Clinical Infectious Diseases
MAJOR ARTICLE

Immunoguided Discontinuation of Prophylaxis for Cytomegalovirus Disease in Kidney Transplant Recipients Treated With Antithymocyte Globulin: A Randomized Clinical Trial

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Background. Antiviral prophylaxis is recommended in cytomegalovirus (CMV)-seropositive kidney transplant (KT) recipients receiving antithymocyte globulin (ATG) as induction. An alternative strategy of premature discontinuation of prophylaxis after CMV-specific cell-mediated immunity (CMV-CMI) recovery (immunoguided prevention) has not been studied. Our aim was to determine whether it is effective and safe to discontinue prophylaxis when CMV-CMI is detected and to continue with preemptive therapy.

Methods. In this open-label, noninferiority clinical trial, patients were randomized 1:1 to follow an immunoguided strategy, receiving prophylaxis until CMV-CMI recovery or to receive fixed-duration prophylaxis until day 90. After prophylaxis, preemptive therapy (valganciclovir 900 mg twice daily) was indicated in both arms until month 6. The primary and secondary outcomes were incidence of CMV disease and replication, respectively, within the first 12 months. Desirability of outcome ranking (DOOR) assessed 2 deleterious events (CMV disease/replication and neutropenia).

Results. A total of 150 CMV-seropositive KT recipients were randomly assigned. There was no difference in the incidence of CMV disease (0% vs 2.7%; P = .149) and replication (17.1% vs 13.5%; log-rank test, P = .422) between both arms. Incidence of neutropenia was lower in the immunoguided arm (9.2% vs 37.8%; odds ratio, 6.0; P < .001). A total of 66.1% of patients in the immunoguided arm showed a better DOOR, indicating a greater likelihood of a better outcome.

Conclusions. Prophylaxis can be prematurely discontinued in CMV-seropositive KT patients receiving ATG when CMV-CMI is recovered since no significant increase in the incidence of CMV replication or disease is observed.

Clinical Trials Registration. NCT03123627.

Keywords. cytomegalovirus infection; kidney transplant; CMV-specific cell-mediated immunity; QuantiFERON-CMV assay; antithymocyte globulin.

Immunosuppression modulates the risk of cytomegalovirus (CMV) infection after solid organ transplantation [1, 2]. In CMV-seropositive kidney transplant (KT) recipients, preemptive therapy is indicated, which consists of monitoring patients with a sensitive diagnostic technique to detect asymptomatic replication and treat it with an antiviral drug before disease

Received 17 February 2021; editorial decision 5 June 2021; published online 22 June 2021.
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Clinical Infectious Diseases® 2022;74(5):757–65

https://doi.org/10.1093/cid/ciab574

develops [1–3]. However, when CMV-seropositive KT recipients receive induction therapy with antithymocyte globulin (ATG), antiviral prophylaxis is recommended for a minimum of 3 months [3]. This recommendation is based on the high risk of CMV disease [3–5], although the published evidence is contradictory [6, 7].

ATG is a potent immunosuppressive drug that acts by reducing T-cell immunity and the incidence of acute rejection [8]. Currently, the indications for ATG have been notably extended in KT recipients. This means that prophylaxis, instead of preemptive therapy, is indicated in >40% of CMV-seropositive KT recipients for the sole reason of receiving ATG induction.

Today, it is possible to individualize the preventive management of KT by assessing the risk for each patient ("individual pathogenic balance") using techniques that quantify cell-mediated immunity [9–12]. Specifically, we know that pre-transplant CMV-specific cell-mediated immunity (CMV-CMI) defines the risk of post-transplant CMV infection [13]. There is also evidence that >80% of KT recipients with pre-transplant CMV-CMI treated with ATG recover (or maintain) this immunity by the first trimester (approximately equal to 30% in the first month) [14]. Our aim in this study was to determine whether it would be effective and safe to prematurely discontinue antiviral prophylaxis when CMV-CMI is detected after induction treatment and to continue with preemptive therapy (immunoguided prevention).

