

Among CMV-positive renal transplant patients receiving non-T-cell depleting induction, the absence of CMV disease prevention is a safe strategy: a retrospective cohort of 372 patients

Hugoline Boulay, Emmanuel Oger, Diego Cantarovich, Philippe Gatault, Antoine Thierry, Yannick Le Meur, Agnès Duveau, Cécile Vigneau, Nolwenn Lorcy

▶ **To cite this version:**

Hugoline Boulay, Emmanuel Oger, Diego Cantarovich, Philippe Gatault, Antoine Thierry, et al.. Among CMV-positive renal transplant patients receiving non-T-cell depleting induction, the absence of CMV disease prevention is a safe strategy: a retrospective cohort of 372 patients. Transplant Infectious Disease, 2021, 23 (3), pp.e13541. 10.1111/tid.13541 . hal-03095269

HAL Id: hal-03095269
https://hal.science/hal-03095269

Submitted on 12 Jan 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Article

MISS HUGOLINE BOULAY (Orcid ID : 0000-0002-3600-1350)

YANNICK LE MEUR (Orcid ID : 0000-0001-8913-415X)

Article type : Original Article

1. MAIN BODY DOCUMENT

TITLE PAGE

TITLE

Among CMV-positive renal transplant patients receiving non-T-cell depleting induction, the absence of CMV disease prevention is a safe strategy: a retrospective cohort of 372 patients

SHORT RUNNING TITLE

CMV Prophylaxis after renal transplantation

AUTHORS' FULL NAMES

Boulay Hugoline (1) (8)

Oger Emmanuel (2)

Cantarovich Diego (3)

Gatault Philippe (4)

Thierry Antoine (5)

Le Meur Yannick (6)

Duveau Agnès (7)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/TID.13541

Vigneau Cécile (1) (8)

Lorcy Nolwenn (1)

AUTHOR CONTRIBUTION STATEMENT

HB : data collection and analysis, manuscript writing.

EO : statistical expertise.

DC, PG, AT, YLM and AD : data collection.

CV and NL : supervision.

All authors approved final version of the manuscript.

AFFILIATIONS

(1) CHU Pontchaillou, Service de Néphrologie, France.

(2) CHU Pontchaillou, Service de Pharmacologie clinique et biologique, France.

(3) Institut de Transplantation Urologie-Néphrologie, Centre Hospitalier Universitaire de Nantes, France.

(4) Service de Néphrologie et Immunologie Clinique, Centre Hospitalier Universitaire de Tours, France.

(5) Service de Néphrologie, Hémodialyse et Transplantation Rénale, Centre Hospitalier Universitaire de Poitiers, France.

(6) Service de Néphrologie, Centre Hospitaliser de Brest, Université de Bretagne Occidentale, France

(7) Service de Nephrologie-Dialyse-Transplantation, Centre Hospitalier Universitaire d'Angers, France.

(8) Univ Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) UMR_S 1085, F-35000 Rennes

CORRESPONDING AUTHOR EMAIL

Accepted Article

Hugoline Boulay, Service de Néphrologie, CHU Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes, France. hugoline.boulay@gmail.com (0033) +2 99 28 94 90

Cécile Vigneau, Service de Néphrologie, CHU Pontchaillou, 2 rue Henri Le Guilloux, 35033 Rennes, France. cecile.vigneau@chu-rennes.fr (0033) +2 99 28 94 90

Accepted Article

ABBREVIATIONS

CMV: Cytomegalovirus

CMV D+/R-: cytomegalovirus seropositive donor to cytomegalovirus seronegative transplant Recipient

CMV D-/R-: cytomegalovirus seronegative donor to cytomegalovirus seronegative transplant Recipient

CMV D-/R+: cytomegalovirus seronegative donor to cytomegalovirus seropositive transplant Recipient

CMV D+/R+: cytomegalovirus seropositive donor to cytomegalovirus seropositive transplant Recipient

CMV R+: cytomegalovirus seropositive transplant Recipient

MDRD: modification of diet in renal disease

MMF: mycophenolate mofetil

SNO: Société de Néphrologie de l'Ouest

Accepted Article

ABSTRACT

Cytomegalovirus (CMV) is the most common opportunistic pathogen affecting renal transplant recipients, especially in the first months. CMV-seropositive renal transplant recipients (CMV R+) are at intermediate risk for CMV disease, but this risk is enhanced among CMV R+ receiving T-cell depleting induction, compared to CMV R+ receiving non-depleting induction. In this second group, data in favour of prophylactic antiviral treatment with valganciclovir to reduce CMV disease is sparse. In this retrospective and multicentric trial, we included 372 CMV R+ transplanted between January 2012 and April 2015 and receiving non-depleting induction. During the first year following transplantation, CMV disease occurred in 5/222 patients (2.25%) in the prophylaxis group and 9/150 (6%) in the no-prophylaxis group (difference + 3.7; 95%CI – 0.5 to 8; p=0.002 for non-inferiority). The incidence of allograft rejection and other infectious diseases was similar between the 2 groups. Graft and patient survival were similar at the end of follow-up. In conclusion, the absence of prophylaxis did not appear to have a deleterious effect for CMV diseases among CMV R+ receiving non-depleting induction.

Accepted Article

Accepted Article

MAIN BODY TEXT

1. Introduction

Cytomegalovirus (CMV) is the most common opportunistic pathogen affecting renal transplant recipients, and it increases mortality and morbidity[1,2]. The manifestations of CMV infection range from asymptomatic infection to acute viral syndrome and organ dysfunction (gastroenteritis/colitis, pneumonitis, hepatitis, and retinitis)[3]. The greatest risk factor is donor-recipient serologic mismatch[4,5]: CMV seropositive donor to CMV seronegative recipient (CMV D+/R-) defines a high-risk group[6], whereas CMV seropositive renal transplant recipients (CMV R+) belong to an intermediate-risk group, and CMV seronegative donor to CMV seronegative recipient (CMV D-/R-) are considered low-risk. Depending on the risk, 3 preventive strategies can be used: 1/ a prophylactic strategy (administration of the antiviral drug valganciclovir over the first 3 to 6 months after transplantation), 2/a pre-emptive strategy (administration of the antiviral drug valganciclovir to asymptomatic patients with evidence of CMV replication) 3/ no preventive treatment[7]. For CMV R+, the 2013 recommendations of the American Society of Transplantation suggest using either the prophylactic or the pre-emptive strategy[1].

However, induction therapy using T-cell-depleting antibody, referred to hereafter as depleting induction, appears an important risk factor for CMV disease[8], compared to non-depleting induction (induction with basiliximab) or no induction therapy. As recommended in the 2000s[9,10] and suggested by Kotton[6], patients receiving a depleting induction are to be treated as CMV D+/R- patients. The intermediate-risk group is then restricted to CMV R+ receiving non-depleting induction. Data addressing the question of preventive treatment in this intermediate-risk group remain scant. A few studies on the CMV R+ category have compared the prophylactic and pre-emptive strategies. However, none of them excluded patients with T-cell depleting induction[11,12].

In the setting of our regional nephrology society, the *Société de Néphrologie de l'Ouest* (SNO), which includes 6 transplant centres, we decided to conduct a retrospective study to determine the incidence of CMV disease according to the preventive strategy used for CMV R+ without T-cell depleting induction.

