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Dosing of MMF in combination with tacrolimus for steroid-resistant vascular rejection in pediatric renal allografts

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Abstract Steroid-resistant vascular rejection was treated in seven adolescent renal allograft recipients using the combination of mycophenolate mofetil (MMF) and tacrolimus (FK506). Since there are no published pediatric dose recommendations for MMF using this combination, trough concentrations and pharmacokinetic profiles were used for therapeutic drug monitoring. In order to keep the mycophenolic acid (MPA) concentrations between 2–5 μg/ml, mean MMF doses were reduced from 600 to 250 mg/m^2 b.i.d. Apparent clearance of MPA decreased from 5 to 1 ml/min per kg within 2 weeks. Pharmacokinetic monitoring revealed substantial variability among patients of both MMF and FK506. The MPA dose ranged from 178 to 1008 mg/m^2 per day to achieve an area under the curve (AUC) of 59.9 μg × h/ml ± 10.5 SD (range 49–65 μg). FK506 dose ranged from 1.3 to 8.8 mg/m^2 per day to achieve an AUC of 116 ng × h/ml ± 27 SD (range 83–145). We recommend adjusting MMF doses using therapeutic drug monitoring.

Key words Steroid-resistant vascular rejection · Adolescents · Mycophenolate mofetil · Tacrolimus · Therapeutic drug monitoring

Introduction

Both mycophenolate mofetil (MMF) and tacrolimus (FK506) have been advocated for the treatment of patients with steroid-resistant vascular rejection (SRVR) in whom prognosis is poor [1, 2]. We previously reported a successful treatment of SRVR in a 15-year-old girl with the combination of MMF and FK506, which was complicated by severe MMF toxicity despite utilizing the recommended dosage [3]. As this patient required a substantial dose reduction of MMF, we report on therapeutic drug monitoring (TDM) in seven adolescent renal transplant recipients treated with this combination.

Patients and methods

Seven (five female, two male) adolescent renal transplant recipients (six cadaver, one living related donor) with a mean age of 15.8 years ± 1.6 SD (range 13.0–18.1) were diagnosed as having an acute rejection episode on the basis of clinical findings (rise of serum creatinine, tender, swollen graft, rise of kidney volume or resistance index on ultrasound, development of acidosis, and others) whilst being on a "triple" immunosuppressive therapy consisting of cyclosporine microemulsion, azathioprin, and steroids. The given rejection episode was a first late acute rejection in two patients. All other cases had experienced steroid-responsive rejection episodes prior to this event. These rejection episodes occurred after a mean of 719 days ± 947 SD (median 281, range 50–2285) after renal transplantation.

All patients received 6 days of methylprednisolone therapy at a dose of 10 mg/kg per day intravenously, and in all cases serum creatinine continued to rise despite this treatment. Percutaneous renal biopsy revealed ongoing tubulointerstitial and vascular rejection in each case.

Subsequently, all patients were converted to FK506 (starting dose of 0.15 mg/kg b.i.d., 8.6 mg/m^2 per day ± 1.6 SD) and MMF

(starting dose 600 mg/m^2 b.i.d., 1127 mg/m^2 per day ± 259 SD). Prednisolone was given at a dose of 12 mg/m^2 per day for 3 days and then tapered down to 4 mg/m^2 per day.

Because as yet no pediatric dose recommendations have been published for MMF in combination with FK506, all patients underwent TDM. The study is in accordance with the ethical standards of the Helsinki declaration of 1975 (revised in 1983) and parents' or 18-year-old patients' gave consent in each case. Drug monitoring was performed by the estimation of trough concentrations and a pharmacokinetic profile between days 10 and 18. FK506 trough concentrations were targeted at 6–15 ng/ml in the first week and 5–11 ng/ml thereafter. FK506 was measured by microparticle enzyme immunoassay using a modified, sensitive Abbot tacrolimus I assay [4]. Mycophenolic acid (MPA) and MPA glucuronate (MPA-G) were measured by HPLC [5]. Pharmacokinetic studies were undertaken by repetitive blood sampling before, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after oral intake of the drugs. The area under the curve (AUC) was calculated by the trapezium rule. Trough concentrations correlated significantly with the AUC, and therefore apparent drug clearance was estimated as the ratio of the MMF dose (expressed as dose of MPA) per kilogram body weight to the corresponding trough concentration similar to the clearance calculation of Bullingham et al. [6]. This apparent clearance was corrected by an assumed bioavailability of 0.84 for MMF [6] and 0.201 for FK506 [7], respectively.