METHODS

Study Design and Participants

This is a multicenter, randomized, open-label, noninferiority clinical trial of immunoguided discontinuation of antiviral prophylaxis followed by preemptive therapy (immunoguided prevention) vs fixed-duration prophylaxis using valganciclovir in CMV-seropositive KT recipients who received ATG induction (Supplementary Table 1). Patients from 8 centers of the Spanish Network for Research in Infectious Diseases and 5 centers of the Spanish Kidney Disease Network were enrolled between August 2016 and October 2018. The ethics committee (institutional review board) of the coordinating hospital (Reina Sofia University Hospital) approved the protocol. Other centers approved the protocol when necessary. All patients or their legal representatives signed the informed consent. The study was conducted following the guidelines of Good Clinical Practice (Helsinki Declaration) and applicable Spanish law. The trial was registered in EudraCT (number, 2015-004406-42).

Patients

Eligible patients were KT recipients, aged ≥18 years, CMV-seropositive, pre-transplant positive CMV-CMI, receiving ATG (accumulate dose ≥1mg/kg for a maximum of 10 days), and had a negative pregnancy test (female of childbearing potential). All patients were advised about the potential teratogen effect of valganciclovir to avoid pregnancy. ATG was indicated in high-risk immunological patients and recipients of organs donated after circulatory death following the clinical protocols of each participating center. High-risk immunological patients were defined as candidates with a panel reactivity antibody (PRA) >30%, candidates with donor-specific antibodies, and retransplantation patients with loss of allograft due to rejection. PRA was defined as the proportion of human leukocyte antigen (HLA) singly or in combination out of a panel reacting with a patient's serum. Exclusion criteria included multiple organ transplant (including kidney–pancreas), living with human immunodeficiency virus, and patients unable to follow the protocol.

Maintenance immunosuppression consisted of the association of a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil/mycophenolic acid, and steroids. When indicated, mechanistic target of rapamycin R inhibitors were used.

Randomization and Masking

Patients were included in the trial when CMV-CMI was tested before transplantation. Patients were randomized within 15 days after transplantation in a 1:1 ratio to immunoguided prevention or fixed-duration prophylaxis by a computer-generated web-based allocation using permuted blocks of 10.

Intervention

Valganciclovir prophylaxis (900 mg orally once daily adjusted by creatinine clearance) was indicated after transplantation when oral medication was tolerated. The protocol allowed the use of intravenous ganciclovir (5 mg/kg/day adjusted by creatinine clearance) until oral medication was tolerated. Patients in the immunoguided arm underwent CMV-CMI assessment at days 30, 45, 60, and 90 after transplantation, with discontinuation of prophylaxis when positive CMV-CMI was achieved. All patients received a minimum of 30 days of prophylaxis. Patients with a negative or indeterminate CMV-CMI at day 90 discontinued the prophylaxis and continued with preemptive therapy until day 180, in accordance with clinical practice. Preemptive therapy was indicated when prophylaxis was discontinued before day 90 and until day 180, following the protocols of each center. A CMV viral load was performed at least every 2 weeks. Valganciclovir 900 mg (adjusted by creatinine clearance) orally twice daily was indicated when clinically significant (see below). In the control arm, patients received valganciclovir 900 mg (adjusted by creatinine clearance) orally once daily for 90 days followed by preemptive therapy until day 180.

Ganciclovir and valganciclovir doses were adjusted based on calculated creatinine clearance (Cockcroft-Gault formula) in accordance with standard recommendations. Patients in whom valganciclovir was interrupted for any reason could resume medication in the study once the cause was determined, provided they had not missed >14 consecutive days. Otherwise, the patient was excluded from the study. Patients were followed up for 12 months or until lost to follow-up, exclusion, or death (whichever occurred first).

