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The Cost-effectiveness of Valganciclovir Prophylaxis Versus Preemptive Therapy in CMV R+ Kidney Transplant Recipients Over the First Year Posttransplantation

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Background. In kidney transplant recipients with positive serology (R+) for the cytomegalovirus (CMV), 2 strategies are used to prevent infection, whose respective advantages over the other are still debated. This study aimed to evaluate the cost-effectiveness and cost utility of antiviral prophylaxis against CMV versus preemptive therapy, considering CMV infection–free survival over the first year posttransplantation as the main clinical outcome. **Methods.** Clinical, laboratory, and economic data were collected from 186 kidney transplant patients CMV (R+) included in the cohort study (85 patients who benefited from CMV prophylaxis and 101 from preemptive therapy). Costs were calculated from the hospital perspective and quality-adjusted life years (QALYs) using the EQ5D form. Using nonparametric bootstrapping, the incremental cost-effectiveness ratio (ICER) and cost utility were estimated (euros) for each case of infection avoided and each QALY gained for 1 y, respectively. **Results.** Prophylaxis significantly decreased the risk of CMV infection over the first year posttransplantation (hazard ratio 0.22, 95% confidence interval = 0.12-0.37, $P < 0.01$). Compared with preemptive therapy, prophylaxis saved financial resources (€1155 per patient) and was more effective (0.42 infection avoided per patient), resulting in an ICER = €2769 per infection avoided. Prophylaxis resulted in a net gain of 0.046 in QALYs per patient and dominated over preemptive therapy with €1422 cost-saving for 1 QALY gained. **Conclusions.** This study shows that CMV prophylaxis, although considered as a more expensive strategy, is more cost-effective than preemptive therapy for the prevention of CMV infections in renal transplant patients. Prophylaxis had a positive effect on quality of life at reasonable costs and resulted in net savings for the hospital.

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Cytomegalovirus (CMV) is the most common infection because of herpes-related virus with noteworthy complications after renal transplantation, including an increased incidence of acute graft rejection.[1-5] The risk of CMV infection increases with immunosuppressants used to limit the risks of rejection after solid organ transplantation. It is also

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linked to the serological status of the donor and the recipient before the transplantation: (1) high risk in recipients who have a negative CMV serology (R–) and receive a transplant from a CMV-positive donor (D+); (2) low risk in R– recipients with a D– transplant; and (3) intermediate risk for positive recipients (R+) whatever the donor's CMV serology (D+ or D–).[6-8] For patients at intermediate risk (R+), the international recommendations leave the choice to the clinicians between CMV prophylaxis and preemptive therapy and the decision is usually taken within the first 8 d after the transplantation.[7,9,10]

CMV prophylaxis consists in the systematic prescription of an antiviral drug, generally valganciclovir,[4] at a rather low dose for a minimum of 3 mo.[7,8] As valganciclovir is an expensive drug and R+ patients represent about 50% of French kidney transplant recipients,[11,12] prophylaxis represents an important economic burden for the healthcare system. With the preemptive strategy, CMV viremia is intensively monitored and a lower number of patients are treated with higher doses of valganciclovir when the viremia becomes positive, evidencing CMV infection. Consequently, the preemptive strategy is regarded as less expensive.

Previous studies have compared the efficacy and cost of the 2 strategies with contradictory results. Several of them did not show any superiority of one strategy over the others,[13-15] whereas others found the prophylaxis strategy better economically or in terms of effectiveness.[3,5,16-18] In most studies, patients with all types of D/R statuses (except D–/R–) were included, and the anti-CMV treatments could also be different, that is, valaciclovir, ganciclovir, or valganciclovir.[13,15,17,19] In addition, prophylaxis duration could vary across studies.[20,21] Finally, given the multiplicity of sometimes contradictory results, a literature review concluded that the inferences were not so clear.[22] Based on available evidence at the time, a consensus on the management of CMV in 2010 made recommendations on the most suitable strategies and adequate durations according to the D/R status.[9] Updates of these recommendations were published in 2013 and 2018.[7,8] In the following years, the impact of this consensus on centers practices was assessed using a questionnaire,[23] showing valganciclovir was the most widely used antiviral.

Furthermore, the clinical signs of a CMV infection can also largely vary, from mild symptoms to severe outcomes, to be balanced with the potential adverse effects of the antivirals, leading to a variable impact on patient quality of life.[24] Considering the changes in immunosuppressants regimens over time and updated recommendations for CMV risk mitigation, further studies are needed to evaluate the efficacy, cost, and impact on patient quality of life of the 2 strategies.

The aim of the present observational study was to compare CMV antiviral prophylaxis and preemptive therapy on CMV infection–free survival of R+ kidney transplant recipients, cost-efficacy and cost utility over the first year posttransplantation.

MATERIALS AND METHODS

The EPHEGREN Study

EPHEGREN (Etude Pharmaco-économique EN Greffe Rénale) is a pharmacological and clinical cohort of adult kidney transplant recipients enrolled between 2013 and 2017,[25,26] who provided written informed consent to participate and followed up in seven French centers (University Hospitals of Amiens, Bordeaux, Limoges, Poitiers, Rouen, Toulouse, and Tours). It was sponsored by the University Hospital of Limoges, complied with the legal requirements of the Declaration of Helsinki and received approval from the regional Ethics Committee (nr.130-2013-30, November 20, 2013) and authorization from the National Committee for Informatics and Liberties (912242 ACT, 2012). During a routine consultation, the nephrologist informed patients about the study and enrolled them only after giving their written consent.