2. Materials and Methods

2.1 Patient population

All patients who undergo kidney transplantation in our six University Hospitals are included in 2 prospective cohorts: 1/ DIVAT for Nantes (*Données Informatisées et VAlidées en Transplantation*

standing for computerized and validated data in transplantation) which was created in 1990, gathering 8 French transplantation centres, and 2/ ASTRE for Brest, Rennes, Angers, Poitiers and Tours (*ASsociation en Transplantation rénale pour la Recherche et l'Enseignement*), created in 1990 and gathering 13 French transplantation centres. Among these transplant recipients, we selected CMV R+ transplanted from 1st January 2012 to 30th April 2015 who did not receive T-cell depleting treatment (rabbit anti-thymocyte globulin), whether for induction or rejection therapy. Exclusion criteria were: age under 18, administration of Rituximab in the first year, early transplantectomy (within 1 month), multiple organ transplantation.

2.2 Data collected

The data collected included the cause of end-stage renal disease, donor characteristics including CMV serologic status, immunosuppressive regimen, antiviral preventive treatment status, occurrence of CMV disease, incidence of other transplant-related complications (other infectious diseases, acute rejection, lymphopenia or neutropenia), allograft function and survival, death. All data were extracted from the 2 above-mentioned prospective cohorts or collected in the hospital medical records when missing. CMV DNAemia was performed with an real-time polymerase chain reaction for CMV DNA quantification on whole blood specimens.

2.3 Clinical Definition

The definitions of CMV infection were based on the guidelines of the American Society of Transplantation[1]. Asymptomatic CMV infection was defined as the presence of CMV replication without symptoms. Symptomatic CMV viremia defines CMV disease, divided into CMV syndrome (manifestations such as fever, leukopenia, thrombocytopenia) and tissue-invasive CMV disease (enterocolitis, pneumonitis, retinitis, other…).

2.4 Preventive strategies

Patients were treated according to standard care in the facility. In most cases, the selected strategy was written in medical reports.

The prophylaxis treatment group (PROPH) received valganciclovir daily for three months. The prophylactic dose was adjusted to the glomerular filtration rate, according to the manufacturer's recommendations.

The no-prophylaxis treatment group (NO-PROPH) did not receive any antiviral prophylactic treatment and CMV viremia was sought only in case of clinical symptoms. In this group, to

Accepted Article

confirm that the patients did not receive a preemptive strategy, we also checked the monitoring for CMV viral load. Over 12 examinations for CMV DNAemia, *i.e.* the number of examinations recommended in the first 12 weeks in the preemptive strategy[1], medicals reports were carefully reviewed to confirm the preventive strategy used.

2.5 Statistical analysis

Descriptive statistics included measures of mean and standard derivation for continuous numerical variables and percentage-frequency distribution for categorical variables. Quantitative parametric data were compared between the groups using Wilcoxon rank test. Qualitative data were analysed using Fisher's exact test. MDRD values measured over time were compared through ANOVA for repeated measurement (PROC MIXED in SAS software version 9.4). Values of $p < 0.05$ were considered statistically significant.

To prove the non-inferiority of the no-prophylaxis strategy over the prophylaxis strategy, we estimated that 235 patients in each group would be needed, with an expected incidence of CMV disease of 5%[11], a power of 85%, a one-sided type 1 error probability of 2.5% and a non-inferiority margin set at 0.1.

We concluded to non-inferiority if the upper limit of the one-sided 97.5% confidence interval for the difference in success rate between the 2 groups was lower than the pre-assigned non-inferiority margin (Δ=0.1). Age and sex-adjusted risk difference was estimated through generalized linear model (PROC GENMOD in SAS).

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, N.C., USA).

This study protocol was approved by the local ethics committee (*Comité d'éthique du CHU de Rennes*, n°16.114) and national committee for the processing of health data (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la Santé*, n°16.839).

3. Results

3.1 Patients

From January 1st, 2012 to April 30, 2015, 1595 patients received renal allografts in the 6 transplant centres of the SNO. Among them, 506 patients were thought to fulfil the criteria for inclusion, but after review of their medical files 134 were excluded: 49 received anti-thymocytes globulin or anti-CD 20 therapy with Rituximab in the first year after transplantation, 10 had a

Accepted Article

transplantectomy in the first month of transplantation, 12 were seronegative, 4 received a combined transplant, 54 met the definition for preemptive strategy, 2 could not be identified and 3 were lost to follow-up. Thus 372 patients (73.5%) were included, as shown in figure 1.

Finally, 228 patients received a prophylactic treatment, and 150 did not receive any prophylactic treatment.

3.2 Patient characteristics

The patient characteristics are summarized in table 1. The median age of transplant recipients was 60 years (17.8 – 79.3) significantly younger in the NO-PROPH group (57[19], p = 0.01). The majority of patients were male (57.8%). Two hundred and nine patients (56.2%) received a graft from a CMV seropositive donor, 138 patients (62.2%) in the PROPH group and 71 patients (47.3%) in the NO-PROPH group (p=0.007).

Induction therapy using basiliximab was given to 367 patients (98.7%). Immunosuppression was based on calcineurin inhibitors for all patients (tacrolimus for 69.4% and ciclosporine for 30.6%), in association with mycophenolate mofetil for 348 patients (93.5%) and corticosteroids in maintenance therapy for 251 patients (67.5%). Ciclosporine was most often used in the NO-PROPH group (47.3%, p < 0.001). Maintenance therapy with corticoids was observed more frequently in the NO-PROPH group (75.3%) than in the PROPH group (62.2%, p < 0.001).

In the first year, the mean (±SD) number of CMV-Monitor tests per patient was 2.8 (±4.92) in the NO-PROPH group.

3.3 CMV disease

Fourteen patients (3.76%) had CMV disease within the first year following transplantation: 6 had CMV syndrome, 8 had tissue-invasive CMV (2 pneumonitis and 6 colitis), as shown in table 2.

Among them, nine patients (64.3%) did not receive any CMV prophylaxis, and 5 (35.7%) received a prophylactic treatment. Eleven (78.6%) had a seropositive CMV donor. Most of them (54.5%) were initially started on basiliximab, tacrolimus, mycophenolate mofetil and long-term treatment with prednisone (more than three months). Three patients had a recent treatment by corticoid *boli* for an acute rejection episode, 1 in the PROPH group and 2 in the NO-PROPH group.

The mean CMV viremia value was 93 172 (2 511 – 34 673 685) UI/mL, respectively 215 108 (2 511 – 630 957) UI/mL in the PROPH group and 3 971 917 (3890 – 34 673 685) UI/mL in the NO-PROPH group (p=0.595). The mean time to occurrence of CMV disease was 194 (±106) days in

Accepted Article

the PROPH group whereas it was 62 (±26) in the NO-PROPH group. Six patients (42.9%) received treatment with oral valganciclovir, including 4 with CMV syndrome. The other patients were treated with intravenous ganciclovir.

One case of ganciclovir resistance was detected. The patient belonged to the NO-PROPH group, had an L5955 mutation of the UL97 gene and was treated with maribavir.

There was no transplant loss, but 2 patients died: 1 in the NO-PROPH group from a metastatic melanoma, 1 in the PROPH group from cardiovascular disease.

3.4 Non-inferiority study

At one year, nine patients (6%) in the NO-PROPH group and 5 patients (2.25%) in the PROPH group had CMV disease. Non-inferiority was met (difference + 3.7; 95% CI – 0.5 to 8; p=0.002) as shown in figure 2. Age and sex-adjustment did not affect the conclusion (difference + 4.0; 95%CI -1.5 to 9.6).