Outcomes

The primary outcome was the proportion of patients with CMV disease in the 12 months after transplantation. CMV disease was defined in accordance with current recommendations [1–3] and the CMV Drug Development Forum recommendations for use in clinical trials [14], that is, evidence of CMV replication in any body fluid or tissue specimen with attributable symptoms. CMV disease can be further categorized as a viral syndrome (ie, fever, malaise, leukopenia, and/or thrombocytopenia) or as organ disease. Secondary outcomes included the proportion of patients with CMV replication (incidence).

Desirability of Outcome Ranking

Desirability of outcome ranking (DOOR) analysis for assessing CMV disease or replication (disease/replication) and neutropenia (<1.500 mm^3) was performed (Table 1). It was defined post hoc knowing that CMV disease was not observed in the immunoguided arm. The best outcome was defined as no CMV disease/replication without neutropenia and the worst as CMV disease/replication with neutropenia. The categories between these 2 extremes were no CMV disease/replication with neutropenia and CMV disease/replication without neutropenia. DOOR is a method for comparing arms using a single, ordinal, patient-centered outcome that represents a global assessment of patient outcome, including efficacy and safety variables. The analysis consists of estimating the probability of a more desirable result in one group relative to another. A probability of 50% implies equality of groups [15, 16], whereas a probability greater than 50%, combined with a 95% confidence interval (CI) that excludes 50%, indicates a significantly greater likelihood of a better outcome in one group compared with the other (and vice versa).

Table 1. Ordinal Outcomes for Efficacy, Safety, and Benefit-Risk Analyses With Categories in Ascending Order of Desirability

Analyses	Outcome
Efficacy	1. CMV disease/replication
	2. No CMV disease/replication
Safety	1. Neutropenia
Benefit-Risk	1. No CMV disease/replication without neutropenia
	2. No CMV disease/replication with neutropenia
	3. CMV disease/replication without neutropenia
	4. CMV disease/replication with neutropenia

Desirability of outcome ranking analysis was defined post hoc. Neutropenia: <1500 neutrophils/mm^3.

Abbreviation: CMV, cytomegalovirus.

Determination of CMV Viral Load

CMV load was analyzed in plasma or whole blood by real-time polymerase chain reaction (PCR) using the technique implemented at each center. Samples available in each laboratory were analyzed, both those carried out according to the protocol and by indication of the responsible physician. Clinically significant CMV replication was defined as >1500 IU/mL in plasma or >5000 IU/mL in whole blood. CMV replication was considered asymptomatic when it was not accompanied by CMV disease (CMV syndrome or CMV disease) [1–3].

Determination of CMV-CMI

CMV-CMI was assessed using the QuantiFERON-CMV (QF) assay, performed according to the manufacturer's instructions (Cellestis, a QIAGEN Company, Melbourne, Australia). In brief, 1 mL of heparinized whole blood was collected in 3 QF collection tubes. The tubes contained a mix of 22 CMV peptides, a negative control (no antigens), or a positive mitogen control (phytohemagglutinin). After incubation for 16–24 hours at 37ºC, supernatants were harvested and analyzed for interferon-gamma (IFN-γ) (IU/mL) by standard enzyme-linked immunosorbent assay. A result for the CMV antigens was "reactive" (positive CMV-CMI) when the CMV antigen response minus the negative control response was ≥0.2 IU/mL of IFN-γ. A result was "indeterminate" when the IFN-γ level in the CMV antigen tube was <0.2 IU/mL and in the mitogen tube was <0.5 IU/mL.

Clinical Assessment and Other Variables

Efficacy and safety were evaluated by clinical assessment including vital signs, laboratory analysis, CMV viral load, and adverse events. Data were collected on basal characteristics, age and gender, retransplantation, type of dialysis, donor type, basal renal disease, PRA, HLA (typed at each center), immunosuppression, pretransplant donor/recipient CMV serostatus, ATG dose and duration, post-transplant CMV-CMI in the immunoguided arm, valganciclovir side effects, concomitant medication, CMV replication, and disease. A senior clinical research monitor revised all data.