The primary objective of EPHEGREN was to evaluate the pharmacoeconomic impact of the different immunosuppressive strategies on adult kidney transplant patients. Its secondary objectives were to (1) evaluate the cost-efficacy ratio of the different anti-CMV strategies in CMV+ transplant recipients from the hospital perspective; (2) determine the pharmacological factors predictive of: long-term graft function; onset of cancer, posttransplant diabetes mellitus, and major adverse cardiovascular events; (3) validate the influence on graft rejection and adverse effects of genetic polymorphisms in immunosuppressive drug metabolizing enzymes, membranes transporters and target proteins; and (4) validate prospectively urine biomarkers of acute graft rejection or chronic dysfunction.

All patients followed up in one of the above-mentioned transplantation centers except those who either did not understand the protocol or were not able to read in French were eligible to participate in the EPHEGREN cohort. They all gave their written informed consent and were enrolled during the first month after transplantation. The predefined study visits were at month 1 (M1), M3, M6, M12, M18, M24, and M36.

Clinical and biological data were collected from medical records on a clinical research form: HLA characteristics, recipient demographics, baseline clinical and biological data at inclusion, then clinical and biological data at each subsequent visit. Calcineurin inhibitors trough concentrations (C_0) were registered exhaustively. Patient-reported outcomes (adherence, health-related quality of life [HR-QoL], and adverse events) were collected at each study visit using a self-administered questionnaire.

Pharmacoeconomic Evaluation of the CMV Prevention Strategies

This substudy was performed on the follow-up data of CMV R+ kidney transplant recipients enrolled in the EPHEGREN cohort. To prevent or mitigate the risk of CMV infection or disease, 2 strategies could be set up according to the international recommendations,[7,9] depending on the donor and recipient CMV statuses and centers practices. Therefore, the choice between the 2 strategies was left to the free choice of the clinicians and reported in the clinical research form. The preemptive therapy consisted in CMV viremia monitoring (CMV DNAemia in a blood sample according to quantitative nucleic acid amplification testing), at a frequency consistent with the recommendations, and initiation of anti-CMV treatment in case of the occurrence of a CMV infection. CMV prophylaxis consisted in giving patients an anti-CMV drug during at least the first 3 mo associated with CMV viremia monitoring at a frequency left to the choice of the clinicians, therefore variable between the centers. The anti-CMV drug was usually valganciclovir adjusted to the patient's renal function, as per the summary of product characteristics.

CMV infection and disease were defined following the international guidelines.[7] CMV infection was characterized by a positive viremia, that is, evidence of CMV replication

regardless of symptoms. The presence of biological and specific clinical symptoms linked with CMV infection evidenced a CMV disease. The treatment administered in case of CMV infection or disease was chosen by the clinician. The type of drug and route of administration (valganciclovir or any other anti-CMV drug, per os or intravenous), dosage and duration actually administered were collected to calculate the real cost of the treatment.

Resource utilization data were collected prospectively, whereas the costs were assigned retrospectively. The economic analysis was conducted from the hospital perspective, that is, the costs incurred for hospital stays and visits, which include drugs and laboratory tests (comprising the costs of CMV DNAemia monitoring). CMV infection treatments costs are excluded from these hospital costs and were therefore evaluated specifically. The costs of the kidney transplantation procedure itself were excluded from this analysis, to avoid a bias related to their large variability because of patients' status before the transplantation, which is not related to the prevention of CMV infection.

Calculations were based on direct and overhead cost items related to the patient's diagnosis-related groups (DRGs; "Groupes Homogènes de Malades" in French), as identified in the French national cost scale published in 2018 (Table 1). The costs of CMV infection treatments were determined from the exact antiviral drug consumption by the patient, based on actual utilization and related unit costs. The 2018 price was used for all patients, and costs are expressed in Euros (€).

Cost-utility analyses could be performed thanks to the evaluation of HR-QoL done using the EQ-5D form, which allows the calculation of the utility index, ranging from 0 (perfect health) to 1 (death). Specific utilities of the French population were extracted based on the valuation of scores in the French population produced by the EuroQol group.[27] Quality-adjusted life years (QALYs) corresponding to the follow-up period (ie, 1 y) were calculated for each patient. The cost-utility study was based on the estimated additional cost in one group compared with the other (preemptive therapy versus prophylaxis) and reported as the difference in QALYs.

TABLE 1.