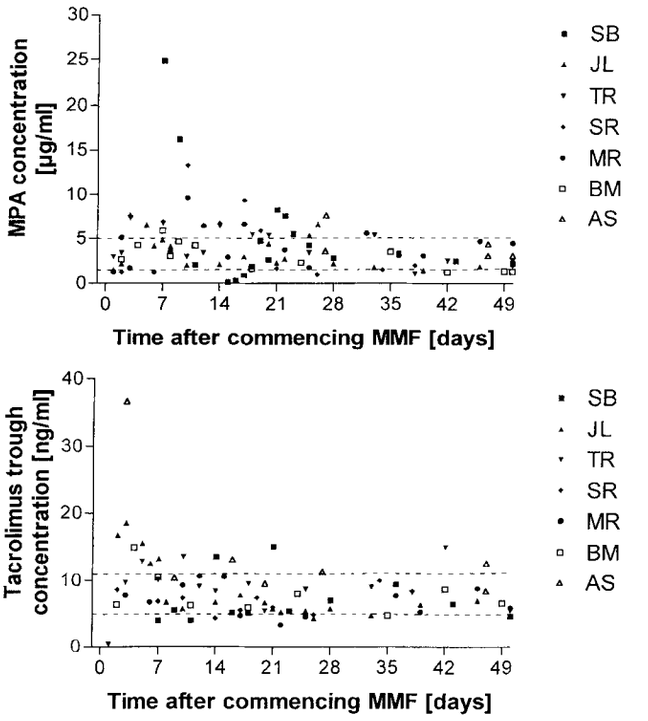

Fig. 1 Mycophenolic acid (MPA) and tacrolimus trough concentrations in seven pediatric renal transplant patients all treated for biopsy proven, steroid-resistent vascular rejection (SRVR) after 6 days of methylprednisolone pulses at a dose of 10 mg/kg

Results

Mean baseline serum creatinine before SRVR was 116 µmol/l ± 38 SD (range 85–195). After 6 days of methylprednisolone, serum creatinine was 269 µmol/l ± 147 SD (range 115–447, $P = 0.0156$). Following initiation of MMF and FK506 rejection therapy, there was an initial further rise of serum creatinine until day 3 (288 µmol/l ± 153 SD, range 117–518, $P = 0.0123$). The mean maximum serum creatinine during the acute rejection episode was 313 µmol/l ± 138 SD (range 177–524). After 7 weeks, serum creatinine declined to 234 µmol/l ± 118 SD (range 111–446, $P = 0.0075$, paired t-test). The decline of serum creatinine was slow, and serum creatinine did not return to baseline creatinine values.

FK506 and MPA were monitored by measurement of trough concentrations. FK506 trough concentrations were kept in the desired therapeutic window (Fig. 1, top). Mean FK506 doses were decreased from 8.6 mg/m^2 per day ± 1.6 SD at day 1 to 5.1 mg/m^2 per day ± 2.8 SD after 7 weeks (Fig. 3, top). The mean FK506 AUC after a median of 14 days (range 10–18 days) at mean tacrolimus dose of 4.9 mg/m^2 per day ± 2.6 SD (range 1.3–8.8) was 116 ng × h/ml ± 27 SD (range 83–145); the median t_{max} of FK506 was 60 min (range 30–180) and the mean C_{max} was 18.8 ng/ml ± 5.6 SD (range 14.0–29.3; Fig. 2).