Statistical Analyses

The sample size was calculated based on the noninferiority of the primary end point (incidence of CMV disease in the 12 months post-transplant). We assumed that the incidence of CMV disease in the fixed-duration prophylaxis arm would not be more than 3% (data on file). With this estimate (alpha error = 0.05, power = 0.80, lost 5%, double tail, and a noninferiority limit of 7%), the calculated sample size was 150 patients, 75 patients in each arm.

The analyzed population included all randomized patients who received at least 1 dose of valganciclovir and who had at least 1 post-randomization safety assessment (intent-to-treat [ITT] population). The results were expressed as medians (interquartile ranges [IQRs]) for the quantitative variables and as percentages for the qualitative variables. Continuous variables were analyzed using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test. The hypothesis of no difference in the proportion of patients with CMV disease in each arm was analyzed using the phi coefficient. Kaplan-Meier curves were used to calculate the cumulative hazard function, which considers the instantaneous risk of CMV replication/disease among patients still at risk of these events. The cumulative hazard by strategy was compared using the log-rank test. For the DOOR analysis, desirability of outcome ranking probabilities were calculated. Since the sample size was calculated for the primary end point, the findings for the analysis of secondary end points should be interpreted as exploratory. *P* values ≤ .05 were considered statistically significant, and all tests were 2-sided. SPSS 25.0 software (SPSS Inc) was used for the statistical analysis. The study protocol is available online.

RESULTS

Participants

Figure 1 shows a diagram of the patient flow in the trial. Of the 336 patients included before transplantation, 150 patients were randomized at a median of 9.5 days (IQR, 6.0–13.0): 74 patients to the fixed-duration prophylaxis arm and 76 patients to the immunoguided arm. Sixty-seven (90.5%) and 69 patients (90.8%) completed the planned follow-up in each arm. Nevertheless, the 150 patients were analyzed since all of them met the criteria for inclusion in the ITT population.

Table 2 shows the baseline characteristics of the ITT population analyzed. There were no differences between the 2 groups regarding the dose of ATG received (median, 4.4 vs 4.0 mg/kg; *P* = .736). Seven patients in the immunoguided group (9.2%; median, 4 days) and 11 patients in the prophylaxis group (14.9%; median, 3 days) received intravenous ganciclovir until oral medication was tolerated.