In the seronegative donor group, only 3 cases of CMV disease were diagnosed (1.84%), 1 in the PROPH group and 2 in the NO-PROPH group. We did not detect a significant interaction across donor CMV status (test for interaction, p = 0.198) nor across use of tacrolimus (test for interaction, p = 0.828).

3.5 Allograft rejection and other infectious diseases

Data on immunologic and infectious complications are presented in table 3.

The overall incidence of allograft rejection was 9.5% (21 patients) in the PROPH group and 8.7% (13 patients) in the NO-PROPH group, with no statistical difference (p=1). The 3 groups did not differ significantly except for acute borderline rejection which was significantly lower in the NO-PROPH group (3.6% vs. 0%, PROPH vs. NO-PROPH group, p=0.025).

No difference was found in the incidence of other infectious diseases (71 patients, 32% in the PROPH group vs. 37 patients, 24.7% in the NO-PROPH group, p=0.28). Comparable incidence was documented for common bacterial infections.

3.6 Tolerance

At 12 months, the median [IQR] PNN nadir were 1.81 [1.74] G/L in the PROPH group and 2.27 [1.40] G/L in the NO-PROPH group, with a statistical difference (p=0.001). The median [IQR]

Accepted Article

leukocyte nadir was 3.30 [1.90] G/L in the PROPH group, statistically different from the NO-PROPH group (4.20 [1.90] G/L, $p < 0.001$).

The incidence of neutropenia (neutrophils < 2 G/L) was higher in the PROPH group (127 patients, 57.2%) than in the NO-PROPH group (52 patients, 34.7%, $p < 0.001$), the same being true for the incidence of severe neutropenia (neutrophils < 0.5 G/L, 11.3% vs. 4.7%, $p=0.0382$) and leukopenia (leukocytes < 4 G/L, 89.6% vs. 39.3%, $p < 0.001$). Twenty nine patients (13.1%) in the PROPH group and 3 patients (2.0%) in the NO-PROPH group discontinued MMF or required a dose reduction because of neutropenia in the first three months. Results are shown in table 3.

3.7 Renal function

Graft function data are presented in table 4. At one year, the mean serum creatinine was 136±48 µmol/L in the PROPH group and 134±45 µmol/L in the NO-PROPH group with no statistical difference ($p=0.747$). Serum creatinine values were also similar at 2, 3 and 4 years after transplantation. There were no significant time effect ($p = 0.220$) nor intervention effect ($p = 0.635$) as regards the Modification of Diet in Renal Disease (MDRD) glomerular filtration rate.

3.8 Patient and graft survival

The mean follow-up time was 33 months.

In the course of the study, in the PROPH group, graft loss occurred for 11 patients (5%) with the following causes: allograft chronic dysfunction for 4 patients, primary disease recurrence for 2 patients, rejection episodes for 2 patients, cardiorenal syndrome for 1 patient and unknown reason for 2 patients. In the NO-PROPH group, graft loss occurred for 7 patients (4.7%) with the following causes: allograft chronic dysfunction for 2 patients, primary disease recurrence for 1 patient, rejection episodes for 2 patients, cardiorenal syndrome for 1 patient and unknown reason for 1 patient. There was no statistical difference as shown in figure 3.

In the PROPH group, 14 deaths (6.3%) occurred with the following causes: 5 pneumonitis, 1 cancer, 2 cardiac arrests and 6 unknown reasons. In the NO-PROPH group, 7 deaths (4.7%) occurred with the following causes: 2 infectious diseases, 3 cardiac arrests, 1 cancer and 1 unknown reason. The mortality rates were similar ($p=0.268$), as shown in figure 4.

4. Discussion

In our study, we found that nine patients (6%) in the NO-PROPH group and 5 patients (2.25%) in the PROPH group had CMV disease. Overall, fewer than 4% of CMV R+ receiving non-depleting

Accepted Article

induction presented a CMV disease in the first year following transplantation. The incidence was even lower among those receiving a graft from a seronegative donor (only 3 out of 163 patients). To our knowledge, our study is the first to focus on CMV R+ receiving non-depleting induction. We opted to exclude patient receiving depleting induction because we considered them to be at high-risk for CMV disease as reported in recent studies[13 4,14,15].

The main objective in this study was to determine the incidence of CMV disease according to the anti-CMV treatment strategy used, in the CMV R+ population receiving non depleting induction. We found only a few studies designed to answer this question in this specific population, and most of them compared prophylactic and preemptive strategies. As none of them excluded patients with depleting induction, it makes them difficult to compare to our protocol.

The most recently published study conducted in Germany from 2006 to 2008 prospectively compared prophylactic and preemptive strategies with valganciclovir in CMV R+[11]. Five percent of the population underwent depleting induction. As expected, the incidence of asymptomatic viremia was higher in the preemptive group than in the prophylactic group (38.7 vs. 11%, $p < 0.0001$). Tissue-invasive CMV disease in the prophylactic group in the German study was 4.1%, comparable to our results. Unexpectedly, it occurred in 12.7% of the patients in the preemptive group. This incidence is markedly higher than in our NO-PROPH group, while patients were treated as soon as CMV viremia was detected, even if patients were asymptomatic, in accordance with a preemptive strategy. We do not find any explanation: the diagnostic criteria were similar; the CMV-seropositive donor rate seemed to be equivalent.

An earlier study, published in 1999, compared prophylactic treatment using valaciclovir (90 days) with a placebo[18]. Six hundred and sixteen renal transplant recipients were prospectively included, among whom 408 CMV R+. The incidence of CMV disease was statistically different between the 2 groups (1% in the valaciclovir group and 6% in the placebo group, $p=0.03$), but 40 % of the patients received depleting induction.

We encountered the same difficulty with another retrospective French study conducted on 282 CMV R+[12]. The incidence of CMV disease was lower in the group receiving prophylactic treatment with valganciclovir but 25 % of the patients received depleting induction.

Accepted Article

Another argument advocating CMV preventive treatment is that it reduces indirect effects of CMV reactivation, influencing allograft rejection and graft and patient survival. In our study, there was no impact on these aspects.

First of all, previous studies showed that symptomatic and asymptomatic reactivations were independent risk factors for allograft rejections in solid-organ transplant recipients[8]. This is thought to be the result of a dysregulation of the expression of histocompatibility complex molecules, growth factors and cytokines, especially in endothelial cells[3,19]. But some authors have suggested that CMV reactivation follows rather than precedes allograft rejection[20]. In studies on renal transplant recipients, the link is still debated. CMV infection and disease are sometimes reported to be independent risks factors for clinical rejection[21], though not always biopsy-proved rejection[23]. In our study, the median rejection rate was about 10%, in accordance in the recent litterature[24]. No rejection increase was detected in the NO-PROPH group. This finding is consistent with that of Lowance[18], who found the same rate of biopsy-proved acute graft rejection in the CMV R+ group treated with Valacyclovir as in the placebo group. However, in their study, the median rejection rate was 30% at six months: immunosuppressive regimen was different in the 1990s and fewer than 5% of the population received mycophenolate mofetil and tacrolimus. Witzke[11] found a higher rate of graft rejection at 12 months than in our study, 18,5% in the prophylactic group and 12,5% in the preemptive group ($p > 0,05$).

