Medical Case Studies Vol. 2(7), pp. 58-68, December 2011
Available online at http://www.academicjournals.org/MCS
DOI: 10.5897/MCS11.029
ISSN 2141-6532 ©2011 Academic Journals

Full Length Research Paper

Tacrolimus adverse events in transplant recipients with diarrhoea or calcium channel blockers: Systematic review

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Accepted 24 November, 2011

Tacrolimus is widely used for solid-organ transplant immunosuppression. Adverse events can happen in recipients with diarrhoea or calcium channel blockers (CCBs) co-administration. We undertook a systematic review on adverse events in recipients treated with Tacrolimus for whom a raised tacrolimus trough level (≥10 ng/ml) was reported, in a situation of diarrhoea or CCB co-administration. From 312 identified studies, 16 were included, representing 65 patients. Sixty-one (94%) patients were suffering from diarrhoea, 3 (5%) received concomitant CCBs, and one (2%) presented with both; 46 (71%) were adults, 45 (69%) were kidney transplant recipients. Only 9 (14%) suffered from clinical symptoms: nephrotoxicity was reported in 9%, and required dialysis in 2%, neurotoxicity in 7%, multi-organ failure in 4%, and transient liver dysfunction in 2%. One patient was found to carry polymorphisms on CYP450 and P-glycoprotein, both involved in the tacrolimus metabolism and influenced by diarrhoea and CCB administration. Although, the risk of adverse events related to raised tacrolimus through blood level in situations of diarrhea or CCB administration is well-known and can be severe, published data is still scarce. The determination of the exact frequency of such events and the risk factors involved, such as pharmacogenetic background, would require observational cohort studies.

Key words: Calcium channel blocker, cytochrome P450, diarrhoea, P-glycoprotein, transplantation, systematic review, tacrolimus.

INTRODUCTION

Solid organ transplant recipients require the administration of immunosuppressive drugs for the prevention and treatment of organ rejection. Calcineurin inhibitors (cyclosporine and tacrolimus) are current cornerstones in the immunosuppression of transplant recipients. Tacrolimus, a macrolide compound, obtained from *Streptomyces tsukubaensi*, has been increasingly used since its discovery in 1984 (Tanaka et al., 1987). The immunosuppressive effects derived from its binding to immunophillin, a cytoplasmic lymphocyte receptor, therefore inhibiting calcineurin/calmodulin activity, cytokines synthesis, and blocking activation of B and T lymphocytes (Suthanthiran et al., 1996).

Following oral administration, tacrolimus is rapidly absorbed in the duodenum and jejunum, but with a low oral bioavailability and highly variable pharmacokinetics, largely as a result of metabolism in the intestine (Herbert, 1997). Tacrolimus is a substrate for cytochrome P450

(CYP) 3A4 and A5 isoforms, and for P-glycoprotein (P-gp), a multi-drug efflux pump (Herbert, 1997). Both CYP3A isoform enzymes and P-gp exist at high levels in the enterocytes as well as, in the liver (Lampen et al., 1996). The extensive metabolism of tacrolimus by CYP3A system during its translocation through the enterocyte, and its active secretory transport mediated by intestinal P-gp are both closely associated with its low oral bioavailability (Saeki et al., 2001). Intestine inflammation and infection such as enteritis thus, influences tacrolimus bioavailability by damaging enterocytes and reducing metabolism (Maezano et al., 2005). Calcium channel blockers (CCBs), frequently administered in renal transplantation, also influence tacrolimus bioavailability as they are competitive substrates for the CYP3A system and P-gp (Daly, 2006), with variable pharmacokinetics involving the same polymorphisms (Daly, 2006; Seifeldin et al., 1997).

In a previous article, we reported the case of a renal transplant recipient who suffered from severe nephrotoxicity related to a toxic tacrolimus trough concentration in a situation of diarrhea and CCBs co-administration. This patient was found to carry polymorphisms in the CYP3A system and P-gp (Leroy et al., 2010). We here, broadened this single case report performing a systematic review in order to identify and pool together all published clinical observation of solid-transplant recipients with a raised tacrolimus trough blood level in a situation of diarrhea and/or CCB's co-administration. Special attention was paid to the CYP3A and P-gp polymorphisms investigations in those patients.

MATERIALS AND METHODS

We conducted the systematic review in accordance with the guidelines from the Centre for Reviews and Dissemination for undertaking systematic reviews (Centre for Reviews and Dissemination, 2009), as well as, the Cochrane Handbook for systematic reviews of interventions (Higgins et al., 2008).

Data source

A thorough search was carried on Medline and Embase databases, from inception to September 2008 for all the clinical reports (case reports, case series, cohorts studies, trials) of transplant recipients (whatever the organ transplanted) presenting with diarrhoea and/or co-administration of a CCB. The search strategy used medical subject heading terms and free text words (list shown in Appendix). The electronic search was enhanced by hand-searching reference lists of all included papers and review articles to identify eligible papers. No language restriction was used. One reviewer (SL) screened the titles and abstracts from the electronic searches against the inclusion and exclusion criteria, and considered for inclusion reports of transplant recipients with a raised trough tacrolimus level in a situation of diarrhoea and/or co-administration of CCBs. In case of insufficient information to make a decision, the full article was read and eventually discussed with a second reviewer (SF) until a consensus was obtained.