Due to our previous observation of an MPA trough concentration of 26 µg/ml[3], we measured MPA trough concentrations and at least one MPA AUC in all patients. MPA AUC correlated with MPA trough concentrations ($r = 0.8294$, $P = 0.0210$). Mean MPA AUC after a median of 14 days (range 10–18 days) at a mean MMF dose of 496 mg/m^2 per day ± 282 SD (range 178–1008) was 59.9 µg × h/ml ± 10.5 SD (range 49–65); the median t_{max} of MPA was 60 min (range 30–120) and the mean C_{max} was 14.5 µg/ml ± 4.7 SD (range 9.7–16.9; Fig. 2). Mean MPA-G AUC was 1137 µg × h/ml ± 612 SD (range 604–2239); the median t_{max} of MPA-G was 90 min (range 60–180) and the mean C_{max} was 139 µg/ml ± 63 SD (range 62–233; Fig. 2). Trough concentrations were used to adjust MMF doses. MMF doses had to be reduced in all patients in order to maintain trough concentrations below 5 µg/ml (Fig. 1, bottom). The mean MPA dose was 1127 mg/m^2 per day ± 259 SD (range 750–1392) on day 2 after commencement of MMF therapy. After 7 weeks, the dose was significantly lower at 320 mg/m^2 per day ± 322 SD (range 74–1008) with trough concentrations in the therapeutic window (Fig. 3, top; $P < 0.0001$, t-test). The apparent clearance of FK506 remained unchanged whereas MPA clearance dropped from 0.5 ml/min per kg ± 0.9 SD (range 4.0–5.6) to 1.0 ml/min per kg ± 0.8 SD (range 0.3–2.5) ($P < 0.0001$, t-test; Fig. 3, bottom).

Side effects of therapy were remarkably little. Apart from one episode of severe diarrhea reported [3], no pa-

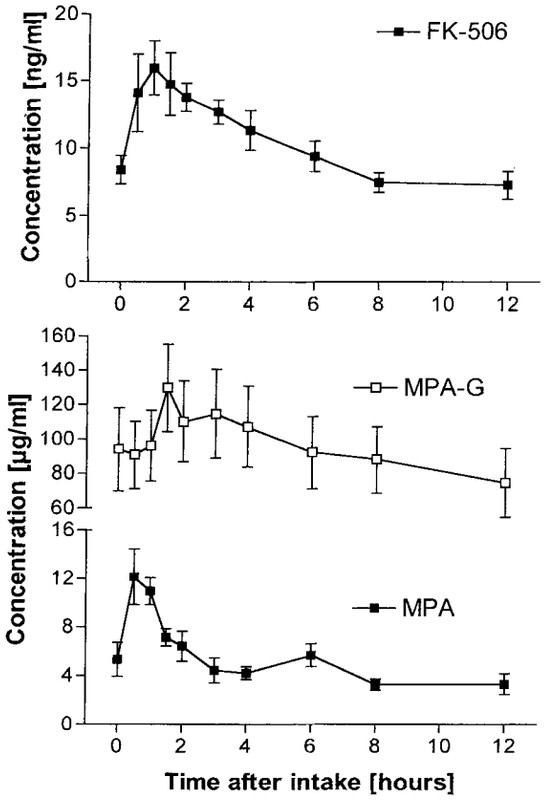

Fig. 2 Pharmacokinetic profiles (mean ± SEM) of FK506, MPA, and MPA glucuronate in seven renal transplant patients with SRVR 10–18 days after start of therapy

