

Observational Study

Combining cytochrome P-450 3A4 modulators and cyclosporine or everolimus in transplantation is successful

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Abstract

AIM: To describe the long term follow-up of kidney allograft recipients receiving ketoconazole with calcineurin inhibitors (CNI) alone or combined with everolimus.

METHODS: This is an open-label, prospective observational clinical trial in low immunologic risk patients who, after signing an Institutional Review Board approved consent form, were included in one of two groups. The first one ($n = 59$) received everolimus (target blood level, 3-8 ng/mL) and the other ($n = 114$) azathioprine 2 mg/kg per day or mycophenolate mofetyl (MMF) 2 g/d. Both groups also received tapering steroids, the cytochrome P-450 3A4 (CYP3A4) modulator, ketoconazole 50-100 mg/d, and cyclosporine with C0 targets in the everolimus group of 200-250 ng/mL in 1 mo, 100-125 ng/mL in 2 mo, and 50-65 ng/mL thereafter, and in the azathioprine or MMF group of 250-300 ng/mL in 1 mo, 200-250 ng/mL in 2 mo, 180-200 ng/mL until 3-6 mo, and 100-125 ng/mL thereafter. Clinical visits were performed monthly the first year and quarterly thereafter by treating physicians and all data was extracted by the investigators.

RESULTS: The clinical characteristics of these two cohorts were similar. During the follow up (66 + 31 mo), both groups showed comparable clinical courses, but the biopsy proven acute rejection rate during the full follow-up period seemed to be lower in the everolimus group (20% vs 36%; $P = 0.04$). The everolimus group did not show a higher surgical complication rate than

the other group. By the end of the follow-up period, the everolimus group tended to show a higher glomerular filtration rate. Nevertheless, we found no evidence of a consistent negative slope of the temporal allograft function estimated by the modification of the diet in renal disease formula in any of both groups. At 6 years of follow-up, the uncensored and death-censored graft survivals were 91% and 93%, and 91% and 83% in the everolimus plus cyclosporine, and cyclosporine alone groups, respectively. The addition of ketoconazole saved 80% of cyclosporine and 56% of everolimus doses.

CONCLUSION: Combining CYP3A4 modulators with CNI or mammalian target of rapamycin inhibitor, in low immunological risk kidney transplant recipients is feasible, effective, safe and affordable even in the long term.

Key words: Kidney transplant; Immunosuppressive; Cyclosporine; Ketoconazole; Everolimus; Cytochrome P-450; Cytochrome P-450 3A4 modulator

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Core tip: Several immunosuppressive (IS) drugs, used in clinical transplantation, are metabolized by the hepatic cytochrome P-450 system as many other drugs. The co-prescription of IS and ketoconazole reshapes the IS pharmacokinetics and appears to confer benefit to patients receiving calcineurin inhibitors (CNI) and mammalian target of rapamycin inhibitors. We describe the long term follow-up of kidney allograft recipients receiving ketoconazole with a CNI alone or combined with everolimus and report good graft and patient survivals and low rates of acute rejection episodes. These combinations, in low immunological risk kidney transplant recipients are feasible, effective, safe and affordable even in the long term.

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INTRODUCTION

The prognosis of kidney transplantation has improved as new immunosuppressive (IS) drugs have been introduced in clinical practice and as prescribing physicians have learned to combine and prescribe them^[1]. Most of the time, IS doses are monitored by measuring patients' drug blood levels based on the results of clinical trials designed to prove that a specific drug blood level window is associated with maximal IS efficacy to prevent acute rejection episodes and minimal incidence of drug-related adverse events.

Several IS drugs are metabolized by the hepatic cytochrome P-450 system^[2]. This elimination pathway is shared by a lot of drugs commonly prescribed both in internal medicine and in clinical transplantation, creating the opportunity for the appearance of drug interactions that could translate to adverse effects. For instance, while rifampin and phenytoin induce activity of the cytochrome, macrolides and azole antifungal agents decrease it, in such a way that certain drug metabolism is secondarily accelerated or retarded, respectively^[2].

Intending to prescribe IS with cytochrome P-450 inhibitors simultaneously, particularly on the cytochrome P-450 3A4 isozyme (CYP3A4), is a practice that has been repeatedly reported in transplant literature, beginning with cyclosporine^[3-26] and tacrolimus^[27-29] and followed by sirolimus and everolimus^[30-33]. These combinations have been associated with favorable clinical short and long term outcomes, but occasionally with more adverse events due to drug induced toxicities. At the same time, these drug combinations give health payers the opportunity to save financial resources^[32,34-39]. Few authors have already shown that for other clinical conditions than transplantation the proposed combination has no adverse effects and saves money.

Combining IS drugs with a low dose of ketoconazole, a well-known CYP3A4 inhibitor, gives the possibility to modulate the isozyme activity in order to change the drug blood concentration vs time curve shape in such a way that the drug's maximal concentration (C_{max}) is reduced alongside its metabolic disposal rate and the area under the time concentration curve (AUC) is reshaped to approximately the pharmacokinetic profile described by a Gamma's distribution curve, from one with lower to another with higher alpha and beta parameters for that function (Figure 1)^[40]. In other words, the addition of a CYP3A4 modulator gives the AUC a more rectangular graphical shape as C_{max} decreases but maintains the clinically driven C_0 target (concentration at the end of the dosing interval and before the next drug intake) and, at the same time, stabilizes AUC, whose magnitude has been related to acute rejection risk in cyclosporine or tacrolimus users.

The interaction between ketoconazole and the IS drugs is believed to result from the imidazole's inhibition of the hepatic microsomal cytochrome P-450 dependent mixed function oxidase system that deactivates drugs. Two mechanisms have been proposed: Competitive inhibition at the substrate binding site and interaction of ketoconazole with the haem moiety of the cytochrome P-450 itself, preventing the binding and activation of oxygen and consequently inhibiting the metabolism of IS drugs^[41].

This therapeutically intended reshaping in IS drug exposure has been correlated, in prospective randomized trials, to a decreased incidence and severity in clinical allograft acute rejection rate and to a better graft function in cyclosporine or tacrolimus treated patients^[42-47]. Preliminary results with sirolimus and everolimus are also

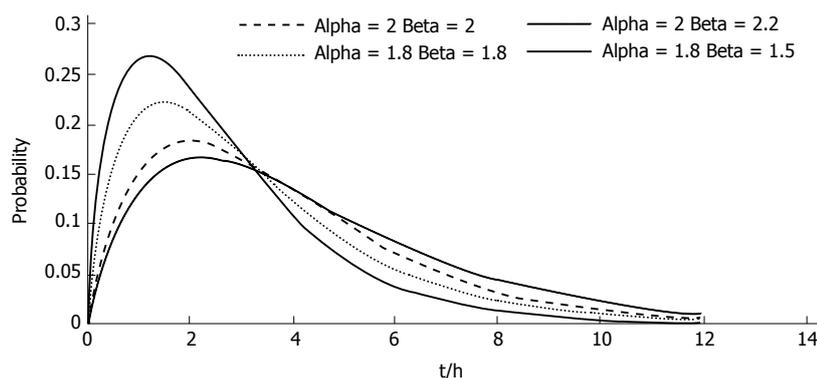


Figure 1 Gamma distribution curves with varying alpha and beta parameters.

promising^[32,33].