Secondly, CMV is thought to impair renal graft function, not only by increasing acute graft rejection, but also by increasing chronic allograft rejection through arterial myointimal thickening[3]. CMV infection is also involved in specific glomerular lesions[25]. This is particularly true in the CMV D+/R- population[19]. In our study, at the end of the first year, the mean glomerular filtration rate using the MDRD formula was 52 mL/min, whereas in Weclawiack's study, including only CMV R+, it was 49.2 mL/min in the prophylactic group and 51.2 mL/min in the preemptive group, using the Cockcroft-Gault formula, with no statistical difference[12]. In our study, graft survival uncensored for death was similar between the 2 groups with a median duration of follow up was 33 months. We can't exclude that it might be too short to see any difference with graft loss from indirect effects of CMV. However, this finding is consistent with that of Lowance's[18] (median time after transplantation 180 and 183 days). This is also in agreement with a more recent study[11], which showed that graft loss was 2.7% in the prophylaxis group compared to 4.7% in the preemptive group, with no statistical difference. But these findings contrast with Kliem's study[26] which suggested that CMV prophylaxis compared to preemptive strategy improves long-term renal graft survival in the CMV D+/R+ population (0% and 26.8% respectively at 4 years,

Accepted Article

p=0.0126). The high rate of graft loss in the preemptive group could be explained by a higher rate of acute rejection, (18.4% and 28.4% respectively).

Thirdly, CMV infection is thought to impact patient survival[20,27], not only because of death directly due to CMV disease, but also because it increases atherosclerosis and cardiovascular mortality[16]. At the beginning of the 1990s, one study reported poorer patient survival in a CMV D+/R+ renal transplant recipient group in comparison to a CMV D+/R- group[28]. The reason was unclear, possibly because of a dual CMV exposure leading to more frequent CMV asymptomatic reactivations[29]. This data was not confirmed in later studies[30]. As in our retrospective work, CMV R+ survival was similar between prophylactic treatment and placebo groups in 2 studies at 1 year[18] and 3 years[19] after transplantation. Witzke[31] published his long-term results, and found no statistically significant difference between prophylactic and preemptive strategies after 7 years. However the assessment of cardiovascular mortality requires very long-term studies.

Finally, there are 2 major benefits to the absence of prophylactic treatment. There were significantly more cases of neutropenia and lymphopenia in the PROPH group, because of the known hematotoxicity of the association valganciclovir-mycophenolate mofetil[32] even in patients with non-depleting induction. There were no more infectious complications in the PROPH group than in the NO-PROPH group, but neutropenia, and especially severe neutropenia, probably led to more consultations and to the prescription of hematopoietic growth factors. The second benefit is economic. In France, the average cost per patient is 3500 euros ($4500) for a three-month prophylactic course of valganciclovir. Pharmaco-economic studies have documented that the cost of the preemptive strategy is comparable to the prophylactic strategy, because of the cost of PCR[33].

There are some limitations to our study. First of all, we had to exclude a significant number of patients and we did not reach the required number of patients: 1/ Fifty-four patients who received a preemptive strategy. All of them were CMV D+/R+ and transplanted in the same centre. Before the beginning of the study, we thought that they belonged to the PROPH group, but after review of the medical file, we realized that all of them were screened for CMV PCR more than 12 times, and indeed belonged to a preemptive group. Creating a third preemptive group that would have been small would have decreased the power of our study. 2/ Thirteen patients who received

Accepted Article

Rituximab therapy, because the use of antibody treatment in allograft rejection is linked to an increased risk of CMV infection[8].

Secondly, although the gender-ratio, the causes of the primitive renal disease and the number of previous transplantations are similar between the 2 groups, the heterogeneity in demographic characteristics should be mentioned: 1/ the proportion of CMV seropositive donors was significantly higher in the PROPH group: as mentioned before, one of the centres adjusted its preventive strategy to donor CMV status (prophylactic strategy for CMV D+/R+ recipients, preemptive strategy for CMV D-/R+ recipients). This is a considerable bias in our study because donor CMV seropositivity is an independent risk factor associated with CMV reactivation[12,17], and CMV D+/R+ patients are at higher risk than CMV D-/R+ for developing CMV disease[6]. This could be explained by dual CMV presence exposing CMV D+/R+ recipients to virotypes against which they are not immunised[29]. It would have been interesting to perform a subgroup analysis, but this was not expected at the outset, and group would have been too small. 2/ Because of local differences in care protocols in the different facilities, the immunosuppressive regimens were different between groups. In the NO-PROPH group, patients were more often treated with cyclosporine. In the same group, corticosteroids were more often used as a maintenance therapy. Using cyclosporine instead of tacrolimus is not described as an independent risk factor for CMV reactivation[14,16,17], except in one study, with a protective effect of cyclosporine. The use of corticosteroids[12] as a maintenance therapy is not an independent risk factor in any of the studies. 3/ Recipient age, known as an independent risk factor for CMV disease (58.6 in the PROPH group, 55.2 in the NO-PROPH group, p=0.02): the difference is indeed significant but had low clinical relevance in our study. 4/ the proportion of deceased donors and median cold ischemia time, but these are not described as independent risk factors for CMV reactivation.

In our study, the incidence of CMV disease was under 4% among CMV R+ receiving non-depleting induction, and less than 2% in those receiving a graft from a seronegative donor. The absence of prophylaxis did not appear to have a deleterious effect on CMV reactivation but our two groups lacked homogeneity. Further prospective research, with more homogenous groups, needs to be conducted to confirm our results in this population.

Accepted Article

ACKNOWLEDGMENTS

The data reported here was supplied by ASTRE and DIVAT databases. The authors thank the Virology Laboratories of Rennes (Vincent Thibault), Poitiers (Nicolas Leveque), Brest (Adissa Tran-Minoui) and Angers (Alexandra Ducancelle) for their help in collecting PCR data. The authors also personally thank: Benjamin Aubry, Stéphanie Bouvier, Franck Bridoux, Mathias Buchler, Fabien Duthe, Sandra Gaboriau, Marvonne Hourmant, Julien Janet, François Lunel-Fabiani, Hervé Maisonneuve, Pauline Marteau, Béatrice Mazé, Johan Noble, Clarisse Kerleau, Matthieu Revest.

Thanks to Angela Verdier for English help.

Accepted Article

DISCLOSURE

The authors of the manuscript have non conflicts of interest to disclose as described by the American Journal of Transplantation.

Accepted Article

FIGURE LEGENDS

Figure 1: Flow of patients through the study

Table 1: Demographic characteristics of patients in each group

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group. a: maintenance therapy with prednisone or prednisolone.

Table 2: Characteristics of CMV disease

Proph = Prophylaxis treatment group. No-proph = No-prophylaxis treatment group. Y = Yes. N = No. D status = Donor CMV serostatus. Tac = tacrolimus. CsA = Ciclosporine. M-tor = m-tor inhibitors. MMF = Mycophenolate mofetil. Cs = maintenance therapy with corticosteroids. Tx = Renal transplantation. d = days. VAL = Valganciclovir. GAN = ganciclovir

Figure 2: Non inferiority study

The x-axis is the difference in the percentage of patients with CMV disease. The vertical line at 10 % is the non-inferiority boundary. Non-inferiority was met (difference + 3.7; 95 % CI – 0.5 to 8; p=0.002).

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group.

Table 3: Complications

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group. HTA = hypertension. MMF = Mycophenolate Mofetil. a. HSV infection. b.HHV6 infection

* One patient can present more than 1 type of acute rejection or infectious disease.

Table 4: Renal function

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group. MDRD = glomerular filtration rate using the MDRD equation (Modification of Diet in Renal Disease).

Figure 3: Kaplan-Meier curves showing survival with functional graft uncensored for death

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group.