Unit costs included in the analyses (based on French national cost scale published in 2018 and expressed in Euros)

Medical resources	€
Foscavir (solution for Injection)	127.00
Valganciclovir (per day)	19.67
Hemodialysis	334.23
CMV PCR (each)	81.00
Mean hospital cost (€)	
Ambulatory transurethral or transcutaneous intervention	1641.61
Fistula	5273.18
Plasmapheresis	1228.05
Transurethral resection of the prostate	2337.19
kidney and urinary tract conditions	1172.67
kidney and urinary tract conditions (very short duration)	585.02
Chemotherapy for nontumor disease	334.72
Hemodialysis training	531.47
Renal infections	
Renal infections (level 1)	1183.92
Renal infections (level 2)	2662.13
Renal failure	
Renal failure, without dialysis, very short duration	580.94
Renal failure, without dialysis (level 1)	1612.48
Renal failure, without dialysis (level 2)	3594.01
Rejection	
Rejection (very short duration)	666.30
Rejection (level 1)	1707.77
Rejection (level 2)	7355.78
Kidney transplant monitoring	811.53
Prophylactic treatments	471.25
Viral diseases including CMV disease	
Viral diseases including CMV disease (level 1)	1716.65
Viral diseases including CMV disease (level 2)	2965.35
Viral diseases including CMV disease (level 3)	5429.28
Viral diseases including CMV disease (level 4)	9229.48
Digestive endoscopy	706.05
Diabetes	1720.38
Transfusions	611.38

Level 1, 2, 3, or 4 is estimated thanks to the hospital stay durations and the comorbidities of the patients. The level is higher if the hospital stay durations is long and/or the comorbidities numerous.
CMV, cytomegalovirus; PCR, polymerase chain reaction.

Statistical Analyses

Statistical analysis was performed using R version 4.2 (http://www.r-project.org). Categorical data are reported as frequencies and percentages, and continuous data as mean ± SD when their distribution was Gaussian, or as median and interquartile range (IQR) when it was not. The groups were compared for proportions using the Pearson chi-square or Fisher exact tests for categorical data, and the Student *t* test or one-way ANOVA were used for continuous variables.

As CMV diseases were generally scarce compared with infections, we grouped CMV infections and diseases under "CMV infection." Cox proportional hazard regression analysis was used to identify the risk factors for CMV infection. A Cox model including the potential confounding factors was built for CMV infection–free survival, first using univariate analyses and then including variables characterized by a *P* value of <0.2 in an intermediate model. The final model was built by backward stepwise selection of the covariates, based on the Bayesian information criterion. The robustness of the results was planned to be assessed by 1000 bootstraps followed by 1000 backward stepwise selections based on the same process. The hazard ratios and 95% confidence intervals derived from the final model and the percentage of selection of each covariate in the bootstrap procedure were calculated. Time-to-CMV infection was estimated using Kaplan-Meier analysis and the groups (prophylaxis/preemptive) were compared using the log-rank test. Values of $P < 0.05$ were considered statistically significant.

As most complications of CMV infections happen during the first year posttransplantation, the time horizon of the cost-effectiveness analysis was fixed at 12 mo; therefore, no discount rate was applied.[28] Cost-effectiveness prophylaxis was assessed through the incremental cost-effectiveness ratio (ICER) by calculating the incremental 12 mo cost per CMV infection avoided, using the formula:

$$\text{ICER} = \left(\text{Cost}_{\text{prophylaxis}} - \text{Cost}_{\text{preemptive}}\right) / \left(\text{Outcome}_{\text{prophylaxis}} - \text{Outcome}_{\text{preemptive}}\right).$$

To handle the sampling uncertainty for ICER estimation and account for non-normal data distribution, nonparametric bootstrapping with 10 000 replications was used. Lambda, which is a fixed value for the "Shadow Price of Health" expressed in DeltaC/DeltaE units, was fixed to 1 as a standard value.[29] The comparative results between the 2 groups were presented graphically on a cost-effectiveness plane with the incremental effect (CMV infections avoided) on the x-axis.[30]

Cost-utility analysis was assessed using the same methodology by calculating the incremental cost-utility ratio, corresponding to the change in incremental cost for 1 QALY gained.

A two-way sensitivity analysis was performed to explore the impact of costs variability in hospitalizations and CMV antiviral treatments. In both analyses, the parameters were varied within ±30% of the mean value to test for the robustness of total costs and cost comparisons between groups.

RESULTS

Among the 383 patients followed up in the EPHEGREN cohort, 186 were R+ patients (figure 1) and therefore included in this study. Their main characteristics are summarized in Table 2. The most prescribed immunosuppressant strategy was the association of mycophenolate mofetil and tacrolimus in both groups (69.3% and 82.4% in the preemptive and prophylaxis groups, respectively). There were more patients on cyclosporine ($P = 0.003$) and benefiting from mycophenolic acid therapeutic drug monitoring based on the area under the curve ($P = 0.016$), in the preemptive than in the prophylaxis group (Table 2).

Fifty-seven patients (40.7%) on tacrolimus and 42 (52.5%) on cyclosporine developed a CMV infection ($P = 0.09$). Induction was based on basiliximab in 65.2% of the patients, among whom 44 (36.7%) developed a CMV infection, versus 36 (61.0%) among patients who received thymoglobulin (ATG) and 1 (33.3%) among those on rituximab ($P = 0.0037$).

Eighty-five patients received prophylaxis and 101 benefited from a preemptive therapy. The median (IQR) prophylaxis duration was of 158 d (91.0–206 d). Valganciclovir was the most prescribed anti-CMV drug in both groups: 99% in the prophylaxis group and 91% of the patients in the preemptive group. Six patients of the preemptive group were on ganciclovir and 2 patients of the prophylaxis group were on valaciclovir.