The aim of this report is to describe the long term follow-up of two cohorts of kidney allograft recipients whose CYP3A4 was modulated with a low ketoconazole dose and who were receiving an IS treatment consisting in a calcineurin inhibitor (CNI) alone or in combination with another CYP3A4 metabolized drug, such as everolimus.

MATERIALS AND METHODS

Study design

We performed an open-label, observational, nonrandomized, prospective, cohort, comparative clinical trial among low immunologic risk patients, who were defined as adult males or non-pregnant females undergoing primary deceased donor, living-unrelated or human leukocyte antigen-mismatched living-related donor kidney transplantations.

Subjects were required to display a rate of panel reactive antibodies (PRA) < 20%, cold ischemia time of < 30 h and a warm ischemia time lower than 45 min in order to undergo transplantation. All patients signed a written informed consent form approved by the local ethics committee. All participating women consented to use an effective contraceptive method.

Immunosuppressive therapy

After transplantation, all patients received IV methylprednisolone for the first 3 d and then oral prednisone at doses tapered to reach 15 mg/d at 6 mo; 10 mg/d at 12 mo; and 5 mg/d thereafter. From 0 d, all patients received oral modified cyclosporine (Neoral, Novartis Pharma AG, Basel, Switzerland), ketoconazole (100 mg/d) and azathioprine (2.0-2.5 mg/kg per day). After 5 d, a cohort of patients without a significant delayed graft function (defined as a requirement for less than one week of dialysis), were switched from azathioprine to everolimus 0.25 mg twice a day without loading dose. The other group continued receiving mainly azathioprine, but some patients were switched to mycophenolate mofetyl (2 g/d) by the treating physicians. No induction therapy was allowed, but one

patient inadvertently received basiliximab.

Immunosuppressant doses were modified according to the following through blood level targets. Everolimus group: Everolimus, 3-8 ng/mL (Innofluor, Seradyn); cyclosporine, 200-250 ng/mL the first month, 100-125 ng/mL the second month and 50-65 ng/mL thereafter (Axiom, Abbott). Azathioprine or mycophenolate mofetyl (MMF) group: Cyclosporine 250-300 ng/mL the first month, 200-250 ng/mL the second month, 180-200 ng/mL until the end of the sixth month and 100-125 ng/mL thereafter.

Primary aim

To describe the pharmacological interaction between the CYP3A4 modulator ketoconazole and cyclosporine alone or in combination with everolimus in kidney transplanted patients.

Secondary aim

To describe, in both groups, the incidence of biopsy proven acute rejection episodes, graft survival and kidney graft function by serum creatinine and modification of the diet in renal disease (MDRD) estimated glomerular filtration rate (GFR) at six years of follow-up. To describe, in both groups, the incidence of selected medical complications, such as new-onset diabetes mellitus (NODAT), neoplasia, and post-transplant lymphoproliferative disorder (PTLD) and BK virus nephropathy and cytomegalovirus (CMV) disease.

Statistical analysis

As this was not a randomized trial, we do not have the intention to formally and strictly compare both groups. All analyses were performed on an intention-to-treat basis. Analysis of variance was used for continuous variables and covariance for repeated measurements; χ^2 and Fisher exact tests for categorical variables. Survival analysis was done with the Kaplan-Meier method and the log-rank test.

RESULTS

Between January 1st 2005 and December 31st 2012,

Table 1 Characteristics of kidney donors and recipients

	Everolimus (<i>n</i> = 59)	Azathioprine/MMF (<i>n</i> = 114)	<i>P</i> value
Donor			
Age (yr)	38.4 ± 13.7	44.1 ± 13.0	< 0.01
Male gender	30 (51%)	65 (57%)	0.44
Living	15 (25%)	14 (12%)	0.03
Non-living	44 (75%)	100 (88%)	0.03
Extended criteria donor	5 (9%)	20 (18%)	0.11
Stroke as donor's cause of death	10 (23%)	28 (28%)	0.51
Hypertension	3 (5%)	22 (19%)	0.01
Type 2 diabetes	0 (0%)	4 (4%)	0.15
Serum creatinine (mg/dL)	0.83 ± 0.26	0.90 ± 0.36	0.19
Cold ischemia time (h)	18.9 ± 5.4	20.1 ± 7.1	0.33
Warm ischemia time (min)	37.3 ± 9.25	41.3 ± 11.2	0.02
Recipient			
Age (yr)	43.1 ± 12.5	45.0 ± 12.1	0.35
Male gender	32 (54%)	79 (69%)	0.05
List waiting time (mo)	27.9 ± 22.7	30.4 ± 28.3	0.57
Previous kidney transplant	0 (0%)	0 (0%)	
Total time in dialysis (mo)	49.0 ± 26.5	58.4 ± 33.6	0.57
PRA (%)	3.0 ± 4.3	3.8 ± 5.2	0.35
HLA-mismatch	2.9 ± 1.4	2.8 ± 1.2	0.68
Double kidney transplant	1 (2%)	5 (4%)	0.36
Hypertension	42 (71%)	79 (69%)	0.80
Type 2 diabetes	0 (0%)	7 (6%)	0.10
Coronary artery disease	1 (2%)	1 (1%)	0.63
IgG CMV (+)	56 (97%)	98 (88%)	0.06
Immunosuppressive treatment			
Induction	0 (0%)	1 (1%)	0.47
Cyclosporine	59 (100%)	114 (100%)	
Azathioprine	59 (100%)	111 (97%)	0.21
Mycophenolate mofetyl	0 (0%)	3 (3%)	0.21
Delayed graft function	3 (5%)	65 (57%)	< 0.01

MMF: Mycophenolate mofetyl; PRA: Panel reactive antibodies; CMV: Cytomegalovirus.

254 transplants were performed. From them, 2 patients abandoned controls and one patient's clinical registries were lost, leaving 251 patients. The sixty one patients having PRA > 20%, those who suffered from a non-functioning graft (*n* = 12; 4.8%) and the five patients who died before they were discharged from first hospitalization (2%) were not considered in further analysis, leaving a total of 173 patients for follow up. From these, 59 patients (34%) began everolimus immunosuppressive treatment during the first month and the other 114 patients (66%) continued receiving azathioprine or MMF combined with cyclosporine, ketoconazole and tapering steroids.

The clinical characteristics of these two cohorts are showed in Table 1. Both groups were very similar, but the group receiving azathioprine/MMF either received more kidneys from non-living or hypertensive donors or underwent a longer warm ischemia time and, as expected, they suffered more delayed graft function (DGF).