Figure 4: Kaplan-Meier curves showing patient survival

PROPH = Prophylaxis treatment group. NO-PROPH = No-prophylaxis treatment group.

Accepted Article

Accepted Article

REFERENCES

1. Razonable RR, Humar A, the AST Infectious Diseases Community of Practice. Cytomegalovirus in Solid Organ Transplantation: CMV in Solid Organ Transplantation. *Am J Transplant*. 2013;13(s4):93-106. doi:10.1111/ajt.12103

2. Weclawiak H, Mengelle C, Ould Mohamed A, Izopet J, Rostaing L, Kamar N. [Cytomegalovirus effects in solid organ transplantation and the role of antiviral prophylaxis]. *Nephrol Ther*. 2010;6(6):505-512. doi:10.1016/j.nephro.2010.06.003

3. Weikert BC, Blumberg EA. Viral Infection after Renal Transplantation: Surveillance and Management. *Clin J Am Soc Nephrol*. 2008;3(Supplement 2):S76-S86. doi:10.2215/CJN.02900707

4. Cordero E, Casasola C, Ecarma R, Danguilan R. Cytomegalovirus disease in kidney transplant recipients: incidence, clinical profile, and risk factors. *Transplant Proc*. 2012;44(3):694-700. doi:10.1016/j.transproceed.2011.11.053

5. Seale H, Dwyer DE, Chapman JR, MacIntyre CR. Cytomegalovirus Disease Amongst Renal Transplant Recipients in Australia and New Zealand. *Virol Res Treat*. 2008;1:VRT.S920. doi:10.4137/VRT.S920

6. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation: *Transplantation*. 2018;102(6):900-931. doi:10.1097/TP.0000000000002191

7. Small LN, Lau J, Snydman DR. Preventing post-organ transplantation cytomegalovirus disease with ganciclovir: a meta-analysis comparing prophylactic and preemptive therapies. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2006;43(7):869-880. doi:10.1086/507337

8. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2009;9 Suppl 3:S1-155. doi:10.1111/j.1600-6143.2009.02834.x

9. Preiksaitis JK, Brennan DC, Fishman J, Allen U. Canadian society of transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final

report. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2005;5(2):218-227. doi:10.1111/j.1600-6143.2004.00692.x

10. van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2001;33 Suppl 1:S32-37. doi:10.1086/320902

11. Witzke O, Hauser IA, Bartels M, Wolf G, Wolters H, Nitschke M. Valganciclovir Prophylaxis Versus Preemptive Therapy in Cytomegalovirus-Positive Renal Allograft Recipients: 1-Year Results of a Randomized Clinical Trial: *Transplantation*. 2012;93(1):61-68. doi:10.1097/TP.0b013e318238dab3

12. Weclawiak H, Kamar N, Mengelle C, et al. Pre-emptive intravenous ganciclovir versus valganciclovir prophylaxis for de novo cytomegalovirus-seropositive kidney-transplant recipients: CMV-transplant recipients and valganciclovir. *Transpl Int*. 2010;23(10):1056-1064. doi:10.1111/j.1432-2277.2010.01101.x

13. Reusing JO, Feitosa EB, Agena F, et al. Cytomegalovirus prophylaxis in seropositive renal transplant recipients receiving thymoglobulin induction therapy: Outcome and risk factors for late CMV disease. *Transpl Infect Dis*. 2018;20(5):e12929. doi:10.1111/tid.12929

14. Leone F, Akl A, Giral M, et al. Six months anti-viral prophylaxis significantly decreased cytomegalovirus disease compared with no anti-viral prophylaxis following renal transplantation. *Transpl Int*. March 2010. doi:10.1111/j.1432-2277.2010.01073.x

15. Bayraktar A, Catma Y, Akyildiz A, et al. Infectious Complications of Induction Therapies in Kidney Transplantation. *Ann Transplant*. 2019;24:412-417. doi:10.12659/AOT.915885

16. Luna E, Caravaca F, Ferreira F, et al. Effect of Cytomegalovirus Infection on Survival of Older Kidney Transplant Patients (D+/R+): Impact of Valganciclovir Prophylaxis Versus Preemptive Therapy. *Transplant Proc*. 2016;48(9):2931-2937. doi:10.1016/j.transproceed.2016.06.062

17. Kamar N, Mengelle C, Esposito L, et al. Predictive factors for cytomegalovirus reactivation in cytomegalovirus-seropositive kidney-transplant patients. *J Med Virol*. 2008;80(6):1012-1017. doi:10.1002/jmv.21176

Accepted Article

Accepted Article

18. Lowance D, Neumayer HH, Legendre CM, et al. Valacyclovir for the prevention of cytomegalovirus disease after renal transplantation. International Valacyclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med*. 1999;340(19):1462-1470. doi:10.1056/NEJM199905133401903

19. Opelz G, Döhler B, Ruhenstroth A. Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: a collaborative transplant study report. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2004;4(6):928-936. doi:10.1111/j.1600-6143.2004.00451.x

20. Pescovitz MD. Benefits of cytomegalovirus prophylaxis in solid organ transplantation. *Transplantation*. 2006;82(2 Suppl):S4-8. doi:10.1097/01.tp.0000230459.22968.26

21. Hartmann A, Sagedal S, Hjelmesaeth J. The natural course of cytomegalovirus infection and disease in renal transplant recipients. *Transplantation*. 2006;82(2 Suppl):S15-17. doi:10.1097/01.tp.0000230460.42558.b0

22. Hartmann A, Sagedal S, Hjelmesæth J. The Natural Course of Cytomegalovirus Infection and Disease in Renal Transplant Recipients. *Transplantation*. 2006;82. doi:10.1097/01.tp.0000230460.42558.b0

23. Sagedal S, Nordal KP, Hartmann A, et al. The impact of cytomegalovirus infection and disease on rejection episodes in renal allograft recipients. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2002;2(9):850-856.

24. Webster AC, Wu S, Tallapragada K, Park MY, Chapman JR, Carr SJ. Polyclonal and monoclonal antibodies for treating acute rejection episodes in kidney transplant recipients. *Cochrane Database Syst Rev*. 2017;7:CD004756. doi:10.1002/14651858.CD004756.pub4

25. Birk PE, Chavers BM. Does cytomegalovirus cause glomerular injury in renal allograft recipients? *J Am Soc Nephrol JASN*. 1997;8(11):1801-1808.

26. Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2008;8(5):975-983. doi:10.1111/j.1600-6143.2007.02133.x

27. Smedbråten YV, Sagedal S, Leivestad T, et al. The impact of early cytomegalovirus infection after kidney transplantation on long-term graft and patient survival. *Clin Transplant*. 2014;28(1):120-126. doi:10.1111/ctr.12288

28. Schnitzler MA, Woodward RS, Brennan DC, Spitznagel EL, Dunagan WC, Bailey TC. The effects of cytomegalovirus serology on graft and recipient survival in cadaveric renal transplantation: implications for organ allocation. *Am J Kidney Dis Off J Natl Kidney Found*. 1997;29(3):428-434. doi:10.1016/s0272-6386(97)90205-5

29. Brennan DC. Cytomegalovirus in renal transplantation. *J Am Soc Nephrol JASN*. 2001;12(4):848-855.

30. Komorowska-Jagielska K, Heleniak Z, Dębska-Ślizień A. Cytomegalovirus Status of Kidney Transplant Recipients and Cardiovascular Risk. *Transplant Proc*. 2018;50(6):1868-1873. doi:10.1016/j.transproceed.2018.03.126