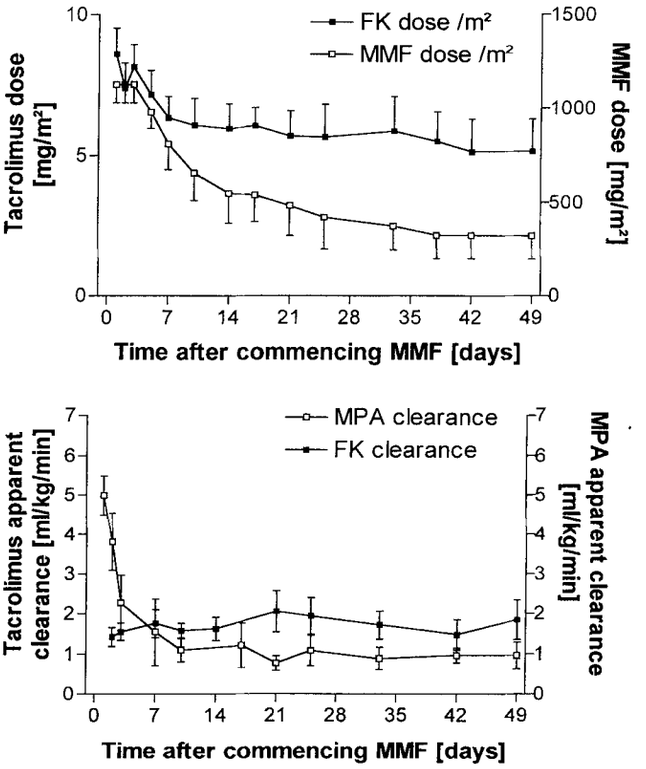

Fig. 3 MPA and tacrolimus doses in mg/m² ± SD in seven pediatric renal transplant patients all treated for biopsy proven SRVR after 6 days of methylprednisolone pulses at a dose of 10 mg/kg *(top)* and apparent drug clearances *(bottom)*

tient developed diarrhea after establishing trough concentrations of MPA below 5 µg/ml. After a mean follow up of 282 days ± 175 SD (range 49–503), five patients still have a functioning graft with stable graft function (serum creatinine 142 µmol/l ± 76 SD). Although the other two patients also had improved graft function for the first 6 months, both lost their graft 339 and 385 days after the start of rescue therapy. Both graft losses were associated with discontinuation of the MMF therapy 6 months after starting MMF and tacrolimus rejection therapy. MMF was discontinued because of the fear that possible overimmunosuppression might increase the risk of posttransplantation lymphoproliferative disease. MMF was successfully discontinued in one patient, and four patients still are on MMF.

Discussion

The combination of MMF and FK506 was effective for the initial control of SRVR in all of these seven pediatric renal transplant patients. Following discontinuation of MMF after 6 months in three patients, two graft losses were noted. No serious side effects were observed when reducing the MMF dose to one-third of the initial doses according to MPA monitoring. Pharmacokinetic monitoring of immunosuppressive drugs provides a useful method for the optimization of drug dosage [8]. Few data are available on dosing with MMF in pediatric kidney transplantation, and data are restricted to MMF in combination with cyclosporine [9]. In combination with cyclosporine a dose of 600 mg MMF b.i.d. has been recommended [9]. No reports are available on the combination of MMF and FK506 in pediatrics.

A 50% inhibition of inosine monophosphate dehydrogenase proposed to be sufficient for immunosuppression was found at MPA concentrations between 2–5 µg/ml [8]. Adult studies revealed substantial variability among patients regarding MPA clearance [8]. It has been reported that after oral administration in humans, serum concentration, as well as AUC, was significantly lower during the immediate post transplant period as compared to day 20 after transplantation [10].

In this study, TDM of MPA resulted in a reduction of the MMF dose from approximately 600 to 250 mg/m² b.i.d. with effective control of rejection and without

toxic side effects. Gastrointestinal side effects were stated in 52.5% of 160 adult renal transplant recipients of the European Mycophenolate Mofetil Cooperative Study Group receiving 1.5 g of MMF b.i.d. [11]. Using a mean dose of approximately 250 mg/m^2 b.i.d. in combination with FK506, we achieved a similar AUC as previously published in five adult renal transplant recipients [8] (59.9 μg × h/ml ± 10.5 SD versus 58.2 μg × h/ml ± 22.8 SD in the Langman et al. study [8]). However, as well as others [12], we emphasize the need for rigorously defined drug monitoring when combining MMF and FK506. It currently remains unclear whether the change of MPA clearance is part of the drug's owns characteristics, may reflect some interaction between FK506 and MMF despite no known common pathways of metabolism, or may be due to pathophysiological mechanisms in this particular group of patients. We conclude that patients treated with FK506 and MMF for SRVR may require a substantial reduction of the MMF dosage when compared to cyclosporine and MMF. TDM is essential to avoid both serious side effects and insufficient immunosuppression.

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