During the follow up (66 + 31 mo, median 66.6 mo, range 1-133), both groups showed comparable clinical courses. However, the biopsy proven acute rejection rate during the full follow-up period seemed to be lower in the everolimus group (20% vs 36%; *P* = 0.04) (Table 2). As expected, those patients who received

azathioprine/MMF tended to show more leukopenia, thrombocytopenia or to develop more pneumonias than those receiving everolimus. The everolimus group did not show a higher surgical complication rate.

Other adverse events were not consistently observed. Nevertheless, at the beginning of each immunosuppressive treatment much attention had to be devoted to adjusting drug doses in order to achieve the therapeutic windows without surpassing their upper limits. There were several times that cyclosporine blood levels transiently reached supra-therapeutic concentrations without more adverse events than tremor. Liver functions tests were monitored at each clinical visit and no alterations were observed.

Renal function and grafts survival

The everolimus group had less DGF than the azathioprine/MMF group, but this happened because of the design of the immunosuppressive protocols, as patients suffering of DGF for more than a week could not receive the mammalian target of rapamycin (m-TOR) inhibitor because of concerns of a risk of prolonging the graft dysfunction.

Regardless of the DGF incidence, both groups recovered kidney function in a comparable way. However, by the end of the follow-up period, the everolimus group

Table 2 Follow up clinical findings and complications *n* (%)

	Everolimus (<i>n</i> = 59)	Azathioprine/MMF (<i>n</i> = 114)	<i>P</i> value
Surgical complication	11 (19)	25 (22)	0.61
Vascular complication	2 (3)	10 (9)	0.22
First year acute rejection episode	6 (10)	25 (22)	0.06
Acute rejection episode during entire follow up period	12 (20)	41 (36)	0.04
Cyclosporine toxicity	8 (14)	22 (19)	0.35
New onset diabetes after transplant	3 (5)	8 (7)	0.75
CMV disease	0 (0)	6 (5.3)	0.10
BK virus nephropathy	1 (2)	5 (4)	0.67
New onset neoplasia	2 (3)	6 (5)	0.72
Post-transplant Lymphoproliferative disease	1 (2)	2 (2)	0.98
Hospitalizations/yr	0.50 ± 0.72	0.62 ± 0.78	0.32
Leucopenia	12 (20)	58 (51)	< 0.01
Thrombocytopenia	29 (49)	73 (64)	0.06
Pneumonia	6 (10)	25 (22)	0.06
Urinary tract infection	27 (46)	46 (40)	0.49

MMF: Mycophenolate mofetyl; CMV: Cytomegalovirus.

Table 3 Graft survival uncensored by recipient death with a functioning graft at different periods after kidney transplant

Time	Everolimus (<i>n</i> = 59)	Azathioprine/MMF (<i>n</i> = 114)
Year 1	98%	97%
Year 2	98%	94%
Year 3	96%	93%
Year 4	94%	88%
Year 5	94%	86%
Year 6	91%	83%

MMF: Mycophenolate mofetyl.

Table 4 Graft survival censored by recipient death with a functioning graft at different periods after kidney transplant

Time	Everolimus (<i>n</i> = 59)	Azathioprine/MMF (<i>n</i> = 114)
Year 1	100%	97%
Year 2	100%	94%
Year 3	98%	93%
Year 4	96%	88%
Year 5	96%	88%
Year 6	93%	83%

MMF: Mycophenolate mofetyl.

tended to show a higher glomerular filtration rate. Nevertheless, we found no evidence of a consistent negative slope of the temporal allograft function in any of both groups (Figure 2).

The uncensored and death-censored graft survival at different time periods are shown in Tables 3 and 4 and Kaplan-Meier graphs are shown in Figure 3. Log-rank tests did not show statistical significant differences between both groups.

CYP3A4 modulator effect

The addition of ketoconazole was associated to a lower dose requirement of both everolimus and cyclosporine in order to achieve the therapeutic blood concentrations. The usual recommended initial cyclosporine and everolimus doses of 8 mg/kg per day and 1.5 mg/d, respectively, were allowed to be decreased, at 30 d post transplantation, to 1.63 + 0.83 mg/kg per day and 0.67 + 0.23 mg/d of cyclosporine and everolimus, respectively. That is to say, the CYP3A4 modulator saved 80% and 56% of drug doses.

In the cyclosporine only group, the same 80% dose reduction necessity was observed. At day 30 post transplantation cyclosporine daily dose was 1.67 + 0.47 mg/kg.

The immunosuppressant daily doses and blood levels during the first year of follow up are shown in Figures 4 and 5. The most relevant findings deployed in those

figures are a lesser dispersion of the daily doses of both IS, cyclosporine and everolimus, in order to achieve and maintain the therapeutic blood concentration windows in all time periods of the follow-up. Obviously, the cyclosporine blood levels in both groups are not comparable, because the target ones are different in both schemes.

There was a slight positive correlation between cyclosporine blood levels and serum creatinine in the everolimus group: $r = 0.1637$; two-tailed probability: 0.004 (Figure 6), but not in the Azathioprine/MMF group: $r = 0.064$; two-tailed probability: 0.256 (Figure 6).

DISCUSSION

The addition of a CYP3A4 modulator to kidney transplant recipients who use a cyclosporine or a cyclosporine and everolimus based immunosuppressive regimen allows to consistently and importantly reduce the drug doses without jeopardizing the ability to achieve and maintain therapeutic blood levels of the IS in both regimens. Moreover, the addition of low doses of ketoconazole stabilizes medium and long term of both everolimus and cyclosporine and makes the periodic control clinical visits easier.

The use of ketoconazole has been a controversial issue in clinical transplantation, in spite of prospective

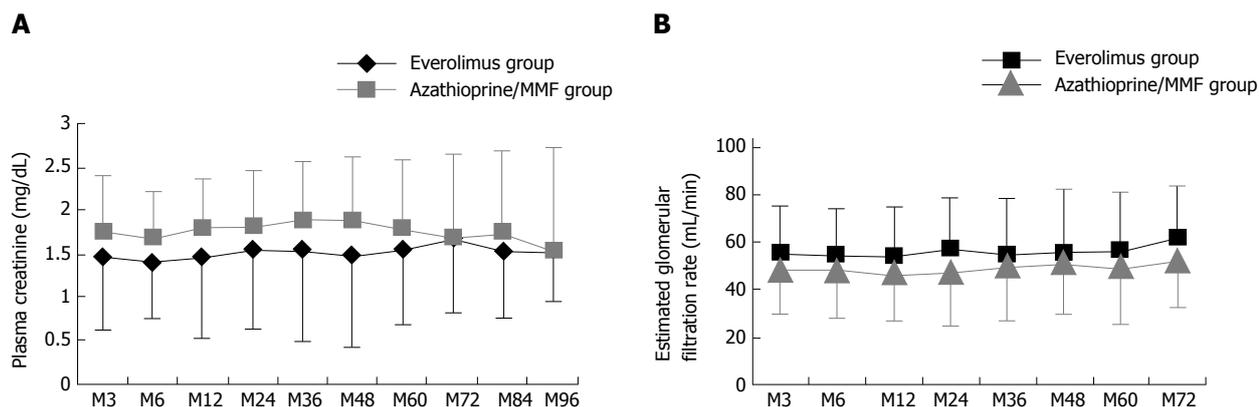


Figure 2 Kidney allograft function estimated by plasma creatinine (A) and glomerular filtration rate estimated by mdrd formula (B). MMF: Mycophenolate mofetyl.