Study eligibility

We included all reports that met the following criteria: solid-organ recipients for whom a raised tacrolimus trough level was reported, in a situation of either diarrhoea or co-administration of a CCB (whatever the CCB involved), or both. A raised tacrolimus trough level was defined as greater than or equal to 10 ng/mL, based on the suggested therapeutic ranges for adults and children in stable graft function period provided by Staatz et al (Staatz et al., 2004). Reports were excluded if they were duplicated. There was no limitation with regard to type of patients, paediatric or adult patients. Also, all types of study design were included. Final decision to include eligible papers was reached by reading the full-text review.

Data extraction

One reviewer abstracted data from the full-text in each study to obtain information on year of publication, the type of study, the number of patients reported, their age (adult or child $\leq$ 18 years), their gender, the type of transplant the recipient underwent (liver or renal, with details on the post-transplantation course), their post-transplant immunosuppressive regimen at the time of the reported adverse event, the co-administration of a CCB (and its type) if any, the presence of a concomitant diarrhoea (with details on course and aetiology) if any, tacrolimus maximum trough level, the event clinically observed, and other information of relevance concerning the patient. The reviewer extracted the data in standardized electronic sheet. Any uncertainties were discussed with a second reviewer to obtain a consensus. Where necessary, authors were contacted for data or to clarify information.

Analysis

We described the included studies in terms of: the characteristics of patients who presented with adverse events, and the clinical and biological characteristics of the observed adverse events. Statistical analyses used Stata/SE 10 software (StataCorp, College Station, TX).

RESULTS

Studies' and patients' characteristics

We retrieved 312 study abstracts of which 23 were considered potentially eligible for inclusion, and the full-text was reviewed (Figure 1). We added one eligible case report by hand-searching in the reference lists, and our case report (Leroy et al., 2010). After full-text review, 9 articles were excluded: two were editorials, three were reviews, and four included post-transplant recipients treated with tacrolimus in a situation of diarrhoea, but none of these patients presented with adverse events. In

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Abbreviations: CCB, Calcium channel blocker; **CYP,** Cytochrome P450; **MDR1**, Multi-drug resistant 1; **P-gp**, P-glycoprotein; **SNP,** Single protein nucleotide.