Fifty-six CMV infections and 2 CMV diseases occurred in the preemptive group compared with 14 infections and 1 disease in the prophylaxis group, leading to considering a total of 58 CMV infections in the preemptive group and 15 in the prophylactic group (Table 2). The median (IQR) time-to-CMV infection was 30.0 d (24.0–56.2 d) in the preemptive group versus 118 d (30.0–288 d) in the prophylaxis group ($P = 0.006$). As expected in the prophylaxis group, all infections except one appeared after the cessation of prophylaxis. Twenty-two patients in the preemptive group versus 5 in the prophylaxis group had >1 CMV infection over the first year posttransplantation. In the preemptive group, 1 patient had a CMV infection beyond the first year and none in the prophylaxis group. No difference was found between groups on resistance to anti-CMV drugs (Table 2).

Leucopenia and neutropenia were more frequent in patients of the prophylaxis group (respectively, 28.2% versus 10.3% and 38.8% versus 7.9%). In the preemptive group, 7/9 had leucopenia and 3 of 8 patients had neutropenia while on antiviral treatment. More patients had received filgrastim in the prophylaxis group (11 versus 1).

The results of the Cox analyses exploring the relationship between the prevention strategy (prophylaxis or preemptive therapy) and CMV infection–free survival over the first year posttransplantation are presented in Table 3. Age, induction, and CMV prevention strategy were significantly associated with CMV infection–free survival, prophylaxis being superior to the preemptive therapy. This was confirmed by bootstrap analysis and Schoenfeld residues analysis, with no deviation from risk proportionality ($P = 0.277$). The prophylaxis strategy was associated with a significantly lower risk of CMV infection over the first year after transplantation than the

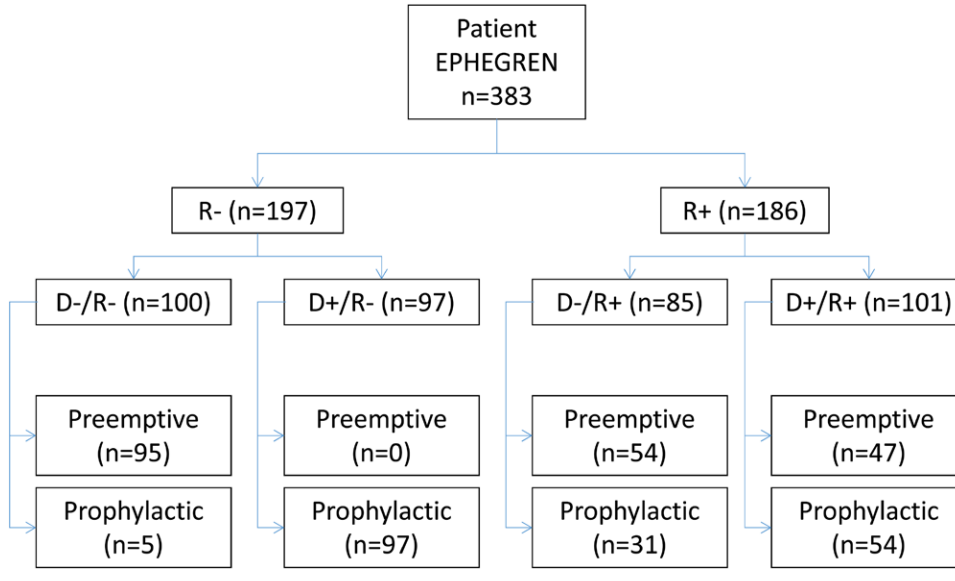

FIGURE 1. Flowchart of the study.

TABLE 2.

Characteristics of the patients included in the study (N = 186)

	Preemptive strategy	Prophylaxis	*P*
n	101	85	
Sex: male, n (%)	63 (62.4)	51 (60.0)	0.857
Age (y), mean (SD)	56.60 (13.42)	55.80 (14.70)	0.697
Hypertension before transplantation, n (%)	95 (94.1)	82 (96.5)	0.674
Diabetes before transplantation, n (%)	22 (21.8)	15 (17.6)	0.603
Dialysis before transplantation, n (%)	93 (92.1)	70 (82.4)	0.074
Rank of kidney transplantation >1, n (%)	14 (14)	18 (21)	0.188
Donor age (y), mean (SD)	56.97 (14.79)	56.71 (16.24)	0.908
Cold ischemia time (min), median (IQR)	817 (620–1031)	802 (650–1021)	0.734
Delayed graft function: yes, n (%)	13(13)	9 (11)	0.631
Duration of follow-up (mo), median (IQR)	851 (603–1150)	817 (561–978)	0.064
Immunosuppressive regimen,[a] n (%)			
MMF	97 (96.0)	84 (98.8)	0.475
Cyclosporine	54 (53.5)	26 (30.6)	**0.003**
Tacrolimus	70 (69.3)	70 (82.4)	0.060
Induction treatment category			0.159
1 (basiliximab)	67 (66.3)	53 (63.9)	
2 (thymoglobulin)	32 (31.7)	27 (32.5)	
3 (rituximab)	0 (0.0)	3 (3.6)	
NK	2 (2.0)		
CMV mismatch, n (%)			**0.027**
D−/R+	54 (53.5)	31 (36.5)	
D+/R+	47 (46.5)	54 (63.5)	
Rejection, n (%)	12 (11.9)	15 (17.6)	0.366
Death, n (%)	2 (2.0)	2 (2.4)	1.000
Return to dialysis, n (%)	8 (7.9)	3 (3.5)	0.341
MPA therapeutic drug monitoring, n (%)	57 (56.4)	32 (37.6)	**0.016**
QALY, mean (SD)	0.85 (0.17)	0.90 (0.11)	0.089
CMV infection/disease, n (%)			**<0.001**
Infection	56 (55.4)	14 (16.5)	
Disease	2 (2.0)	1 (1.2)	
None	43 (42.6)	70 (82.4)	
Mutations (presence), n (%)			1
UL97			
Unknown	100 (99)	85 (100)	
No	1 (1.0)	0 (0)	
UL94			1
Unknown	99 (98)	84 (99)	
Yes	1 (1.0)	1 (1.2)	