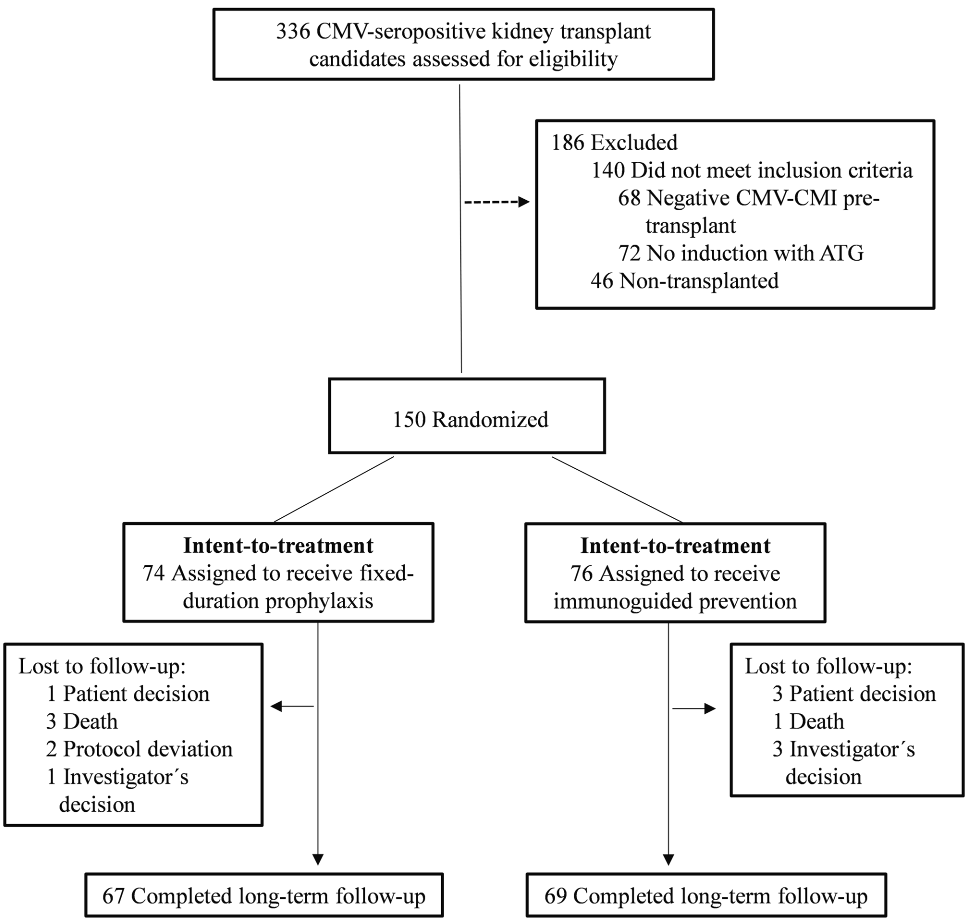


Figure 1. Patient flow through the study. Abbreviations: ATG, antithymocyte globulin; CMI, cell-mediated immunity; CMV, cytomegalovirus.

Table 2. Baseline Characteristics of the Study Population and Ganciclovir/Valganciclovir Use During the Trial (N = 150)

Characteristics	Immunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	*P* Value[a]
Age, median (IQR), years	60 (50.2–67.0)	59.5 (50.5–68.0)	.855
Gender			.003
Female	29 (38.2)	46 (62.2)	
Male	47 (61.8)	28 (37.8)	
Hemodialysis	54 (71.1)	55 (74.3)	.197
Retransplantation (yes)	32 (42.1)	25 (33.8)	.317
Donor status			.952
CMV seropositive	60 (78.9)	58 (78.4)	
CMV seronegative	13 (17.1)	12 (16.2)	
Unknown	3 (3.9)	4 (5.4)	
Source of donor organ			.057
Donor after brain death	47 (61.8)	39 (52.7)	
Donor after circulatory death	29 (38.2)	30 (40.5)	
Living	0 (0.0)	5 (6.8)	
Hyperimmunized	30 (39.5)	39 (52.7)	.140
Chronic kidney disease			.705
Glomerulonephritis	12 (15.8)	17 (23.0)	
Unknown	23 (30.3)	15 (20.3)	
Polycystic kidney disease	9 (11.8)	12 (16.2)	
Diabetes mellitus	6 (7.9)	4 (5.4)	
Autoimmune	6 (7.9)	8 (10.8)	
Hypertension	6 (7.9)	6 (8.1)	
Other	14 (18.4)	12 (16.2)	
Immunosuppression			
Antithymocyte globulin total dose, median (IQR), mg/kg	4.4 (2.9–5.4)	4 (3.0–5.8)	.736
mTOR	13 (17.1)	9 (12.2)	.392
mTOR, median (IQR), days	180 (35.0–231.5)	184 (19.0–195.0)	.764

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: CMV, cytomegalovirus; IQR, interquartile range; mTOR, mechanistic target of rapamycin.

[a]The χ^2 or Fisher exact test was used.