31. Witzke O, Nitschke M, Bartels M, et al. Valganciclovir Prophylaxis Versus Preemptive Therapy in Cytomegalovirus-Positive Renal Allograft Recipients: Long-term Results After 7 Years of a Randomized Clinical Trial. *Transplantation*. 2018;102(5):876-882. doi:10.1097/TP.0000000000002024

32. Brum S, Nolasco F, Sousa J, et al. Leukopenia in kidney transplant patients with the association of valganciclovir and mycophenolate mofetil. *Transplant Proc*. 2008;40(3):752-754. doi:10.1016/j.transproceed.2008.02.048

33. Khoury JA, Storch GA, Bohl DL, et al. Prophylactic Versus Preemptive Oral Valganciclovir for the Management of Cytomegalovirus Infection in Adult Renal Transplant Recipients. *Am J Transplant*. 2006;6(9):2134-2143. doi:10.1111/j.1600-6143.2006.01413.x

Accepted Article

Accepted Article

Table 1

	PROPH (n=222)	NO-PROPH (n=150)	Total (n=372)	P-value
Recipient				
Age (years; median[IQR])	62 [16]	57 [19]	60 [19]	0.010
Gender (male; n, %)	122 (55)	93 (62.0)	215 (57.8)	0.199
Cause of renal disease (n, %)				0.130
Glomerulonephritis	47 (21.2)	41 (27.3)	88 (23.7)	
Polycystic disease	36 (16.2)	33 (22.0)	69 (18.5)	
Hypertensive nephrosclerosis	28 (12.6)	13 (8.7)	41 (11.0)	
Diabetic nephropathy	24 (10.8)	7 (4.7)	31 (8.3)	
Tubulointerstitial nephritis	22 (9.9)	8 (5.3)	30 (8.1)	
Uropathy	16 (7.2)	12 (8.0)	28 (7.5)	
Other	5 (2.3)	5 (3.3)	10 (2.7)	
Unknown	44 (19.8)	31 (20.7)	75 (20.2)	
Previous transplantation (n, %)				0.636
0	211 (95)	145 (96.7)	356 (95.7)	
1	10 (4.5)	4 (2.7)	14 (3.8)	
2	1 (0.5)	1 (0.7)	2 (0.5)	
Donor				
CMV serostatus				0.007
Positive	138 (62.2)	71 (47.3)	209 (56.2)	
Negative	84 (37.8)	79 (52.7)	163 (43.8)	
Age (years; median[IQR])	61 [21]	53 [22]	59 [20]	<0.001
Donor type (Deceased; n, %)	195 (87.8)	146 (97.3)	341 (91.7)	<0.001
Cold ischemia time (hr, median[IQR])	15 [7.1]	16 [6.6]	15 [6.6]	0.110
Immunosuppression (n, %)				
Basiliximab	219 (98.6)	148 (98.7)	367 (98.7)	1
Tacrolimus	180 (81.1)	78 (52.0)	258 (69.4)	<0.001
Ciclosporine	43 (19.4)	71 (47.3)	114 (30.6)	<0.001
Mycophenolate	209 (94.1)	139 (92.7)	348 (93.5)	0.668
M-tor inhibitors	13 (5.9)	11 (7.3)	24 (6.5)	0.521
Corticosteroïds[a]	138 (62.2)	113 (75.3)	251 (67.5)	0.009

Accepted Article

Table 2

Patient	Group	D status	CMV DNAemia (UI/mL)	Time from Tx (d)	CMV disease type	Curative treatment		Immunosuppressive regimen					Survival	
						Type	Resistance	Basiliximab	FK/CsA	M-tor	MMF	Cs	Patient	Graft
1	No-proph	+	169 825	60	Syndrome	VAL	N	Y	CsA	N	Y	Y	Y	Y
2	No-proph	+	34 673 685	69	Colitis	GAN	Y	Y	Tac	N	Y	Y	Y	Y
3	No-proph	+	371 535	49	Colitis	VAL	N	Y	Tac	N	Y	Y	Y	Y
4	No-proph	+	37 153	46	Colitis	GAN	N	Y	Tac	N	Y	Y	Y	Y
5	No-proph	+	144 543	36	Syndrome	VAL	N	Y	Tac	N	Y	Y	Y	Y
6	No-proph	-	3 890	113	Syndrome	GAN	N	Y	Tac	N	Y	Y	Y	Y
7	No-proph	-	89 125	36	Syndrome	GAN	N	Y	CsA	N	Y	Y	Y	Y
8	No-proph	+	251 188	55	Colitis	GAN	N	Y	CsA	N	Y	Y	Y	Y
9	No-proph	+	6 309	93	Colitis	GAN	N	Y	CsA	N	Y	N	N	Y
10	Proph	+	630 957	180	Pneumonit	GAN	N	Y	CsA	Y	N	Y	Y	Y

Accepted Article

					is									
11	Proph	-	2 511	146	Syndrome	VAL	N	N	Tac	N	Y	Y	Y	Y
12	Proph	+	295 120	319	Pneumonit	GAN	N	Y	Tac	N	Y	N	Y	Y
					is									
13	Proph	+	8 912	325	Colitis	VAL	N	Y	Tac	N	Y	Y	N	Y
14	Proph	+	138 038	227	Syndrome	VAL	N	Y	Tac	N	Y	N	Y	Y

Accepted Article

Table 3

	PROPH	NO-PROPH	P-value
Side effects (n, %)			
Leucopenia < 4 G/L	199 (89.6)	59 (39.3)	< 0.001
Neutropenia < 2 G/L	127 (57.2)	52 (34.7)	< 0.001
Neutropenia < 0.5 G/L	25 (11.3)	7 (4.7)	0.0382
Decrease or discontinuation of MMF because of neutropenia in the first trimester	29 (13.1)	3 (2)	< 0.001
Infectious Diseases (n, %)*	71 (32.0)	37 (24.7)	0.289
Urinary tract infections			
Nephritis	45 (20.3)	21 (14.0)	0.211
Others urinary tract infections	4 (1.8)	6 (4.0)	0.196
Pneumonia	20 (9.0)	10 (6.7)	0.563
Gastro-intestinal disease	7 (3.2)	1 (0.7)	0.158
Cutaneous infections	3 (1.4)	2 (1.3)	1
Invasive fungal infections	4 (1.8)	0 (0)	0.161
Other bacterial infections	1 (0.5)	2 (1.3)	0.563
Bacteremia without a source	1 (0.5)	1 (0.7)	1
Viral infections	1 (0.5)[a]	1 (0.7)[b]	1
Endocarditis	0 (0)	1 (0.7)	0.388
Acute rejections (n, %)*	21 (9.5)	13 (8.7)	1
Acute cellular rejection	12 (5.4)	9 (6.0)	0.818
Acute borderline rejection	8 (3.6)	0 (0)	0.0251
Acute humoral rejection	1 (0.5)	3 (2.0)	0.303
Not proven acute rejection	1 (0.5)	2 (1.3)	0.563
Metabolic complications (n, %)			
HTA	158 (71.2)	95 (63.3)	0.159
New-onset diabetes	49 (22.1)	26 (17.3)	0.563