Bold indicates significant *P* values.

[a]Some patients appear in both tacrolimus and cyclosporine groups because they were switched from one to the other over the first year.

CMV, cytomegalovirus; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; QALY, quality-adjusted life year.

preemptive strategy (hazard ratio = 0.22, 95% confidence interval 0.12-0.37, $P < 0.01$) (Figure 2).

Effectiveness analysis confirmed that prophylaxis was significantly more effective than the preemptive strategy to prevent CMV infection, with a 60% lower incidence (Figure 3).

The median (IQR) costs of anti-CMV treatments (including preventive and curative treatments) did not differ between the preemptive (€1034 [670–1798]) and the prophylaxis group (€956 [626–1595], $P = 0.522$). Similarly, there was no difference between the 2 groups on hospital costs (€3708 [1623–9363] versus €3605 [1623–8155], $P = 0.628$) and hospital stay durations (9 d [3–20] versus 7 d [2–16], $P = 0.49$). The median CMV viremia monitoring cost was €1053 (IQR 729–1296) in the preemptive group and €810 (IQR 324–1458) in the prophylaxis group ($P = 0.105$). This resulted in a median total cost over the first year posttransplantation of €7210 (4853–12 629) for patients in the preemptive group versus €7013 (5082–11 707) for patients in the prophylaxis group ($P = 0.743$) (Figure 3). From the hospital perspective and at a 12-mo time horizon, the prophylactic strategy had a higher mean effect on the avoidance of CMV infections (0.42) and a lower bootstrapped mean cost per patient (€1155). Consequently, the cost-effectiveness analysis showed that the prophylaxis strategy saved resources, with an ICER of €2,769 per event avoided. Figure 4 represents the scatter plot of the mean differences between groups (DRG approach) and efficacy estimated by repeated sampling as part of the bootstrap analysis: 79.9% of bootstrapped incremental cost/effect pairs were located in the "SE" region (more effective and less costly) and 20.1% in "NE" region (more effective and more costly). Therefore, prophylaxis dominated the preemptive strategy, by generating larger health benefits at lower costs.

TABLE 3.

Univariate and multivariate Cox analyses of the association of CMV infection–free survival over the first year posttransplantation and potential risk factors

	Univariate analyses			Multivariate analyses			
	HR	95%CI	*P*	HR	95%CI	*P*	% Bootstrap selection
Sex (male)	1.23	0.78-1.92	0.372				
Age	**1.03**	**1.01-1.04**	**0.001**	**1.02**	**1.00-1.04**	**0.01**	**91.1**
Hypertension before transplantation (yes)	1.42	0.45-4.51	0.548				
Diabetes before transplantation (yes)	1.35	0.82-2.23	0.243				
Dialysis before transplantation (yes)	**2.17**	**0.95-4.99**	**0.067**				
Rank of kidney transplantation >1 vs 1	0.95	0.52-1.71	0.860				
Cold ischemia time	1.00	1.00-1.00	0.090				
Delayed graft function (yes)	1.14	0.60-2.15	0.687				
Duration of follow-up	1.00	1.00-1.00	0.018				
CMV mismatch, D−/R+ vs D+/R+	1.00	0.63-1.59	0.992				
Therapeutic drug monitoring	1.08	0.70-1.65	0.732				
CMV strategy (prophylaxis vs preemptive)	**0.25**	**0.15-0.41**	**<0.001**	**0.19**	**0.11-0.33**	**<0.01**	**99.9**
Immunosuppressive strategy							
MMF	2.64	0.37-18.94	0.336				
Cyclosporine	1.46	0.95-2.24	0.085				
Tacrolimus	0.60	0.38-0.95	0.030				
Induction treatment category	**1.71**	**1.18-2.49**	**0.005**	**2.67**	**1.76-4.05**	**<0.01**	**100**

Bold indicates significant *P* values.
CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; MMF, mycophenolate mofetil.