Primary Outcome: DOOR Analysis

Only 2 patients (2.7%) in the fixed-duration prophylaxis group developed CMV disease. One patient suffered from viral syndrome on day 39 and another from disseminated disease on day 181. Both patients responded to intravenous ganciclovir and were cured. No patient in the immunoguided group developed CMV disease (n = 76; phi coefficient; *P* = .149; Table 3). Table 3 also shows the classification of patients in the 4 DOOR mutually exclusive hierarchical levels in descending order of desirability. A total of 66.1% (95% CI, 64.4%–67.7%) of patients in the

Table 3. Outcome of Selected End Points for DOOR Analysis (Intent-to-Treat Population)

End points	Immunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	*P* Value
Primary outcome			
Incidence of CMV disease	0 (0.0)	2 (2.7)	.243
Secondary outcome			
Incidence of CMV replication	13 (17.1)	10 (13.5)	.542
DOOR at 12 months			
No CMV disease/replication without neutropenia	57 (75.0)	39 (52.7)	<.001
No CMV disease/replication with neutropenia	6 (7.9)	25 (33.8)	<.001
CMV disease/replication without neutropenia	12 (15.8)	7 (9.5)	.248
CMV disease/replication with neutropenia	1 (1.3)	3 (4.1)	.323
DOOR components at 12 months			
CMV disease/replication	13 (17.1)	10 (13.5)	.542
Neutropenia	7 (9.2)	28 (37.8)	<.001

Data are presented as no. (%) unless otherwise indicated. DOOR analysis was performed. For this analysis, the composite variable of incidence of CMV disease or replication was considered. Given that the 2 patients with CMV disease also had CMV replication, only 1 event was considered in these patients. Neutropenia: <1500 neutrophils/mm^3.

Abbreviations: CMV, cytomegalovirus; DOOR, desirability of outcome ranking.

Table 4. **Results of the QuantiFERON Cytomegalovirus Assay Performed in the Immunoguided Group (76 Patients)**

	Time Point			
Parameter	**Day 30**	**Day 45**	**Day 60**	**Day 90**
Patients with QuantiFERON-CMV assay results[a]	74 (97.3)	73 (96.1)	72 (94.7)	72 (94.7)
Negative	16 (21.1)	22 (28.9)	23 (30.3)	18 (23.7)
Indeterminate	24 (31.6)	11 (14.5)	4 (5.3)	2 (2.6)
Positive	34 (44.7)	40 (52.6)	45 (59.2)	52 (68.4)
Interferon-gamma, median (interquartile range), IU/mL	2.4 (0.9–9.4)	2.9 (1.0–11.7)	3.6 (1.2–14.0)	8.1 (1.0–16.3)
Discontinuation of prophylaxis[b]	32 (42.1)	7 (9.2)	6 (7.9)	28 (36.8)

Data are presented as no. (%) unless otherwise indicated. Once prophylaxis was discontinued, the clinical decisions were based on viral load monitoring. No further clinical decision was made based on the negativization of cytomegalovirus (CMV)-specific cell-mediated immunity since the serum from the QuantiFERON-CMV tests performed at the time points after discontinuation was frozen at –80° C and the results were analyzed a posteriori.

[a] QuantiFERON-CMV assay results were not available for some patients due to either investigator/patient decisions or technical reasons.

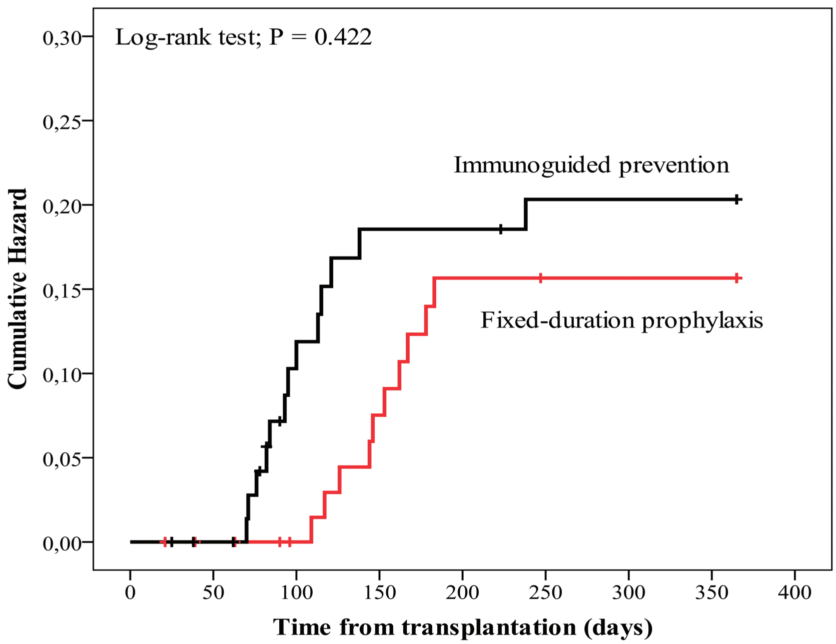
[b]A total of 31 patients reached day 90 with prophylaxis, although 3 withdrew from the study (1 by investigator's decision, 1 patient decision, and 1 death).