Accepted Article

Table 4

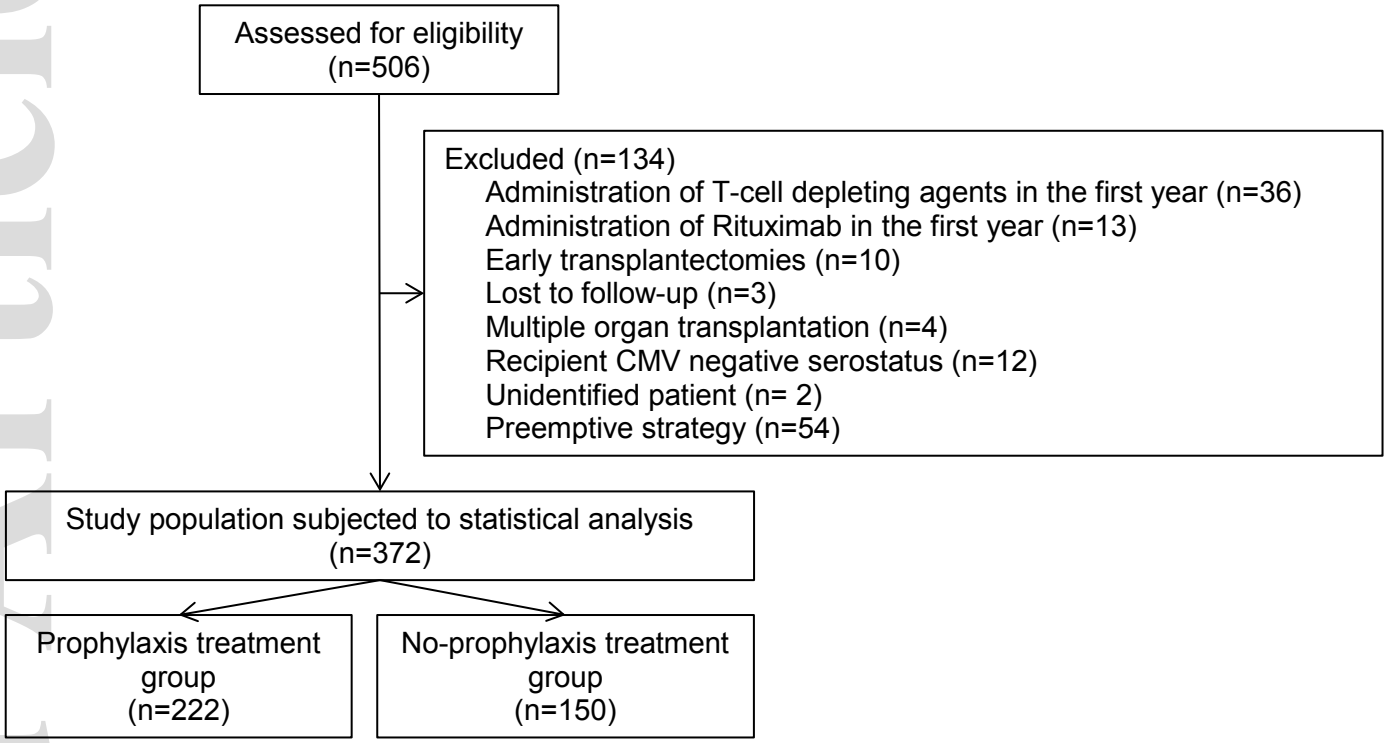
Creatinine, µmol/L, mean±SD

(MDRD, mL/min, mean±SD)

	N	PROPH	N	NO-PROPH	p-value
1st year	212	136±48	145	134±45	0.747
		(47 [28])		(50 [25])	
2nd year	170	133±51	132	134±45	0.832
		(49 [31])		(49 [27])	
3rd year	94	140±62	87	138±46	0.854
		(47 [24])		(51 [31])	
4th year	34	131±54	39	131±47	0.977
		(54 [39])		(52 [38])	