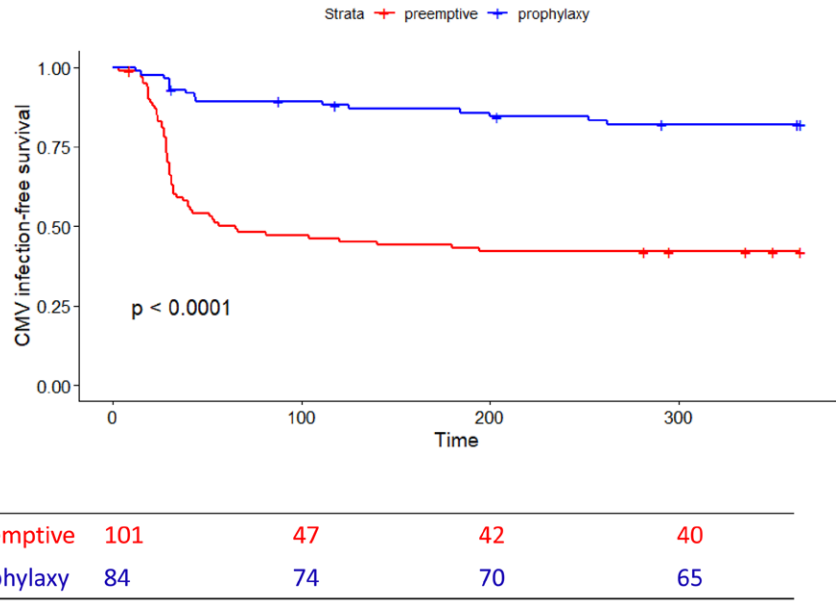

FIGURE 2. Kaplan-Meier curves of CMV infection–free survival in kidney transplant patients in the prophylaxis vs preemptive groups. CMV, cytomegalovirus.

The results of the sensitivity analysis of the costs are presented in Table 4 (expenditures presented in the first raw are the actual calculated costs). Two main components of the total costs (hospital costs for CMV infection and costs for anti-CMV drugs) were chosen as input parameters in the sensitivity analysis. After varying these costs by ±30%, probabilistic sensitivity analysis of all scenarios confirmed the results observed in the base-case scenario.

Prophylaxis strategy generated a higher incremental QALY, with an additional 0.046 QALY per patient, when compared with the preemptive strategy. The cost of the preemptive strategy was also higher, with an additional cost of €1422 per QALY versus prophylaxis (Figure 5).

DISCUSSION

This pharmacoeconomic analysis shows that CMV prophylaxis in the first months posttransplantation is cost-saving while decreasing the incidence of CMV infection over the first year after transplantation. As expected, there were more CMV infections in the preemptive than in the prophylaxis group. The benefits obtained with prophylaxis in terms of

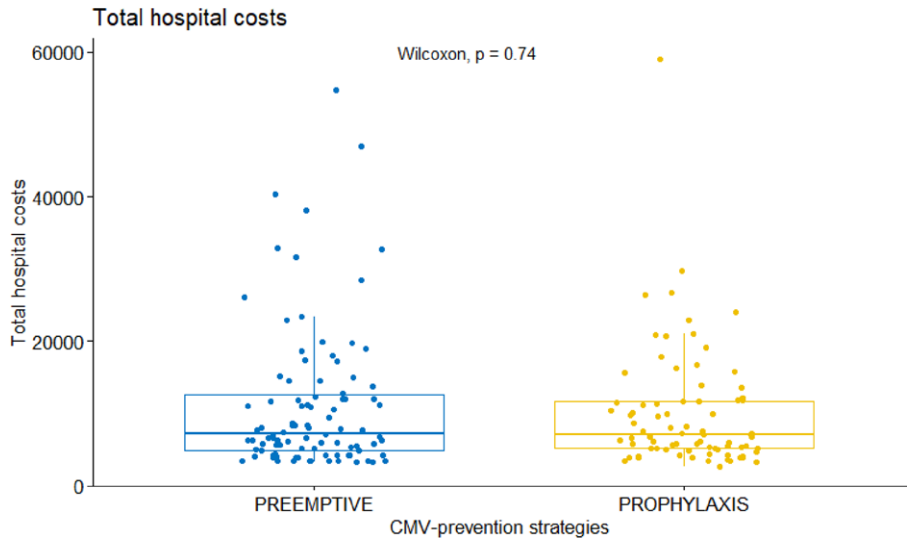

FIGURE 3. Total cost over the first year posttransplantation in the prophylaxis vs preemptive groups. CMV, cytomegalovirus.

