate, required to achieve a final pH between pH 6 and pH 7, has to be determined for each lot of 4 mol/L perchloric acid and 2.5 mol/L potassium carbonate solution. Prior to HPLC analysis, the samples are deep-frozen at -20°C for at least 30 min, thawed, and centrifuged 5 min at 13000 rpm in a desktop centrifuge.

5.3 HPLC chromatography

Determination of the amounts of xanthine-monophosphate and adenosine-monophosphate is carried out by ion-pair reversed-phase high-performance liquid chromatography on a computerized isocratic HPLC system from Shimadzu (Kyoto, Japan) consisting of a system controller SCL-10A VP, an HPLC pump LC-10AT VP, an autoinjector SIL-10AF, a column oven CTO-10AS VP, and an UV-VIS detector SPD-10A VP, controlled by Shimadzu LC Solution data collection software.

For the assay 6 µl of the samples are loaded onto a 250 mm x 3.1 mm Prontosil 120 to 5 ODS AQ column (Bischoff Chromatography, Leonberg, Germany). Column oven temperature is set to 40°C. Chromatographic separation is achieved using a mobile phase containing 50 mmol/L potassium-dihydrogen-phosphate, 7 mmol/L tetra-n-butyl-ammonium hydrogen sulfate, and 6% (v/v) methanol at a flow rate of 1 mL/min. The analytes are detected at 254-nm wavelength. Incubation efficacy is verified by including a sample from a healthy volunteer as incubation control in each incubation cycle. For calibration, two standards containing 500 and 2500 pmol xanthin-monophosphate and adenosin-monophosphate, respectively, in 0.4% BSA solution are processed in several independent experiments, and repeatedly measured, like the patient specimen: protein denaturation with perchloric acid followed by neutralization with potassium carbonate. This calibration curve allows to deduct the amount of XMP synthesized during incubation and the amount of AMP in the sample. The specific IMPDH activity is then expressed as pmol XMP synthesized per second, which is normalized to 1 pmol of AMP [pmol XMP/(pmol AMP s)].

6. Summary and conclusion

Mycophenolic-acid (MPA) is a selective, non-competitive inhibitor of Inosine-Monophosphate-Dyhydrogenase (IMPDH) leading to the inhibition of the de-novo synthesis of guanosine-nucleotides. In human lymphocytes inhibition of IMPDH results in altered cellular proliferation with arrest in the S-phase of the cell cycle. Due to the absence of a salvage pathway, proliferating activated t-cells are severely affected by the inhibitory effects of MPA.

In patients after renal transplantation, MPA is a well-established part of immunosuppressive therapy, applied either as mycophenolate-mofetil (MMF, Cellcept) or as mycophenolate-sodium (MPS, Myfortic). MMF is used in prophylaxis of kidney rejection for nearly 15 years in daily doses of 2 - 3 g/d. The enteric-coated MPS is available since a few years; the recommended daily dose is 1440 mg/d. Both preparations are equipotent, when given in equimolar doses.

In recent years drug monitoring of MPA gained more and more attention proving its usefulness in clinical setting. Relevant information could be collected by measuring MPA drug exposure by calculating the MPA-Area under the curve (MPA-AUC) with pharmacokinetic modeling allowing estimating the degree of immunosuppression.

In different clinical studies MPA-AUC target concentrations of 30 - 60 µg*h/ml were correlated to a low rate of rejections and less occurrence of drug induced side effects. Clinically important, MPA metabolism is influenced not only by the choice of immunosuppressive medication, but also by renal function and concomitant medication.

Recently pharmacodynamic measurement of MPA was introduced into clinical practice. Especially with the use of reversed-phase HPLC, it becomes possible to monitor the immunosuppressive effect of MPA in its target cell population by quantifying the activity of IMPDH. IMPDH activity is inversely correlated to MPA blood concentrations. Maximum inhibition of IMPDH activity ranges between 60% and 80% and the reported IC (50) of IMPDH activity corresponds to MPA blood levels of 2-3 μ /l. In renal transplant recipients, IMPDH shows relevant inter-individual variability. However, pre-transplant IMPDH activity was predictive for increased risk of rejection when additional dose reductions of MMF were necessary. In a cross-sectional studies better transplant function was associated with lower IMPDH-activity and probably the usage of EC-MPS. Pharmacokinetic and pharmacodynamic parameters of MPA are influenced by additional immunosuppression. In addition, concomitant therapy especially the use of proton-pump inhibitors affects MPA-levels, whereas an effect of IMPDH-activity, at least in renal transplant recipients could not be disclosed. Therefore, it can be concluded, that pharmacokinetic and pharmacodynamic measurements of MPA adds relevant information to improve clinical care of renal transplant recipients.

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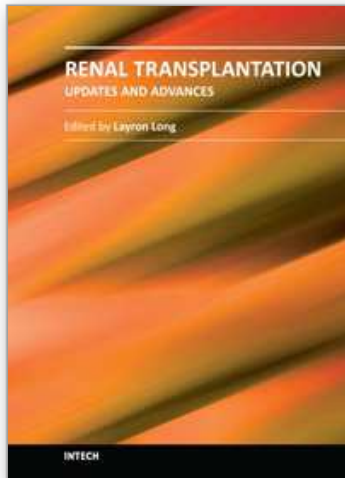
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