immunoguided arm showed a better DOOR than those in the control arm.

Secondary Outcomes

A detailed report of the QF assay results during the follow-up period is shown in Table 4. The QF test results were provided to the clinicians at a median of 4.5 days (IQR, 3.0–7.0) from the time they were available. The clinicians took a median of 4 days (IQR, 2.0–6.0) to discontinue the medication, although prophylaxis was discontinued later in 3 patients (16, 21, and 36).

Prophylaxis was prematurely discontinued in 45 patients (59.2%) in the immunoguided group: 32 at day 30, 7 at day 45, and 6 at day 60. Therefore, duration of prophylaxis was significantly reduced in this group, with the antiviral being administered for a median of 57 days (IQR, 35.5–86.5) and for a median of 90 days (IQR, 83.7–97.0) in the control group (P < .001). After prophylaxis discontinuation, valganciclovir was preemptively administered for a median of 38 days (IQR, 27.5–54.5) in the immunoguided group and for 58 days (IQR, 22.5–90.0) in the control group (P = .294).



Number at risk								
Immunoguided prevention	76	74	62	58	58	56	56	56
Fixed-duration prophylaxis	74	72	69	64	59	58	58	58

Figure 2. Cumulative hazard curves of cytomegalovirus disease/replication according to the strategy followed by the patients (immunoguided prevention vs fixed-duration prophylaxis).

CMV replication was observed in 13 patients in the immunoguided group and in 10 patients in the control group (incidence, 17.1% vs 13.5%; odds ratio [OR], 1.32; 95% CI: .54–3.23). All CMV replication episodes in both groups occurred after prophylaxis was discontinued and the patients had received antiviral treatment.

Figure 2 shows the cumulative hazard curves for CMV disease/replication at 12 months according to the strategy. All episodes of CMV replication in the control arm occurred later than in the immunoguided arm. The curves begin to separate after the first month when prophylaxis began to be suspended in patients with positive CMV-CMI in the immunoguided arm but continued in the fixed-duration prophylaxis arm. Afterward, both curves joined when prophylaxis was suspended in the control group. The median time until the appearance of CMV replication was 95 days (IQR, 79.0–118.0) in the immunoguided group compared with 149.5 days (IQR, 123.7–169.7) in the fixed-duration prophylaxis group (P = .003).

Adverse Events

Although no significant differences were observed in the global incidence of adverse events, a lower incidence of neutropenia (<1500 mm^3) was observed in the immunoguided arm (9.2% [7/76] vs 37.8% [28/74]; OR, 6; 95% CI: 2.4–14.8; P <.001; Table 5).

DISCUSSION

In this randomized clinical trial in CMV-seropositive KT patients receiving ATG induction, immunoguided prevention was not inferior to fixed-duration prophylaxis for the prevention of CMV disease during the first 12 months after transplantation, nor were differences observed in other secondary outcomes considered exploratory. Additionally, no differences were found in the incidence of clinically significant viral replication. The incidence of viral replication increased several weeks after the antiviral was discontinued in both groups. Due to the trial design, the prophylaxis time was longer in the control group, which explains why CMV replication appeared later in this group but in a similar proportion to that of the immunoguided arm.