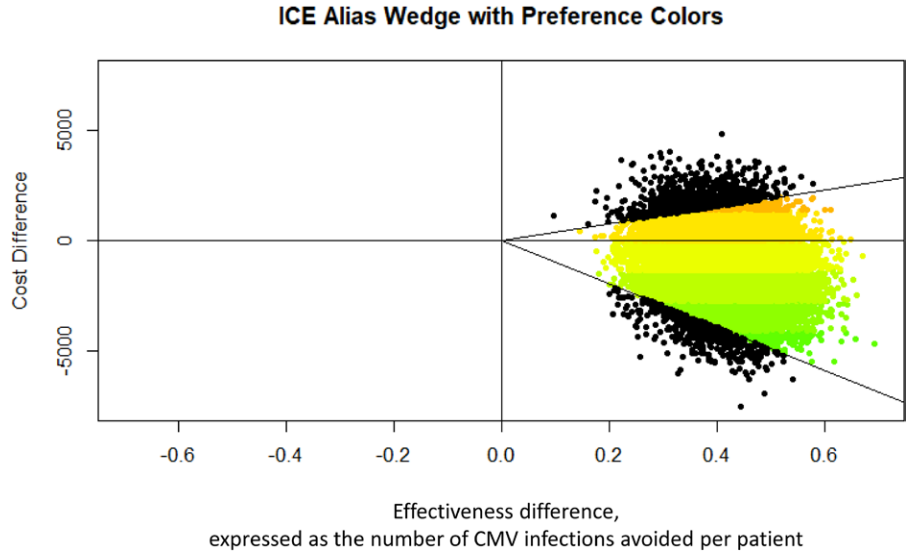

FIGURE 4. Cost-effectiveness plane; X-units = infections avoided and Y-units = costs; bootstrap replication number = 10 000. Scatter plot of the mean differences between groups in costs (DRG approach) and efficacy estimated by repeated sampling as part of the bootstrap analysis. Each quadrant (Q) represents a scenario where cost increases when moving from bottom to top and CMV events avoided increase when moving from left to right: (SE) more effective and less costly, (NE) more effective and more costly, (SW) less effective and less costly, and (NW) less effective and more costly. The part in color represents 95% Confidence Wedge of incremental cost-effectiveness. The wedge-shaped regions of the ICE plane are symmetrically positioned relative to the x = –y diagonal (Laupacis et al. 1992). The green color wedge correspond to highly favorable situation, the yellow wedge in favorable and red wedge to high unfavorable case. CMV, cytomegalovirus; DRG, diagnosis-related group; ICE, incremental cost-effectiveness.

CMV infections over the first year (83.1% reduction in the incidence of CMV infection), is of the same order of magnitude as in previous reports: 32% versus 6% in a population of D+/R+ ($P = 0.01$)[31]; 39.1% versus 10.8% ($P < 0.0001$) in R+ patients.[5] Most CMV infection episodes occurred within the first 100 d in the preemptive group (median, 30 d) which is also consistent with previous reports. In the prophylaxis group, CMV infections occurred later, with a median time of 118 d after transplantation, which is consistent with the observation of late infections made by Cunha et al.[32] The recurrence of infections during the first year was more frequent in the preemptive group (22 versus 5 in the prophylaxis group), whereas only one infection occurred after the first year in the preemptive group.

With an economy of €2769 per CMV infection avoided, our study demonstrates the cost-effectiveness of CMV prophylaxis over preemptive treatment. Unfortunately, because of the high price of valganciclovir and limited hospital resources, the prophylaxis strategy is sometimes difficult to set up.[33] On the other hand, depending on the country and center, quantitative nucleic acid amplification testing monitoring could meet logistical difficulties. In this context, the choice between the 2 strategies is still debated, and both have been accepted in the third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation.[8] However, the numerous hospitalizations potentially necessary for the management of CMV infections must be taken into consideration in terms of cost,

TABLE 4.

Results of one-way sensitivity analysis taking into account increases and decreases by 30% of hospitalization and drug costs (all costs expressed in 2018 €)

Hospitalization increase/ decrease, %	CMV drugs[a] increase/ decrease, %	Average cost difference per patient (€)	ICER (€/infection avoid)
0	0	−1154	2769
−30	0	−788	1890
+30	0	−1521	3648
0	−30	−1320	3167
0	+30	−989	2372
−30	−30	−954	2288
+30	+30	−1355	3250
+30	−30	−1687	4045
−30	+30	−623	1493

[a]CMV drugs, drugs for prevention and treatment of CMV (ganciclovir, valganciclovir, etc.)
CMV, cytomegalovirus; ICER, incremental cost-effectiveness ratio.

hospital resources, and logistical aspects. Of note, although costs were similar between the 2 strategies in the primary analysis, bootstrapping evidenced significant cost savings and ICERs. This could be because of a wider dispersion of costs in the high values in the preemptive than in the prophylaxis group, leading to the absence of a significant difference in the EPHEGREN cohort because of small groups (85 + 101) versus a significant difference in the bootstrap analysis thanks to the 10 000 replications. Also, although not in a significant manner, hospitalization duration was higher in the preemptive group, maybe because of less effective prevention of CMV infection, as also put forward by Witzke et al.[5] Furthermore, hospital stays could worsen HE-QoL of transplanted patients. In our study, the cost utility of prophylaxis has been highlighted by a cost reduction of €1422 for each QALY point gained.