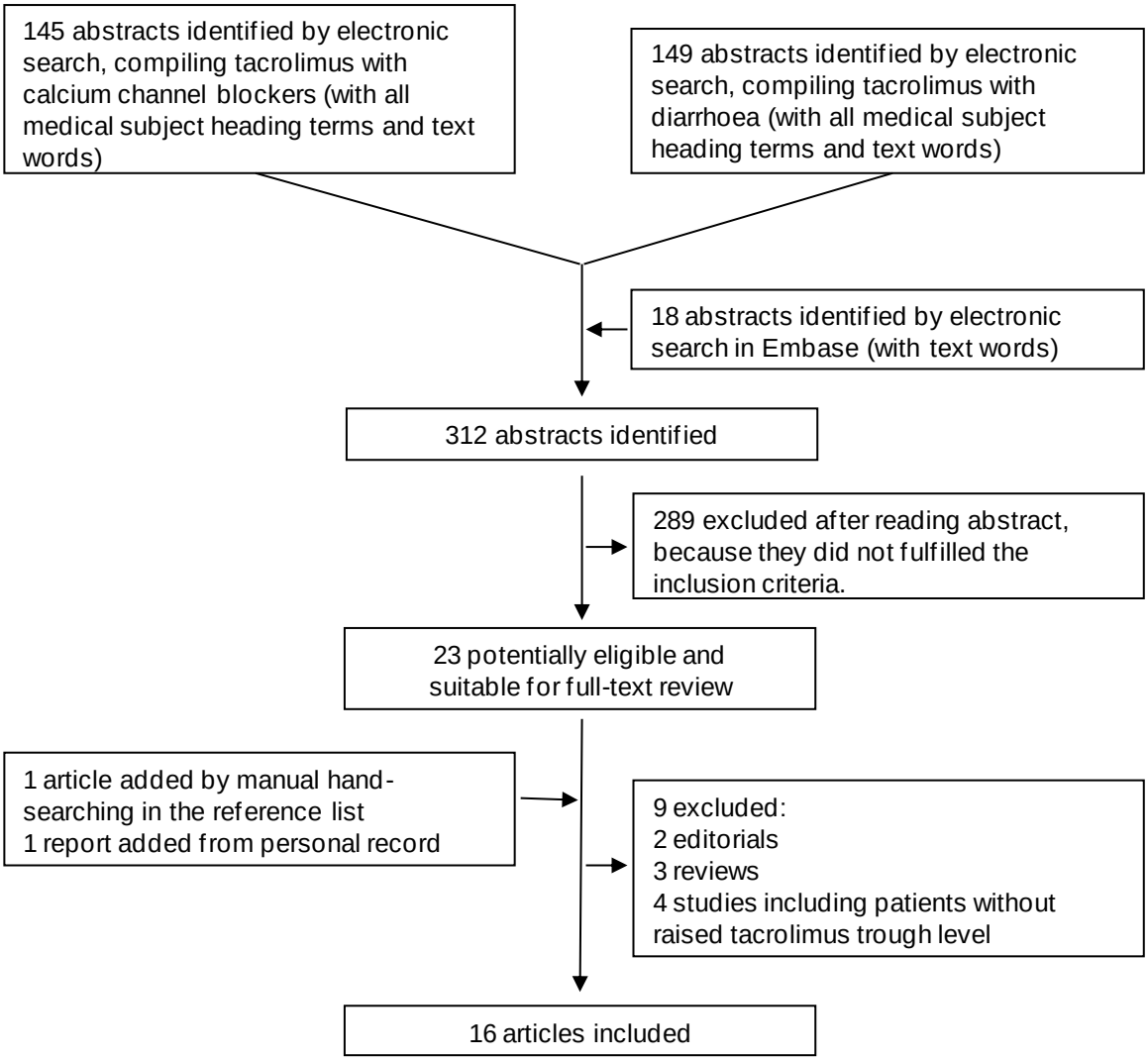

Figure 1. Diagram flow chart.

total, 16 studies, representing 65 patients, were included in the final systematic review (Asano et al., 2004; Berengue et al., 2003; Eades et al., 2000; Fruhwirth et al., 2001; Fruhwirth et al., 2001; Hochleitner et al., 2001; Krahenbuhl et al., 1998; Leroy et al., 2010; Maes et al., 2005; Matsui et al., 1996; Ocran et al., 1999; Sato et al., 2004; Teisseyre et al., 2003; Zylber-Katz et al., 2001). Most of the articles were case reports (Asano et al., 2004; Eades et al., 2000; Fruhwirth et al., 2001; Krahenbuhl et al., 1998; Leroy et al., 2010; Maes et al., 2005; Ocran et al., 1999; Sato et al., 2004; Zylber-Katz et al., 2001) or cases series (Berengue et al., 2003; Fruhwirth et al., 2001; Hochleitner et al., 2001; Matsui et al., 1996; Teisseyre et al., 2003) with a maximum of six reported patients (Teisseyre et al., 2003). Two articles were cohort studies of patients treated by tacrolimus and presenting with diarrhea (Maes et al., 2002; Sato et al., 2004) but with a maximum of 20 included patients (Sato et al., 2004). No trial was identified and included in this systematic review. The first patients reported were two pediatric liver transplant recipients who presented diarrhea resulting in an increased tacrolimus trough blood level in 1996 (Matsui et al., 1996). The first report of raised tacrolimus trough level due to the co-administration of tacrolimus and CCBs was an adult liver transplant recipient who suffered from acute renal failure necessitating hemodyalisis in 1998 (Krahenbuhl et al., 1998). Our case report was the only one with both condition of diarrhea and CCBs co-administration at the same time (Leroy et al., 2010). No patients were treated at the same time by macrolide antibiotics or azole antifungals.

Sixty-five patients were retrieved in the systematic review. Sixty-one (94%) patients were suffering from diarrhoea, 3 (5%) received concomitant CCBs, one (2%) presented with both. Forty-six (71%) patients were adults, 45 (69%) were kidney transplant recipients. Only 9 (14%) out of the 45 had clinical data available suffered from

Table 1. Systematic review of clinical reports of recipients presenting with a raised trough blood level of tacrolimus in association with diarrhoea (or not) and/or co-administration of a calcium channel blocker.

Reference	n	Adult or children	Gender	Age (y)	Type of transplantation	Immuno-suppressive regimen	Ca blocker	Diarrhea	Clinical feature	FK trough level (ng/mL)	Side-effects reported
Asano[14]	1	Adult	M	32	Renal	CT, FK, MMF,	No	Acute	Severe acute enterocolitis.	28.7	No clinical or biological side-effects were observed. The renal function remained normal.
Berengue[15]	4	Children	2F/2M	1-4	Liver	+/-CT, FK	No	Severe	Acute viral diarrhea for one, C Albicans diarrhea for another, unidentified for the others.	13.7 to 20.1	Liver, renal functions remained unaffected.
Eades[16]	1	Child	F	9	Renal	CT, FK, MMF	No	Acute	Acute viral diarrhea.	27.6	Liver, renal functions remained unaffected.
Fruhwirth[17]	2	Adult/ Child	1F/1M		Liver	FK	No	Acute	Acute Rotavirus positive diarrhea.	20.9 to 26.2	Liver and renal functions remained unaffected.
Fruhwirth[18]	1	Child	M	1	Renal	FK	No	Acute	Acute Rotavirus positive diarrhea.	20.7	In the days following high FK trough level, *Pneumocystis carinii* severe pneumonia, leading to a multi-organ failure requiring mechanical ventilation and haemodialysis.
Hebert[28]	1	Adult	M	63	Liver	CT, FK, Aza	Diltiazem	No	Post-transplant course unremarquable.	54	Neurotoxicity: delirium, agitation, confusion. No nephrotoxicity.
Hochleitner[20]	6	Adult/ Child	2F/4M	1-60	5 Renal/ 1 liver	FK, +/-CT, Aza, MMF	No	Acute		20 to >60	One patient presented with a severe *Pneumocystis Carinii* pneumonia (mechanical ventilation), nephrotoxicity (peritoneal dialysis needed) and neurotoxicity (FK level higher than 60 mg/L). A second patient presented only with transient nephrotoxicity. Liver, renal functions remained unaffected for the others.
Krähenbühl[21]	1	Adult	F	62	Liver	CT, FK, Aza	Nifedipine then Mibefradil	No	Chronic rejection at 15 months.	100	Acute renal failure (no requirement to dialysis) and confusion.
Leroy[10]	1	Child	M	14	Renal	CT, FK, Aza	Amlodipine	Acute	Acute viral diarrhea	38.8	Acute renal failure (leading to haemodialysis for 20 days.
Maes[21]	16	Adult	—	—	Renal	FK, MMF, CT	No	Chronic	Diarrhea related to MMF.	20.0-/+6.8	Liver, renal functions remained unaffected, except for two patients with chronic rejection diagnosed 5 months after onset of diarrhea leading to renal replacement.