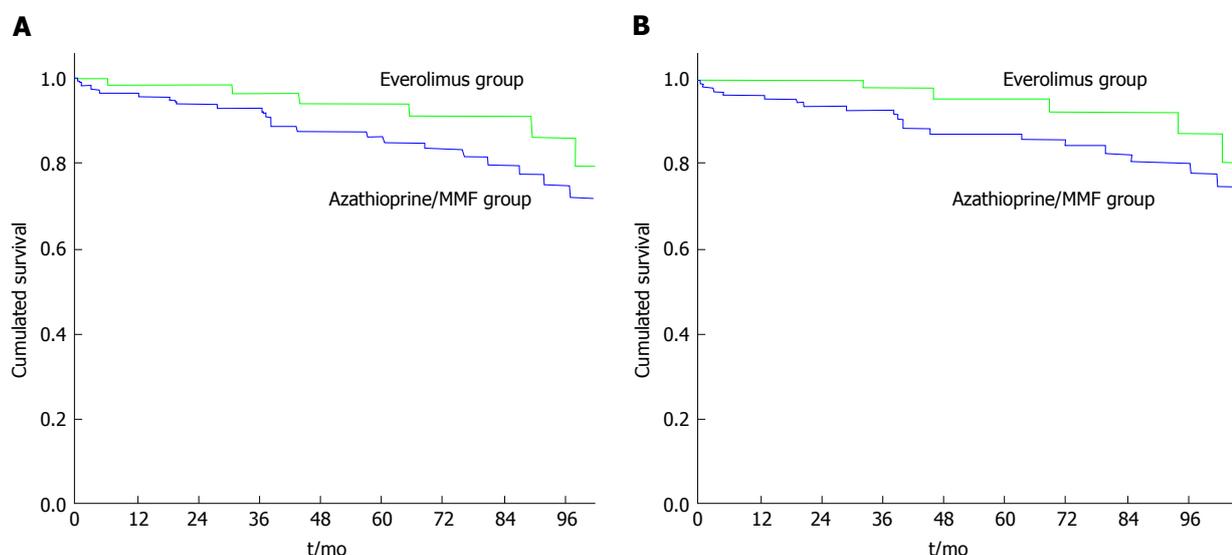


Figure 3 Graft survival un-censored (A) and graft survival censored (B) for patient death with a functioning graft. MMF: Mycophenolate mofetyl.

randomized trials that do not show worse clinical results in comparison to not using the CYP3A4 modulator^[42-47]. Moreover, it has been suggested that ketoconazole could behave as an immunomodulator agent, as it reduced the acute rejection rate in heart transplant patients^[44]. Our biopsy proven acute rejection (BPAR) rate of both groups was comparable to similar schemes without the CYP3A4 modulator. For example, the everolimus and cyclosporine group showed a first year BPAR of 10% that compares favorably with the three arms containing a calcineurin inhibitor in the Elite-Symphony trial^[48] (low-dose tacrolimus 12.3%, standard-dose cyclosporine 25.8% and low-dose cyclosporine 24.0%) and also with another trial with a similar design of everolimus and low exposure of cyclosporine that reported a first year incidence of BPAR of 16.2%^[49]. For the cyclosporine only group, the first year BPAR rate was 22% in comparison with 23% in the azathioprine group and 18% of the mycophenolate mofetyl group of the MYSS trial^[50] and also alike the cyclosporine and MMF rates in the Elite-Symphony trial^[48].

We did not construct formal pharmacokinetic time-curves in any of the study groups. However, in a previous experience, we learned that in order to maintain the blood cyclosporine concentration constant before the next dose (C0) combining cyclosporine with ketoconazole, it is necessary to adjust the CNI dose in such a way that the pharmacokinetic profile changed decreasing both C_{max} and AUC^[51]. That is to say that ketoconazole changed the cyclosporine blood concentration time function in the same way as increasing the alpha and beta parameters of a Gamma type distribution (Figure 1)^[40].

The main limitation of using CYP3A4 modulators could be related to the occurrence of adverse events due to a theoretically increased exposure to IS drugs, which could translate to more infective episodes or a higher frequency of hospitalizations. Nevertheless, our data does not show an increase in the incidences of NODAT, CMV or BK virus diseases, new onset neoplasia or PTLN or more hospitalizations as compared with the other trials^[48-50]. The key issue to achieve these comparable rates is to actively adjust the IS doses to