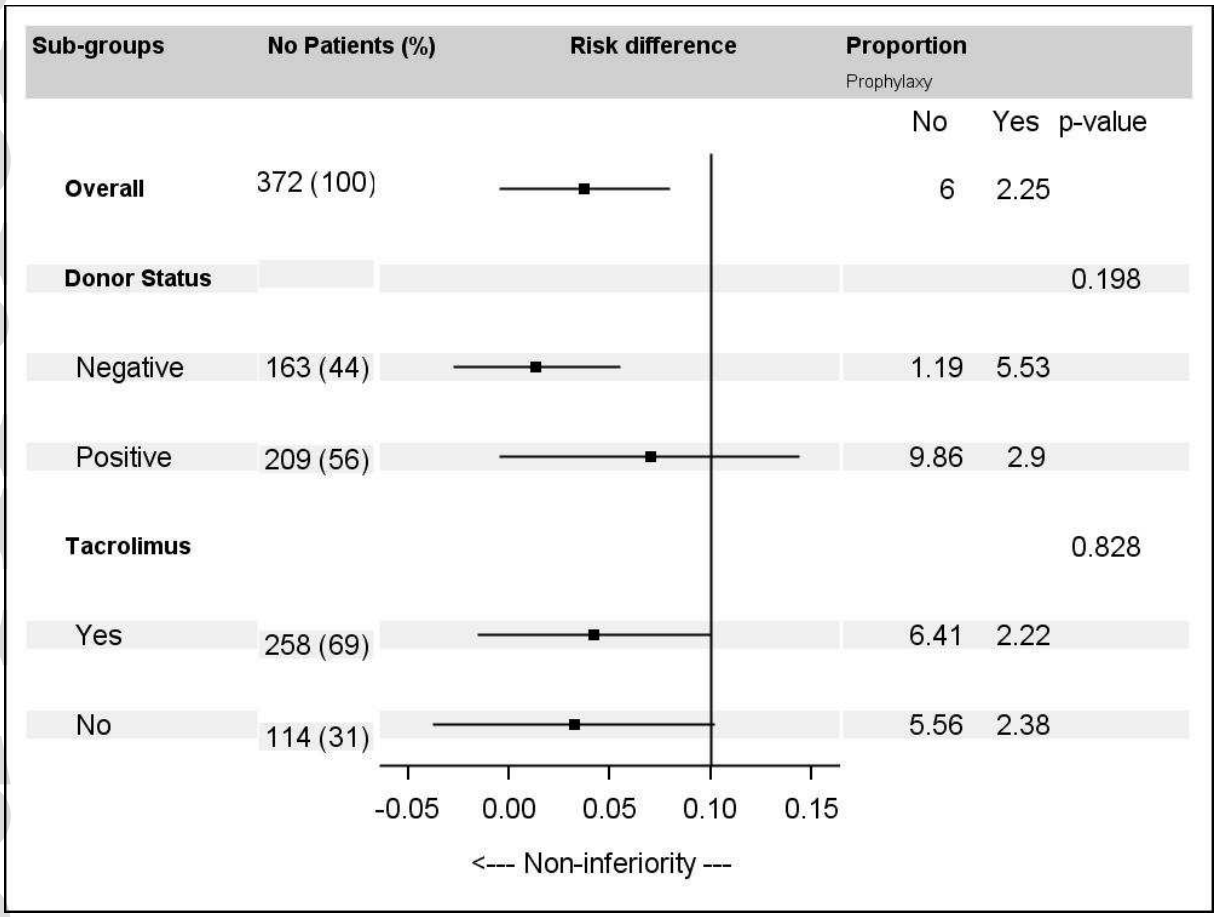
Accepted Article

Figure 1



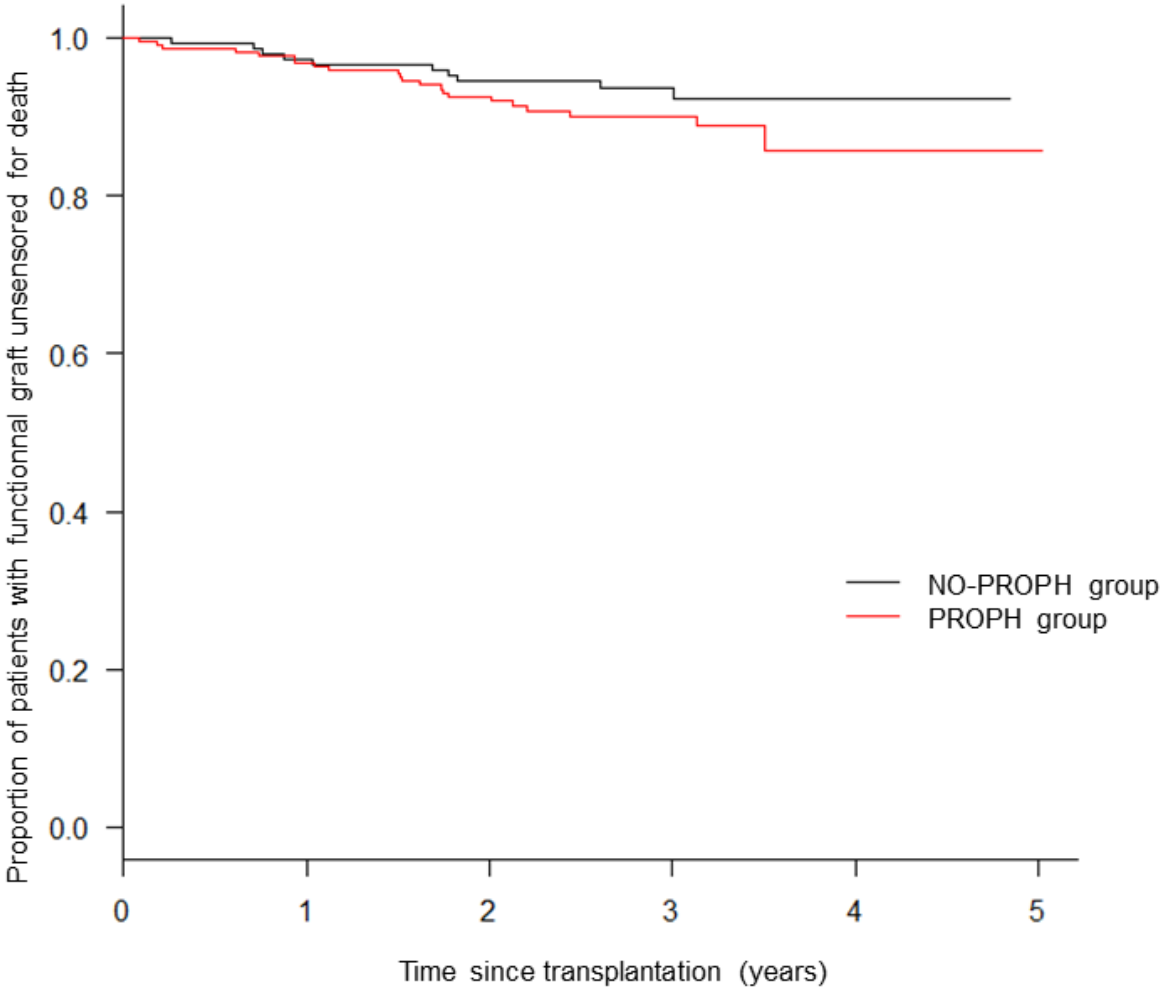
Accepted Article

Figure 2



Accepted Article

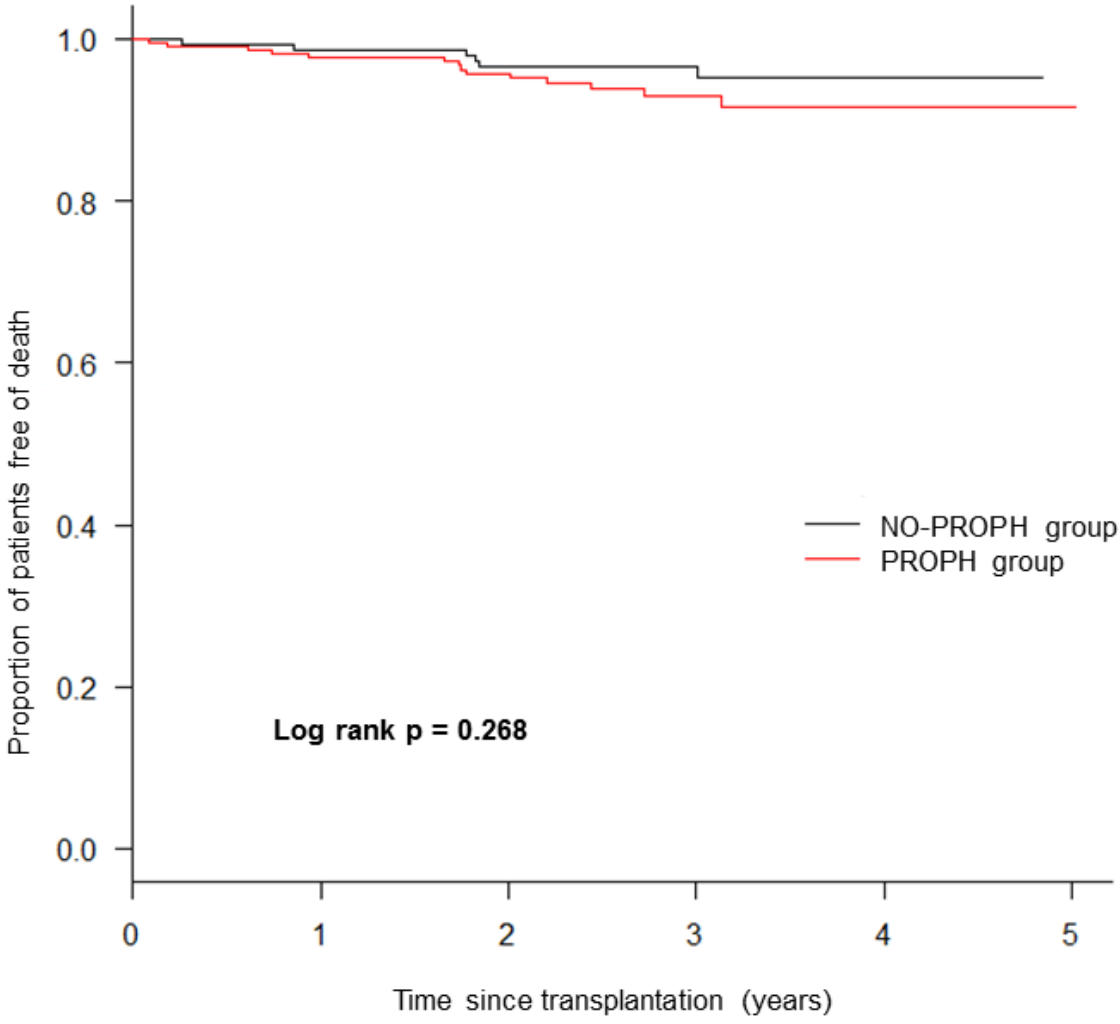
Figure 3



Number of patients					
NO-PROPH group	144	122	79	31	0
PROPH group	211	169	88	35	1

Accepted Article

Figure 4



Number of patients					
NO-PROPH group	145	122	79	31	0
PROPH group	211	171	89	35	1