Table 1 Contd.

Reference	n	Adult or children	Gender	Age (y)	Type of transplantation	Immuno-suppressive regimen	Ca blocker	Diarrhea	Clinical feature	FK trough level (ng/mL)	Side-effects reported
Maezono[7]	1	Child	F	2.3	Liver	FK, CT	No	Acute	Acute Rotavirus positive diarrhea.	18	Liver and renal functions remained unaffected.
Matsui[22]	2	Children	F	1.8	Liver	FK, CT	No	Acute	10% of weight lost	27.3, 30.4	Liver functions remained unaffected. One of the two patients presented with acute renal failure, but without requiring haemodialysis.
Ocran[23]	1	Adult	M	54	Liver	CT, FK, Aza	Mibefradil	No	Hypertension.	54	Acute renal failure (no requirement to dialysis), and clinical features compatible with paresis of the deltoid muscle despite a normal electromyography.
Sato[24]	20	Adult	—	—	Renal	FK	No	Severe		x1.3	Some had symptoms, headache, nausea.
Teissyere[25]	6	Children	4F/2M	1-12	Liver	FK, CT	No	Acute	4 infectious diarrhoea.	18.3-24.8	Liver and renal functions remained unaffected.
Zylber-Katz[26]	1	Child	F	8	Liver	FK	No	Acute	Shigella infection.	22.0	Liver function was affected and then normalized.

Aza, azathioprine; Ca, calcium; CT, corticosteroids; F, female; FK, tacrolimus; M, male; MMF, mycophenolate mofetil.

symptoms other than a raised tacrolimus trough serum level, all patients with CCBs presented with symptoms. None of the reported patients died, and all recovered in varying times.

Patients' and events' characteristics of patients with raised tacrolimus trough level and diarrhea

Twelve articles reported a total of 62 patients with raised tacrolimus trough blood level and diarrhea (Tables 1 and 2); 45 (73%) were kidney transplant (Asano et al., 2004; Eades et al., 2000; Fruhwirth et al., 2001; Hochenleitner et al., 2001; Leroy et al., 2010; Maes et al., 2001; Sato et al., 2004), 43 (69%) were adults (Asano et al., 2004; Fruhwirth et al., 2001; Hochleitner et al., 2001; Maes et al., 2002; Sato et al., 2004), with age ranging from 1 to 60. Of the 26 patients for whom this information was available (that is, all reports except two cohort studies for which authors were contacted with no success (Maes et al., 2002; Sato et al., 2004)), 13 (50%) were male (Asano et al., 2004; Berengue et al., 2003; Eades et al., 2000; Fruhwirth et al., 2001; Fruhwirth et al., 2001; Hochleitner et al., 2001; Leroy et al., 2010; Teisseyre et al., 2003).

The raised tacrolimus trough blood concentration ranged from 13.7 ng/mL (Berengue et al., 2003) to more than 100 ng/mL (Krahenbuhl et al., 1998) (Table 1). Of the 42 (68%) for whom clinical signs were reported (Asano et al., 2004; Berengue et al., 2003; Eades et al., 2000; Fruhwirht t al., 2001; Fruhwirth et al., 2001;Hochleitner et al., 2001; Leroy et al., 2010; Maes et al., 2002; Maezano et al., 2005; Matsui et al., 1996; Teisseyre et al., 2003 ; Zylber-Katz et al., 2001), a raised tacrolimus trough concentration (from 13.7 to 27.6 ng/mL) was the only observed event in 36 (86%) patients (Asano et al., 2004; Berengue et al., 2003; Eades et al., 2000; Fruhwirth et al., 2001;Hochleitner et al., 2001; Maes et al., 2002; Maezano et al., 2005; Matsui et al., 1996; Teisseyre et al., 2003). Six patients (14%) suffered from clinical signs: two patients, who had high tacrolimus trough blood level (30.4 and 60 ng/mL) of the patients with diarrhoea, had severe multi-organ failure related to an acute *Pneumocystis carinii* pneumonia, possibly partly caused by the increased immunosuppression induced (Fruhwirth et al., 2001; Hochleitner et al., 2001), two patients suffered from nephrotoxicity (Hochleitner et al., 2001; Leroy et al., 2010; Matsui et al., 1996) rendering at least one of them to hemodialysis (Leroy et al., 2010), and two recipients presented with a transient increase in

Table 2. Clinical and biological signs in transplant recipients presenting with adverse events related to the use of tacrolimus in situation of diarrhoea and/or calcium channel blockers.