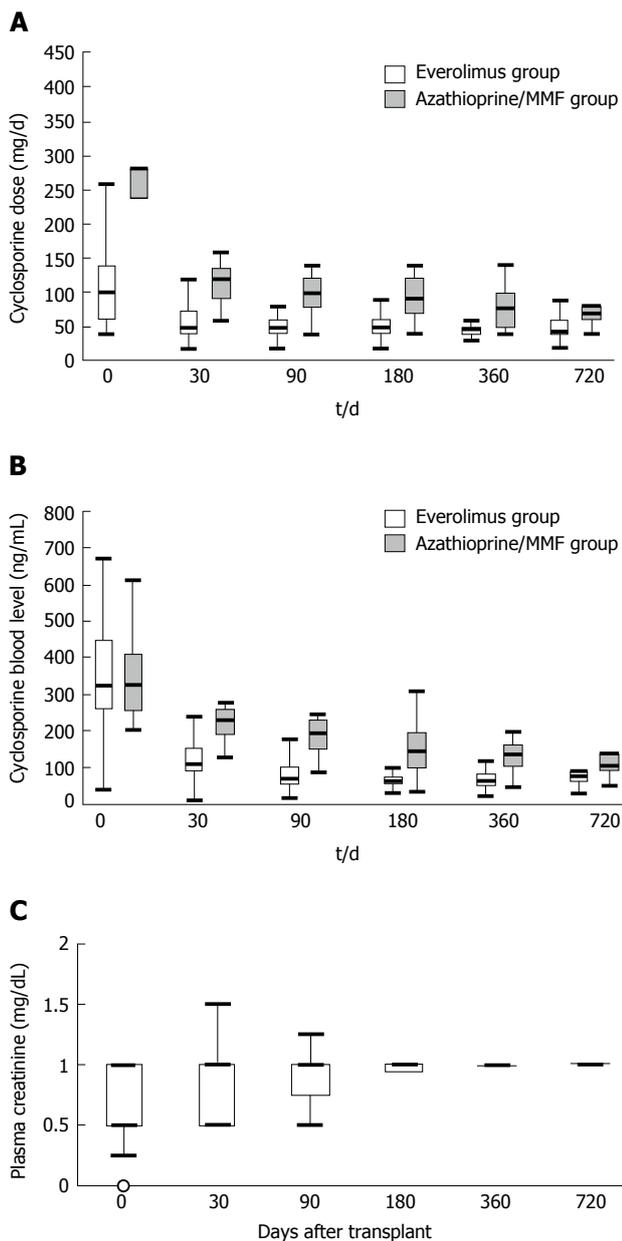


Figure 4 Cyclosporine daily dose (A), cyclosporine blood concentrations (B) and everolimus daily dose (C) during the first two years of follow-up. MMF: Mycophenolate mofetyl.

the usual therapeutic windows reducing everolimus and cyclosporine in almost 60% and 80%, respectively (Figures 3 and 4).

Both graft survival functions, censored and uncensored by recipients death with a functioning graft, were positive. At year six of follow-up, those receiving everolimus show 93% and 91%, respectively, and those receiving azathioprine/MMF 83% and 81%. Both compare favorably with the follow-up of the Elite-Symphony trial that showed uncensored graft survival between 85% and 90% in the four experimental groups after 3 years of follow-up, and they are certainly better than other clinical trials exploring CNI and m-TOR inhibitor combination^[49,52,53].

The kidney allograft functions of both immunosu-

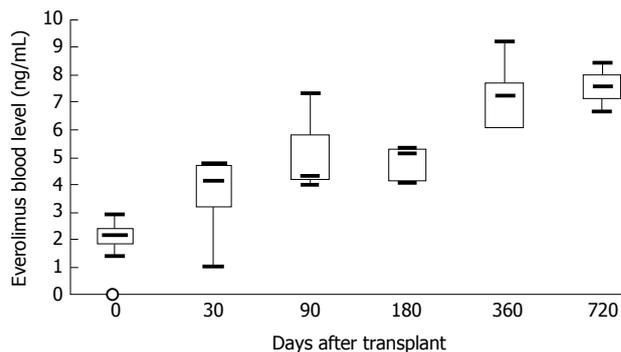


Figure 5 Everolimus blood concentrations during the first years of follow-up.

ppressive regimens show similar behaviors. In spite of several time points with significant differences in plasma creatinine or MDRD estimated glomerular filtration rate, both show follow-up stability and, interestingly, there appears to be no progressive GFR deterioration in the full cyclosporine exposure scheme in comparison with the other scheme with reduced exposure of the CNI. These findings put in doubt the real importance of CNI exposure and its postulated related nephrotoxicity that was once named as chronic allograft nephropathy and correlated with histological kidney graft interstitial fibrosis and tubular atrophy^[54].

Still more important, we found no evidence that the CYP3A4 modulator could predispose to a graft functional progressive deterioration, either because of a deficient immunosuppressive efficacy or chronic CNI associated nephrotoxicity, as both regimens did have different CNI exposures.

This idea of co-administering CYP3A4 modulators enhancing the immunosuppressive efficacy and safety of commonly used drugs in solid organ transplantation has been transferred to a completely different clinical field such as medical oncology. In fact, there is an increasing interest of exploring this particular pharmacological interaction to better preserve the health of cancer patients^[55-57]. Nevertheless, it is necessary to be conscious that ketoconazole could be related to adverse events, mainly liver injury, if they are prescribed in higher doses than 200 mg a day^[58] and that newer combinations of drugs in internal medicine, solid organ transplantation or oncology can be a better choice than the use of CYP3A4 modulators.

In summary, we have described our long term experience of combining the CYP3A4 modulator ketoconazole with a lone CNI or in combination with an m-TOR inhibitor, in low and medium immunological risk kidney transplant recipients and our main findings were that these combinations are clinically feasible, effective, safe and affordable even in the long term. In spite of that, these strategies have not received much attention and have not been explored in adequately designed, prospective, randomized and long term trials; they deserve all of the transplant community's attention because they could potentially allow for better global

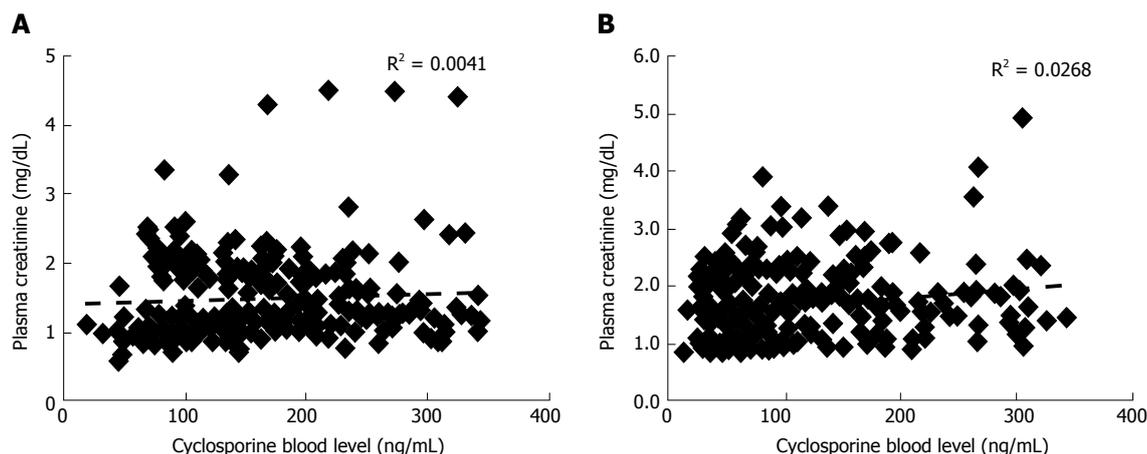


Figure 6 Correlation between plasma creatinine and blood cyclosporine concentration in the everolimus group (A) and mycophenolate mofetyl group (B).

clinical results in kidney, and even other solid organ, transplantation.

COMMENTS

Background

Kidney transplantation is a well-accepted treatment for end stage renal disease as it maximizes patient survival in comparison to remaining in chronic dialysis. Immunosuppressive (IS) treatment is the main therapy used to prevent acute rejection episodes and to avoid premature allograft losses. In spite of improving IS schedules, graft survival is not satisfactory.