The risk of CMV infections was higher with ATG than with basiliximab, which is consistent with the literature, in which a higher incidence of CMV infections was reported with basiliximab even with a reduced dose of ATG, related to T-cell depletion.[16,34-36] A similarly increased risk could be expected with rituximab because of plasmocytes depletion but this could not be tested in our study, because of the too small number of patients on rituximab. Regarding maintenance immunosuppression, despite a higher proportion of patients on cyclosporine in the preemptive than in the prophylaxis group, potentially inducing a confusion bias in the analysis, the type of immunosuppressant was not a significant covariate in Cox analysis. This confirms that the risk of CMV infection was independent of the immunosuppressive strategy and is consistent with the meta-analysis of Tang et al,[37] in which tacrolimus and cyclosporine were considered as uncertain risk factors for CMV infections. Based on these observations, we suggest that prophylaxis should be favored, particularly in patients who had an induction based on ATG or rituximab,[38] no matter the CNI included in the maintenance immunosuppressive strategy.

Regarding safety, more patients had neutropenia (38.8% versus 7.9%) or leukopenia (28.2% versus 10.3%) in the prophylaxis group than in the preemptive group. Although these results are consistent with a previous study (28.4% versus 23.2% for leukopenia),[5] they are contradictory with other studies, in which no difference was reported.[5,31] Furthermore, no significant difference between groups was found on the number and length of hospitalization, suggesting that these adverse events did not lead to hospitalization or prolongation of hospitalization. Overall, this suggests that despite the risk of leukopenia or neutropenia, prophylaxis is worth being favored. Of note, leukopenia is also a frequent adverse drug reaction of mycophenolate mofetil, largely prescribed in renal transplantation.

This study has some limitations, mostly because of its cohort design, in which potential selection biases could

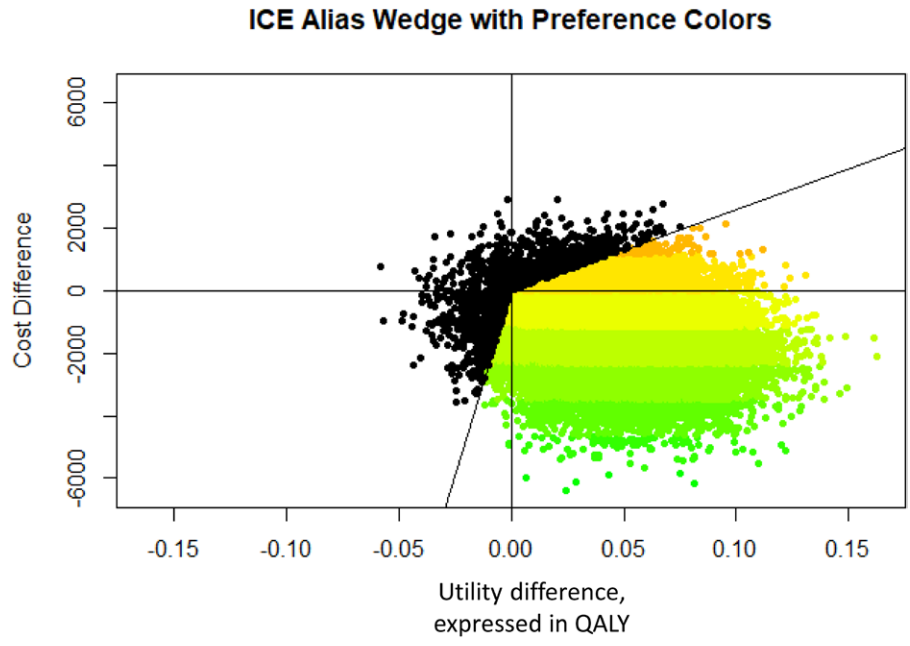

FIGURE 5. Cost-utility plane. X-units = QALY and Y-units = costs; bootstrap replication number = 10 000. ICE, incremental cost-effectiveness; QALY, quality-adjusted life year.

remain. Nevertheless, the potential confounding factors were considered in the analysis. Furthermore, the reported costs for the follow-up of renal transplant patients vary greatly depending on the country. Still, the cost difference and infections avoided between the two arms may probably be the same whatever the country and its national health system. Our economic evaluation using boostrapping was based on patient-level data, with a limited sample, which could have increased the uncertainty on the results. A deeper insight could have been obtained through additional probabilistic sensitivity analysis, but unfortunately, this could not be done because of the too few data available on French renal transplant patients since the new international recommendations.[7,9] A similar study on a dataset collected from patients of other countries would be of great interest, to evaluate the generalizability of our results and give an insight on the external validity. Finally, this study did not evaluate the costs and efficacy of CMV prevention strategies beyond the first year posttransplantation. Nevertheless, most CMV infections appear during the first year, rendering the study of costs beyond the first year less relevant. Some authors evaluated long-term outcomes because of CMV infection such as rejection, graft loss or death between the 2 strategies, but the results were somewhat contradictory.[2,5,16,39-41]

CONCLUSION

This study evaluates the cost-effectiveness of the two recommended CMV prevention strategies in R+ kidney transplant patients, with a prospective cohort design allowing the evaluation of real-life patient care based on data gathered along time after the 2013 update of the international recommendations. CMV infections are known to increase the risk of poor graft outcome such as graft rejection, which must be avoided as much as possible. By preventing CMV infection better and preserving patients' quality of life while saving costs, prophylaxis seems to be superior in terms of efficacy, cost-effectiveness and cost utility. Overall, prophylaxis should be preferred for R+ patients to manage CMV infections.

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