Clinical, biological signs and features	Recipients presenting with diarrhoea (n=62)*	Recipients receiving CCBs (n=4)*	Overall population (n=65)¶
Age			
Children	19 (31)	1 (25)	19 (29)
Adults	43 (69)	3 (75)	46 (71)
Organ transplanted			
Kidney	45 (73)	1 (25)	45 (69)
Liver	17 (27)	3 (75)	20 (31)
Raised tacrolimus trough blood level	62 (100)	4 (100)	65 (100)
Raised tacrolimus trough blood level only**	36 (86)	0 (0)	9 (14)
Other added symptoms**	6 (14)	4 (100)	9 (14)
Detailed clinical and biological symptoms**			
Neurotoxicity	0 (0)	3 (75)†	3 (7)
Nephrotoxicity	2 (5)‡	3 (75)	4 (9)
Dialysis needed	0 (0)	1 (25)	1 (2)
Multi-organ failure	2 (5)§	0 (0)	2 (4)
Transient abnormal liver function	2 (3)	0 (0)	1 (2)

*Values are presented as n (%). The total number of patients is 65, one of the recipients presented with both diarrhoea and CCBs treatment.
**N=45 (41 patients presenting with diarrhoea, and 3 patients with CCBs, and 1 with both), as the detailed clinical symptoms were not available for 20 patients (Sato et al., 2004). Thus percent are calculated based on 42 patients for recipients with diarrhoea, based on 4 patients for recipients with CCBs co-administration, and based on 45 patients in total (third column).
†Two patients presented with central neurological symptoms (confusion, agitation, etc) (Hebert et al., 1999; Kahen buhl et al., 1998), one suffered from peripheral neurological non proven by electromyography (Ocran et al., 1999).
‡Two kidney transplant recipients were not counted here, as the reported renal failure was linked to a chronic renal graft rejection that occurred 5 months after the acute diarrhoea and increased tacrolimus trough blood level. Renal failure was thus not considered as related to tacrolimus adverse events.
§Patients presenting with multi-organ failure consecutively to a *Pneunocystis Carinii* pneumonia, with tacrolimus trough blood level of 60 and 20.7 ng/mL respectively (Fruhwirth et al., 2001; Hochleitner et al., 2001). These patients were not counted into recipients suffering from nephrotoxicity because renal failure was considered as part of the multi-organ failure, not as tacrolimus direct nephrotoxicity.
¶The total number of included patient was 65: 61 patients presented with diarrhoea, 3 were treated with CCBs, and one patient presented with both diarrhoea and CCBs co-administration.

serum levels of liver enzymes (Zylber-Katz, 2001).

Patients' and events' characteristics of patients with raised tacrolimus trough level and CCBs co-administration

Four articles (25%) reported patients with raised tacrolimus blood level, and CCBs co-administration (Hebert et al., 1999; Krahenbuhl et al. 1998; Leroy et al., 2010; Ocran et al., 1999). Among the four patients who received CCBs, two were treated with Mibefradil (Krahenbuhl et al. 1998; Ocran et al., 1999), which was withdrawn from the market in 1998 (Laboratoire Roche, 1998), two were treated with dihydropyridine calcium antagonists (Amlodipine (Leroy et al., 2010), and Nifedipine (Krahenbuhl et al. 1998)), and one received Diltiazem (Hebert et al., 1999). Three were males (Hebert et al., 1999; Leroy et al., 2010; Ocran et al., 1999), three were adults (Hebert et al., 1999; Krahenbuhl et al. 1998; Ocran et al., 1999), and their age ranged from 14 (Leroy et al., 2010) to 63 years (Table 2). Three were adults who received liver transplants (Hebert et al., 1999; Krahenbuhl et al. 1998; Ocran et al., 1999). The median Tacrolimus trough level was 54 ng/mL (range: 38.8 to 100 ng/mL). All four patients suffered from severe clinical symptoms (Hebert et al., 1999; Krahenbuhl et al. 1998; Leroy et al., 2010; Ocran et al., 1999): nephrotoxicity (Hebert et al., 1999; Leroy et al., 2010; Ocran et al., 1999) necessitating transient dialysis for two patients (Krahenbuhl et al. 1998; Leroy et al., 2010), and/or neurotoxicity (Hebert et al., 1999; Ocran et al., 1999). The patients who suffered from neurological symptoms (that is, confusion, paresis) had been treated with Nifedipine, Mibefradil or Diltiazem, but not with Amlodipine (Hebert et al., 1999; Krahenbuhl et al. 1998; Ocran et al., 1999), whereas the only patient without nephrotoxicity was given Diltiazem (Hebert et al., 1999).