Research frontiers

At the beginning of the 1990s, it was reported in biomedical literature that combining IS drugs metabolized by the hepatic cytochrome P-450 system with ketoconazole or diltiazem could slow the disposal metabolic rate of IS, giving the opportunity to save money in disadvantaged countries. Shortly afterwards, it was also postulated that the addition of ketoconazole could, in fact, modulate the cytochrome function allowing some kind of accommodation of the IS regimens that could theoretically improve graft survivals. In fact, this imidazole agent changes the pharmacokinetic curve both of calcineurin and mammalian target of rapamycin (m-TOR) inhibitors.

Innovations and breakthroughs

With the entry of newer IS, like mycophenolate acid derivatives and m-TOR inhibitors, that strategy was abandoned, just remaining in isolated clinical reports. In Hospital del Salvador, in Chile, the modulation of the cytochrome P-450 system with ketoconazole is part of almost all IS regimens since the early 1990s. In the middle of the last decade, the authors began an experience combining ketoconazole, cyclosporine and everolimus that is yet continuing and in this paper, the authors communicate this experience compared with another similar cohort receiving only cyclosporine and ketoconazole [plus azathioprine or mycophenolate mofetyl (MMF)].

Applications

The obtained results are certainly encouraging as the authors observed similar or even lower acute rejection episode and viral infection rates and similar or better 5 year graft survival compared with other well validated IS regimens as those containing antibody induction followed by the combination of tacrolimus and MMF and with a very favorable safety profile. Obviously, this experience must be validated with double-blind, randomized, prospective and controlled trials, even considering the economic disincentive to conduct a clinical trial that allows saving more than 50% of cytochrome P-450 metabolized agent doses and, in parallel, important quantities of valuable money.

Peer-review

It is an interesting manuscript evaluating the association of cyclosporine and

ketoconazole in transplantation.

REFERENCES

- 1 **USRDS.** The 2014 Annual Data Report. Chapter 6. [accessed 2015 Jun 27]. Available from: URL: http://www.usrds.org/2014/view/v2_06.aspx
- 2 **Zeitlinger M.** Drug interactions in medicine. In: Univ.-Prof. Dr. Markus Müller, eds. *Clinical Pharmacology: Current Topics and Case Studies*. ISBN: 978-3-7091-0143-8 (Print) 978-3-7091-0144-5
- 3 **Ray JE, Keogh AM, McLachlan AJ.** Decision support tool to individualize cyclosporine dose in stable, long-term heart transplant recipients receiving metabolic inhibitors: overcoming limitations of cyclosporine C2 monitoring. *J Heart Lung Transplant* 2006; **25**: 1223-1229 [PMID: 17045935 DOI: 10.1016/j.healun.2006.07.002]
- 4 **Carbajal H, Soltero L, Rodríguez-Montalvo C, Valdés A.** Cyclosporine and low-dose ketoconazole in renal transplant recipients: a single center experience. *Transplantation* 2005; **79**: 252-253 [PMID: 15665782 DOI: 10.1097/01.tp.0000140769.31248.79]
- 5 **Carbajal H, Soltero L, Rodríguez-Montalvo C, Valdés A.** Cyclosporine and low-dose ketoconazole in renal transplant recipients: a single-center experience. *Transplantation* 2004; **77**: 1038-1040 [PMID: 15087768 DOI: 10.1097/01.tp.0000122343.51904.c3]
- 6 **Dominguez J, Kompatzki A, Foradori A, Norambuena R.** Ketoconazole alters cyclosporine pharmacokinetic profile and may predispose to acute rejection. *Transplant Proc* 2003; **35**: 2522-2523 [PMID: 14612002 DOI: 10.1016/j.transproceed.2003.09.022]
- 7 **Zakliczynski M, Krynicka A, Szweczyk M, Wojarski J, Zembala M.** Limited utility of cyclosporine C2 monitoring in heart transplant recipients receiving ketoconazole. *Transplant Proc* 2003; **35**: 2333-2334 [PMID: 14529932 DOI: 10.1016/s0041-1345(03)00771-1]
- 8 **Ray JE, Keogh AM, McLachlan AJ, Akhlaghi F.** Cyclosporin C(2) and C(0) concentration monitoring in stable, long-term heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2003; **22**: 715-722 [PMID: 12873538 DOI: 10.1016/s1053-2498(02)00649-6]
- 9 **Jeng S, Chanchairujira T, Jusko W, Steiner R.** Prednisone metabolism in recipients of kidney or liver transplants and in lung recipients receiving ketoconazole. *Transplantation* 2003; **75**: 792-795 [PMID: 12660503 DOI: 10.1097/01.tp.0000055099.97542.5d]
- 10 **Akhlaghi F, Keogh AM, McLachlan AJ, Kaan A.** Pharmacokinetics of cyclosporine in heart transplant recipients receiving metabolic inhibitors. *J Heart Lung Transplant* 2001; **20**: 431-438 [PMID: 11295581 DOI: 10.1016/s1053-2498(00)00234-5]
- 11 **Foradori A, Mezzano S, Videla C, Pefaur J, Elberg A.** Modification of the pharmacokinetics of cyclosporine A and metabolites by the concomitant use of Neoral and diltiazem or ketoconazol in stable adult kidney transplants. *Transplant Proc* 1998; **30**: 1685-1687

- [PMID: 9723244 DOI: 10.1016/s0041-1345(98)00393-5]
- 12 **Watanabe T**, Gao ZH, Shinozuka N, Schulick RD, Kuo A, Burdick JF. Unexpectedly low immunocompetence in transplant patients on ketoconazole. *Clin Transplant* 1997; **11**: 599-603 [PMID: 9408692 DOI: 10.1034/j.1399-0012.2001.150207.x]
 - 13 **Videla C**, Vega J, Borja H, Gatica A, Clavero R, Aldunate T. [Conversion from +Sandimmune to Neoral in kidney transplant recipients treated with cyclosporine and ketoconazole]. *Rev Med Chil* 1997; **125**: 438-445 [PMID: 9460285 DOI: 10.1016/s0041-1345(96)00118-2]
 - 14 **Sorenson AL**, Lovdahl M, Hewitt JM, Granger DK, Almond PS, Russlie HQ, Barber D, Matas AJ, Canafax DM. Effects of ketoconazole on cyclosporine metabolism in renal allograft recipients. *Transplant Proc* 1994; **26**: 2822 [PMID: 7940888]
 - 15 **Patton PR**, Brunson ME, Pfaff WW, Howard RJ, Peterson JC, Ramos EL, Karlix JL. A preliminary report of diltiazem and ketoconazole. Their cyclosporine-sparing effect and impact on transplant outcome. *Transplantation* 1994; **57**: 889-892 [PMID: 8154037 DOI: 10.1097/00007890-199403270-00021]
 - 16 **Karlix JL**, Cheng MA, Brunson ME, Ramos EL, Howard RJ, Peterson JC, Patton PR, Pfaff WW. Decreased cyclosporine concentrations with the addition of an H2-receptor antagonist in a patient on ketoconazole. *Transplantation* 1993; **56**: 1554-1555 [PMID: 8279039]
 - 17 **Becerra E**, Torres H, Gonzalez R, Borja H, Pedemonte O, de Prada MT, Kaplan J. Two-year follow-up of a heart transplant patient being treated with cyclosporine and ketoconazole. *J Heart Lung Transplant* 1993; **12**: 338-340 [PMID: 8476909 DOI: 10.1016/s1053-2498(99)80159-4]
 - 18 **Gandhi BV**, Kale S, Bhowmik DM, Jain AK. Concomitant administration of cyclosporine and ketoconazole in renal transplant patients. *Transplant Proc* 1992; **24**: 1715 [PMID: 1412806]
 - 19 **First MR**, Schroeder TJ, Alexander JW, Stephens GW, Weiskittel P, Myre SA, Pesce AJ. Cyclosporine dose reduction by ketoconazole administration in renal transplant recipients. *Transplantation* 1991; **51**: 365-370 [PMID: 1994529 DOI: 10.1097/00007890-199102000-00018]
 - 20 **García R**, Marín C, Herrera J, Henríquez La Roche C, Rubio L, Rodríguez-Iturbe B. [Usefulness of ketoconazole combined with cyclosporin in renal transplantation]. *Invest Clin* 1991; **32**: 115-121 [PMID: 1814474]
 - 21 **Frey FJ**. Concomitant cyclosporin and ketoconazole. *Lancet* 1990; **335**: 109-110 [PMID: 1967388 DOI: 10.1016/0140-6736(90)90573-n]
 - 22 **First MR**, Schroeder TJ, Weiskittel P, Myre SA, Alexander JW, Pesce AJ. Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989; **2**: 1198-1201 [PMID: 2572912 DOI: 10.1016/s0140-6736(89)91802-3]
 - 23 **Girardet RE**, Melo JC, Fox MS, Whalen C, Lusk R, Masri ZH, Lansing AM. Concomitant administration of cyclosporine and ketoconazole for three and a half years in one heart transplant recipient. *Transplantation* 1989; **48**: 887-890 [PMID: 2815266 DOI: 10.1097/00007890-198911000-00039]
 - 24 **Charles BG**, Ravenscroft PJ, Rigby RJ. The ketoconazole-cyclosporin interaction in an elderly renal transplant patient. *Aust N Z J Med* 1989; **19**: 292-293 [PMID: 2673179 DOI: 10.1111/j.1445-5994.1989.tb00264.x]
 - 25 **White DJ**, Blatchford NR, Cauwenbergh G. Cyclosporine and ketoconazole. *Transplantation* 1984; **37**: 214-215 [PMID: 6320510 DOI: 10.1097/00007890-198402000-00020]
 - 26 **Ferguson RM**, Sutherland DE, Simmons RL, Najarian JS. Ketoconazole, cyclosporin metabolism, and renal transplantation. *Lancet* 1982; **2**: 882-883 [PMID: 6126744 DOI: 10.1016/s0140-6736(82)90851-0]
 - 27 **Khan E**, Killackey M, Kumbala D, LaGuardia H, Liu YJ, Qin HZ, Alper B, Paramesh A, Buell J, Zhang R. Long-term outcome of ketoconazole and tacrolimus co-administration in kidney transplant patients. *World J Nephrol* 2014; **3**: 107-113 [PMID: 25332902 DOI: 10.5527/wjn.v3.i3.107]
 - 28 **Elamin S**, El-Magzoub AR, Dablouk N, Mahmoud F, Abbas M. Co-administration of ketoconazole and tacrolimus to kidney transplant recipients: cost minimization and potential metabolic benefits. *Saudi J Kidney Dis Transpl* 2014; **25**: 814-818 [PMID: 24969193 DOI: 10.4103/1319-2442.135033]
 - 29 **Soltero L**, Carbajal H, Rodríguez-Montalvo C, Valdés A. Co-administration of tacrolimus and ketoconazole in renal transplant recipients: cost analysis and review of metabolic effects. *Transplant Proc* 2003; **35**: 1319-1321 [PMID: 12826147 DOI: 10.1016/s0041-1345(03)00450-0]
 - 30 **Kovarik JM**, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Blood concentrations of everolimus are markedly increased by ketoconazole. *J Clin Pharmacol* 2005; **45**: 514-518 [PMID: 15831774 DOI: 10.1177/0091270005275368]
 - 31 **Thomas PP**, Manivannan J, John GT, Jacob CK. Sirolimus and ketoconazole co-prescription in renal transplant recipients. *Transplantation* 2004; **77**: 474-475 [PMID: 14966432 DOI: 10.1097/01.tp.0000112935.43362.37]
 - 32 **González F**, Espinoza M, Reynolds E, Herrera P, Espinoza O, Rocca X, Lorca E, Hidalgo J, Roessler E. Effectiveness and cost of replacing a calcineurin inhibitor with sirolimus to slow the course of chronic kidney disease in renal allografts. *Transplant Proc* 2010; **42**: 284-287 [PMID: 20172332 DOI: 10.1016/j.transproceed.2009.12.049]
 - 33 **Gonzalez F**, Espinoza M, Herrera P, Rocca X, Reynolds E, Lorca E, Roessler E, Hidalgo J, Espinoza O. Everolimus versus azathioprine in a cyclosporine and ketoconazole-based immunosuppressive therapy in kidney transplant: 3-year follow-up of an open-label, prospective, cohort, comparative clinical trial. *Transplant Proc* 2010; **42**: 270-272 [PMID: 20172327 DOI: 10.1016/j.transproceed.2009.12.048]
 - 34 **Odocha O**, Kelly B, Trimble S, Murigande C, Toussaint RM, Callender CO. Cost-containment strategies in transplantation: the utility of cyclosporine-ketoconazole combination therapy. *Transplant Proc* 1996; **28**: 907-909 [PMID: 8623456]
 - 35 **Abraham MA**, Thomas PP, John GT, Job V, Shankar V, Jacob CK. Efficacy and safety of low-dose ketoconazole (50 mg) to reduce the cost of cyclosporine in renal allograft recipients. *Transplant Proc* 2003; **35**: 215-216 [PMID: 12591369 DOI: 10.1016/s0041-1345(02)03839-3]
 - 36 **Gerntholtz T**, Pascoe MD, Botha JF, Halkett J, Kahn D. The use of a cyclosporin-ketoconazole combination: making renal transplantation affordable in developing countries. *Eur J Clin Pharmacol* 2004; **60**: 143-148 [PMID: 15083250 DOI: 10.1007/s00228-004-0745-0]
 - 37 **Becerra E**, Aranguiz E, Pedemonte O, De Prada MT, Merello L, Orfali C, Aninat M, Torres H, González R, Chadid P. [Cardiac transplantation: economizing cyclosporin A by including ketoconazole in the immunosuppressive schedule]. *Rev Med Chil* 1991; **119**: 1038-1042 [PMID: 1845097]
 - 38 **Butman SM**, Wild JC, Nolan PE, Fagan TC, Finley PR, Hicks MJ, Mackie MJ, Copeland JG. Prospective study of the safety and financial benefit of ketoconazole as adjunctive therapy to cyclosporine after heart transplantation. *J Heart Lung Transplant* 1991; **10**: 351-358 [PMID: 1854763]
 - 39 **Randall T**. Cyclosporine-ketoconazole combination offers promise in reducing antirejection therapy costs. *JAMA* 1990; **264**: 430-431 [PMID: 2366269 DOI: 10.1001/jama.1990.03450040018004]
 - 40 The Gamma distribution. [accessed 2015 Jun 27]. Available from: URL: <http://www.mathworks.com/help/stats/gamma-distribution.html>
 - 41 **Ah-Sing E**, Poole TW, Ioannides C, King LJ. Mechanism of the ketoconazole-cyclosporin interaction. *Arch Toxicol* 1990; **64**: 511-513 [PMID: 2275609 DOI: 10.1007/bf01977638]
 - 42 **Agroudy AE**, Sobh MA, Hamdy AF, Ghoneim MA. A prospective, randomized study of coadministration of ketoconazole and cyclosporine a in kidney transplant recipients: ten-year follow-up. *Transplantation* 2004; **77**: 1371-1376 [PMID: 15167592 DOI: 10.1097/01.tp.0000121133.84763.26]
 - 43 **Sobh MA**, Hamdy AF, El Agroudy AE, El Sayed K, El-Diasty T, Bakr MA, Ghoneim MA. Co-administration of ketoconazole and cyclosporine for kidney transplant recipients: long-term follow-up