The only patient who presented both conditions (diarrhoea and CCB co-administration) was a pediatric kidney transplant recipient (Leroy et al., 2010). This child was the only one of the 65 patients who was investigated for CYP3A system and P-gp SNPs: he was found to have a CYP3A5 deficiency with a non-expressor *CYP3A5*3/*3*

genotype, and was heterozygous for the *C3435T* allele in MDR1 gene that could possibly have influenced the P-gp activity (Leroy et al., 2010).

DISCUSSION

Performing this systematic review, we summarized the available information on solid organ transplant recipients with a raised tacrolimus trough level in situations of diarrhoea or CCBs co-administration. We confirmed that (i) the clinical events related to a raised Tacrolimus trough level due to the co-administration of CCBs and Tacrolimus are poorly reported (4 cases, all symptomatic) whereas they are thought to be well-known by transplant clinicians, and they can be severe, (ii) tacrolimus raised blood level in a situation of diarrhea is much more reported (62 cases) even though less clinically severe (signs in only 14% of patients), and (iii) polymorphisms of key-enzymatic proteins for Tacrolimus were studied only in one observation (Leroy et al., 2010).

Intestinal CYP3A system and P-gp both play key roles in bioavailability after oral administration and pharmacokinetics of tacrolimus (Daly, 2006; Fruhwirth et al., 2001; Fruhwirth et al., 2001; Herbert, 1997; Mittal et al., 2001). Tacrolimus is primarily metabolized by CYP3A4 and CYP3A5 isoforms while cytochrome P450 enzymes localized in intestinal microsomes (Daly, 2006; Herbert, 1997; Lampen et al., 1996), with a high expression in the duodenum that declines progressively towards the colon (Eades et al., 2000; Lampen et al., 1996; Mittal et al., 2001). Tacrolimus is also a substrate for P-gp, encoded by multi-drug resistant 1 (MDR1) gene (Herbert, 1997). This membrane efflux pump transports tacrolimus back into the intestinal lumen as soon as it begins to be absorbed (Herbert, 1997; Lampen et al., 1996), its level increases longitudinally along the intestine, with concentrations being lowest in the stomach and highest in the colon (Eades et al., 2000; Lampen et al., 1996; Mittal et al., 2000).

Intestinal epithelial cells may be destroyed during enterocolitis (Maezano et al., 2005), particularly in the case of rotavirus replication (Fitts et al., 1995). This reduces the global enzymatic activity of CYP3A system and P-gp in enterocytes, thereby increasing the levels of tacrolimus (Eades et al. 2000). The delay before normalization of tacrolimus blood level may thus reflect the time required for enterocyte regeneration and recovery of CYP3A enzymatic activity and P-gp function after gastrointestinal injury (Lampen et al., 1996). The shortened intestinal transit time during diarrhoea also may contribute to the elevated tacrolimus levels by increasing absorption (Mittal et al., 2001). CYP3A system is highly expressed in the duodenum and declines then progressively to the colon (Eades et al., 2000; Lampen et al., 1996; Mittal et al., 2001). If higher concentrations of tacrolimus reach the colon, in which CYP3A system activity is lower; this may theoretically contribute to elevated blood levels (Fitts et al., 1995).

CCBs are frequently administered in renal transplantation in order to control hypertension, partly attributed to the widespread use of calcineurin-inhibitors (Van der Schaaf et al., 1995). CCBs are thus theoretically well suited for their dominant dilatory effect on the afferent glomerular arteriole, where the vasoconstriction of calcineurin inhibitors is most prominent (Ruggenenti et al., 1993), and Amlodipine is widely used for that purpose, especially in pediatric transplantation. However, CCBs have a potential interaction with calcineurin inhibitors, such as tacrolimus, through their common metabolism by the CYP3A system and P-gp (Daly, 2006), and decrease the clearance of tacrolimus by partial competitive inhibition of metabolic pathway, leading to a significantly elevated blood level. This is demonstrated for the interaction of diltiazem and cyclosporine with several reports of decreased clearance of cyclosporine in transplants recipients who received cyclosporine as part of their immunosuppressive regimen (Chrysostomou et al., 1993). The necessity of decreasing Tacrolimus daily doses after 90 days of nifedipine treatment was reported in a cohort study of transplant recipients, suggesting such interaction (Seifeldin et al., 1997). The only patients who suffered from neurological symptoms were treated with CCBs, except with Amlodipine. Neurotoxicity might be explained by the fact that P-gp is part of the blood–brain barrier and inhibition of P-gp by CCBs may enhance the brain exposure to tacrolimus (Hebert et al., 1999). Calcineurin inhibitors are well known to induce severe neurotoxicity even if the pathogenesis remains unclear (Sklar, 2006). Tacrolimus nephrotoxicity might be related to a direct mechanism on renal tubular epithelial cells (Pallet et al., 2008). CYP3A5 and P-gp are found at high levels in epithelial cells in the kidney (Chowbay et al., 2005; Kuehl et al., 2001), and cyclosporine was found to be responsible for endoplasmic reticulum stress in *in vitro* cultures of human tubular cells, leading to epithelial phenotypic changes, partly explaining cyclosporine nephrotoxicity (Pallet et al., 2008). Therefore, if CYP3A5 and P-gp are partially inhibited by CCBs, we could hypothesize that non metabolised tacrolimus may accumulate in the renal epithelial cells with a direct toxicity on cells, as it may occur for cyclosporine. The fact that only one patient treated with Amlodipine and presented with nephrotoxicity, had other risk factors for raised tacrolimus trough level (that is, diarrhoea, CYP3A and P-g polymorphisms), makes the balancing of all CCBs difficult and may interact with tacrolimus leading to an adverse effect. Indeed, too few observations were reported to draw any conclusion, especially regarding Amlodipine, and further prospective observational cohort studies (that could be part of a pharmovigililance process) are warranted.

The only patient to have been investigated and found to have CYP3A system and P-gp SNPs leading to a

decreased enzymatic activity presented with the most severe clinical signs: acute renal failure necessitating 20 days of dialysis, possibly because of the combination of both conditions (diarrhoea and CCBs co-administration) (Leroy et al., 2010). *CYP3A* system and *MDR1* SNPs result in a variable expression and activity of the corresponding proteins that participate in the large inter-individual variability in tacrolimus pharmacokinetics (Utecht et al., 2006), and were unfortunately reported to have been investigated in only this one recipient (Leroy et al., 2010). CYP3A5 represents a considerable proportion of total CYP3A and significantly contributes its catalytic activity (Kuehl et al., 2001). The most common *CYP3A5* SNP (80% in Caucasians (Daly, 2006)) is a splice site mutation *16986G*, encoding for an aberrantly spliced mRNA (Kuehl et al., 2001). This mRNA translates into a protein that is prematurely terminated and unstable and thus leading to an absence of CYP3A5 enzymatic activity (Kuehl et al., 2001). CYP3A4 also influences tacrolimus pharmacokinetics (Kuehl et al., 2001). The most frequent variation of functional CYP3A4 expression is due to the *CYP3A4*1B* variant allele, a SNP transition in position -392, in the promoter region (Kuehl et al., 2001), but its exact influence is still debated. *In vitro* experiments argue in favour of an increased transcription of the *CYP3A4*1B* variant allele which should result in higher enzymatic activity (Vn Schaik et al., 2000), and *in vivo* observations demonstrated a lower activity, after adjustment on CYP3A5 genotype, underlying the influence of *CYP3A5* genotype on the overall functional activity of CYP3A4 (Op den Buijsch et al., 2007). The MDR1 gene is also highly polymorphic with different frequencies of allelic variants among different ethnic groups (Kuehl et al., 2001). Three partly linked polymorphisms in the MDR1 gene located on exons 12 (*C1236T*), 21 (*G2177T*), and 26 (*C3435T*) have been extensively studied for tacrolimus pharmacokinetics, and again contradictions are found: a few authors have reported an influence of these SNPs on tacrolimus pharmacokinetics, while others have not (Masuda et al., 2006). Part of the reasons for these discrepancies could be the fact that *MDR1* SNPs, particularly *C3435T* SNP is not the only polymorphism influencing P-gp expression levels (Chowbay et al., 2005), but *CYP3A4* SNPs may also play a role (Goto et al., 2002), indicating that unique combination of SNPs within a haplotype or polygenic traits involving more than one gene may be responsible for influencing P-gp expression.

No underlying condition (except being a transplant recipient) was reported in any of the patients. However, we hypothesized that SNPs may have also played a role, and it would be pertinent to perform pharmacogenetic analyses in the 65 reported recipients, in order to analyse the potential relationship between the severity of observed adverse event and the genetic background of the patient in one hand, and to compare it to that of patients without any occurrence of clinical event in the same clinical situation of diarrhoea and/or co-administration of CCBs. Pharmacogenetics analysis would have been very interesting and would have highlighted that knowledge of the patient's genetic background would not only help clinicians to choose the right day-to-day tacrolimus dose but also guide them in adapting it in situations of high risk. Search for *CYP3A* or *MDR1* SNPs had been reported in cohort studies designed for the analysis of their influence on tacrolimus dose-adjusted trough levels and the daily tacrolimus doses chosen (Chowbay et al., 2003; Daly, 2006; Hesselink et al., 2003; Op den Buijsch et al., 2007), and in one case report (Leroy et al., 2010).