- and study of metabolic consequences. *Am J Kidney Dis* 2001; **37**: 510-517 [PMID: 11228175 DOI: 10.1053/ajkd.2001.22075]
- 44 **Keogh A**, Spratt P, McCosker C, Macdonald P, Mundy J, Kaan A. Ketoconazole to reduce the need for cyclosporine after cardiac transplantation. *N Engl J Med* 1995; **333**: 628-633 [PMID: 7637723 DOI: 10.1056/nejm199509073331004]
- 45 **Sobh M**, el-Agroudy A, Moustafa F, Harras F, el-Bedewy M, Ghoneim M. Coadministration of ketoconazole to cyclosporin-treated kidney transplant recipients: a prospective randomized study. *Am J Nephrol* 1995; **15**: 493-499 [PMID: 8546171 DOI: 10.1159/000168892]
- 46 **First MR**, Schroeder TJ, Michael A, Hariharan S, Weiskittel P, Alexander JW. Cyclosporine-ketoconazole interaction. Long-term follow-up and preliminary results of a randomized trial. *Transplantation* 1993; **55**: 1000-1004 [PMID: 8497871 DOI: 10.1097/00007890-199305000-00009]
- 47 **El-Dahshan KF**, Bakr MA, Donia AF, Badr Ael-S, Sobh MA. Ketoconazole-tacrolimus coadministration in kidney transplant recipients: two-year results of a prospective randomized study. *Am J Nephrol* 2006; **26**: 293-298 [PMID: 16804292 DOI: 10.1159/000094133]
- 48 **Ekberg H**, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gürkan A, Margreiter R, Hugo C, Grinyó JM, Frei U, Vanrenterghem Y, Daloze P, Halloran PF. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562-2575 [PMID: 18094377 DOI: 10.1056/nejmoa067411]
- 49 **Tedesco Silva H**, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, Walker R, Wang Z, Zibari G, Kim YS. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant* 2010; **10**: 1401-1413 [PMID: 20455882 DOI: 10.1111/j.1600-6143.2010.03129.x]
- 50 **Remuzzi G**, Lesti M, Gotti E, Ganeva M, Dimitrov BD, Ene-Iordache B, Gherardi G, Donati D, Salvadori M, Sandrini S, Valente U, Segoloni G, Mourad G, Federico S, Rigotti P, Sparacino V, Bosmans JL, Perico N, Ruggenti P. Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. *Lancet* 2004; **364**: 503-512 [PMID: 15302193 DOI: 10.1016/s0140-6736(04)16808-6]
- 51 **Roessler E**, Herrera S, Espinoza M, Ayala A, Reynolds E, González F, Espinoza O, Undurraga A, Muñoz R, Arcos O, Galaz G. Conversion from Sandimmune to Neoral in renal transplant: functional histopathological, and pharmacokinetic changes. *Transplant Proc* 1998; **30**: 1756-1757 [PMID: 9723268 DOI: 10.1016/s0041-1345(98)00417-5]
- 52 **Ekberg H**, Bernasconi C, Tedesco-Silva H, Vitko S, Hugo C, Demirbas A, Acevedo RR, Grinyó J, Frei U, Vanrenterghem Y, Daloze P, Halloran P. Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. *Am J Transplant* 2009; **9**: 1876-1885 [PMID: 19563339 DOI: 10.1111/j.1600-6143.2009.02726.x]
- 53 **Guerra G**, Ciancio G, Gaynor JJ, Zarak A, Brown R, Hanson L, Sageshima J, Roth D, Chen L, Kupin W, Tueros L, Ruiz P, Livingstone AS, Burke GW. Randomized trial of immunosuppressive regimens in renal transplantation. *J Am Soc Nephrol* 2011; **22**: 1758-1768 [PMID: 21807891 DOI: 10.1681/ASN.2011010006]
- 54 **Nankivell BJ**, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; **349**: 2326-2333 [PMID: 14668458 DOI: 10.1056/nejmoa020009]
- 55 **Cohen EE**, Wu K, Hartford C, Kocherginsky M, Eaton KN, Zha Y, Nallari A, Maitland ML, Fox-Kay K, Moshier K, House L, Ramirez J, Undevia SD, Fleming GF, Gajewski TF, Ratain MJ. Phase I studies of sirolimus alone or in combination with pharmacokinetic modulators in advanced cancer patients. *Clin Cancer Res* 2012; **18**: 4785-4793 [PMID: 22872575 DOI: 10.1158/1078-0432.CCR-12-0110]
- 56 **Veroux M**, Tallarita T, Corona D, D'Assoro A, Veroux P. Exploring new frontiers: sirolimus as a pharmacokinetic modulator in advanced cancer patients. *Expert Rev Anticancer Ther* 2013; **13**: 17-20 [PMID: 23259423 DOI: 10.1586/era.12.151]
- 57 **Zee YK**, Goh BC, Lee SC. Pharmacologic modulation strategies to reduce dose requirements of anticancer therapy while preserving clinical efficacy. *Future Oncol* 2012; **8**: 731-749 [PMID: 22764771 DOI: 10.2217/fon.12.53]
- 58 **FDA Drug Safety Communication**. FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. [accessed 2015 Sept 13]. Available from: URL: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM362444.pdf>

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