Not only CCBs may interact with tacrolimus and potentially affect its pharmacokinetics. Macrolide antibiotics including erythromycin and clarythromycin have been known as inhibitors of CYP, and their concomitant use with tacrolimus have been reported to increase effect on tacrolimus blood concentration (Jensen et al., 1994). This drug interaction is very well known from clinicians, especially paediatricians as bacterial infectious and there are common complications in solid-organ pediatric transplantation. Interestingly, azithromycin, possessing a unique azalide structure, shows a pharmacokinetics and metabolism different from other macrolides (Amacher et al., 1990). Indeed, it does not affect CYP, leading to a much rarer reported interaction. To our knowledge, only one clinical observation has been reported on interaction between cyclosporine and azythromycin in a transplant recipient (Ljutic et al., 1995), and in allogeneic bone marrow transplant recipient (Mori et al., 2005). In both cases, patients presented with raised trough tacrolimus blood level, without clinical signs. This rare adverse effect, with no clinical incidence may explain why azithromycin has been proposed to treat cyclosporine-induced gingival hyperplasia (Citterio et al., 2001). Fluoroquinolones are another class of antibiotics frequently used for the treatment of bacterial infection because of their broad spectrum of activity; some of them, such as ciprofloxacin and norfloxacin, are reported to increase blood concentration of cyclosporine because they are metabolised by the liver through the same CYP system (McLellan et al., 1995; Elston et al. 1988). Pharmacokinetics studies demonstrated that levoflaxin, which undergoes a limited hepatic metabolism, partially inhibits tacrolimus metabolism in renal transplant recipient, leading to caution with co-administration even this fluroquinolone with calcineurin inhibitors (Federico et al., 2006). To end with anti-infectious drugs, a clinical observation of a drug interaction between protease inhibitors and tacrolimus, both metabolised through CYP 3A4 enzymes, was reported (Mertz et al., 2009). In a patient with HIV-associated focal segmental glomerulosclerosis leading to kidney transplantation, HIV salvage therapy was started with darunavir and boosted with ritonavir, two protease inhibitors. Tacrolimus trough

levels dramatically increased to 106.7 ng/ml. The patient presented with temporary renal failure that fully recovered with no graft damage, when he was back to a normal tacrolimus blood concentration under a dosage of 3.5% of the usual dose. Proton pump inhibitor are known to share CYP 3A4 too for their elimination. A clinical-analytical cohort study followed renal transplant recipients whose immunosuppression included tacrolimus, and whose omeprazole was progressively stopped (Pascual et al., 2005). The level/dose tacrolimus ratio remained unchanged, supporting that clinical management is not affecting by the possible competition between omeprazole and tacrolimus (Pascual et al., 2005). However, further studies included CYP genotyping in living-donor liver transplant patients treated with tacrolimus and omeprazole, and demonstrated that patients with variants (*2 or *3) for intestinal CYP2C19 had higher level/dose tacrolimus than in wild-type homozygotes and heterozygotes (Hosohata et al., 2009). This effect was attenuated when patients were *CYP3A4*1* noncarriers. Another study on CYP3A5 non-expressors, renal transplant recipients with tacrolimus, concluded that there is no significant difference in tacrolimus kinetic with or without coadministration of omeprazole (Katsakiori et al., 2010). This particular case of drug interaction between tacrolimius and omeprazole highlight how much genetic background of CYP system may influence the clinical output of the known interaction. Another clinical observation reported an interaction between tacrolimus and ranolazine, a piperazine derivative agent approved for treatment of chronic angina in combination with β-antagonists, nitrates, CCBs (Pierce et al., 2010). Tacrolimus trough concentration raised from 7.0 to 10.1 ng/mL to 17.6 ng/mL in 24 h when introducing ranolazine, because it shares CYP3A enzymes an P-gp efflux transport system with tacrolimus. Even though those drugs are very rare in Pediatrics, it has to be mentioned as solid-organ transplant recipient may have a risk for cardiovascular disorders. Another more current drug used in adult medicine than in Pediatrics, mirtazapine (antidepressant drug), has been reported to interact with tacrolimus in a recent renal transplant recipient (Fraile et al., 2009). Mitarzapine was interrupted during the engraftment, and led to hypotension 2 h only after being re-applied in post-transplant period, with a 15 ng/mL tacrolimus though level. Because this antidepressant drug is also metabolised through CYP3A4, the authors hypothesized that the hypotensive effect of mitarzapine was boosted by the high level of tacrolimus, and possibly the lack of elimination of this immunosuppressive through the renal pathway (Fraile et al., 2009). Lastly, an observational cohort study showed that corticosteroids and tacrolimus may interact (Anglicheau et al., 2003). Adult renal transplant recipients were stratified according to their dose of corticosteroids in three groups, and a pharmacokinetic interaction between steroids and tacrolimus was demonstrated: the higher the steroid dosage, the higher the tacrolimus dosage needed to achieve target trough levels in these patients, through specific CYP3A and/or P-gp enzymatic induction [59]. Therefore special attention must be paid during steroid sparing or tapering.

Conclusion

Whatever the pathogenic mechanisms involved, we summarized the information available on clinical, biological characteristics of transplant recipients with a raised Tacrolimus trough level in a situation of diarrhea, or co-administration of CCBs. We acknowledged that our systematic review probably gathered information intuitively known by physicians from daily clinical practice. However, although transplant clinicians are aware of these situations, sometimes severe, the information available is sparse, and the variability in the importance of the raised Tacrolimus blood level, and its clinical consequences have not been yet fully investigated. Observational cohort studies would be warranted to appreciate the real frequency of such events, and to determine their risk factors, underlying condition, such as specific genetic background, that may predispose some patients to severe events.

ACKNOWLEDGEMENTS

We sincerely thank Allison Hirst for helpful discussions and re-reading. This work was partly presented as a poster during the International Pediatric Nephrology Association congress in Budapest (Hungary) in September 2007. Sandrine Leroy was funded by a post-doctoral fellowship grant from the Fondation pour la Recherche Medicale, and the French Society of Nephrology. The authors' work was independent of this funding.

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