It is well known that the efficacy of valganciclovir prophylaxis is limited by the incidence of neutropenia [17], which sometimes requires the antiviral to be discontinued [18]. Preemptive therapy is also not exempt from this problem but with a much lower incidence [19]. This study shows that although both regimens do not differ in efficacy, the immunoguided regimen had the advantage of safety since the prophylaxis time with valganciclovir was significantly reduced. Therefore, the incidence of neutropenia, the main adverse effect of this drug, was much lower in the immunoguided arm. When we applied a DOOR analysis, which takes into account efficacy and safety (neutropenia), the immunoguided strategy was superior to fixed-duration prophylaxis. In other words, by changing prophylaxis to preemptive therapy when CMV-CMI is reactive, preventive efficacy is not lost and neutropenia is reduced.

There are 2 high-risk scenarios for CMV disease in KT recipients in which prophylaxis is recommended [1, 3]: transplants from CMV-seropositive donors to CMV-seronegative recipients (D+/R–) and patients receiving ATG induction. It has recently been reported that early therapy is associated with a lower incidence of CMV disease than prophylaxis in D+/R– liver transplant recipients [20]. Although there is no evidence of this in kidney transplantation, preemptive therapy could be an option in those groups with the logistical capacity to do so. Our study provides evidence that prophylaxis can also be avoided in the other risk scenario, treatment with ATG. Both strategies can prevent the adverse effects of prolonged valganciclovir therapy.

Table 5. Overview of Safety and Common Adverse Events (Incidence ≥10%) in Either Arm

Adverse events	Immnunoguided Prevention (n = 76)	Fixed-Duration Prophylaxis (n = 74)	P Value[a]
Overview of safety			
Patients with any adverse event	44 (57.9)	51 (68.9)	.161
Patients with serious adverse events	14 (18.4)	18 (24.3)	.378
All-cause mortality at 12 months	1 (1.3)	3 (4.1)	.363
Common adverse events[b]			
Neutropenia[c]	7 (9.2)	28 (37.8)	<.001
Increased blood creatinine[d]	23 (30.3)	19 (25.7)	.532
Urinary tract infection[e]	12 (15.8)	11 (14.9)	.875
Biopsy-proven acute rejection	12 (15.8)	8 (10.8)	.370
Diarrhea	8 (10.5)	4 (5.4)	.248

Data are presented as no. (%) unless otherwise indicated.

[a]The χ^2 or Fisher exact test was used.

[b]Occurring in ≥10% of patients between time of first drug intake and 28 days after last drug intake. Multiple occurrences of the same adverse event in 1 patient counted only once.

[c]Neutropenia: <1500 neutrophils/mm^3. All patients who had neutropenia also had leukopenia.

[d]Increased blood creatinine: (>2.5 mg/dL).

[e]Urinary tract infection included BK virus infection.

Numerous studies have demonstrated the usefulness of different CMV-CMI techniques to identify transplanted patients at risk of CMV disease/replication [11–14, 21]. A recently published study has validated the usefulness of CMV-CMI monitoring to guide preemptive therapy in CMV-seropositive KT not receiving ATG treatment [22]. Our trial is complementary to this, as it demonstrates the usefulness of CMV-CMI monitoring in CMV-seropositive KT recipients receiving induction with ATG. Both interventional studies demonstrate that the time has come to apply CMV-CMI monitoring in clinical practice [23].

Our study has several strengths: the preventive strategy was allocated randomly; the primary efficacy outcome (CMV disease) is clinically relevant; the proportion of patients who developed CMV disease in the control group was predetermined in the calculation of the sample size; the combination of efficacy and safety has been taken into account in a DOOR analysis; QF determinations, which were crucial in the experimental arm, were done centrally at the coordinating center; and the preemptive therapy has taken into account the clinical practice of each center, thus reflecting what can happen in real practice.

The trial also has limitations: for logistical reasons the trial could not be blinded; CMV-CMI monitoring was not included in the fixed-duration prophylaxis group; to detect CMV replication, the biological sample (plasma or whole blood) and the PCR technique used varied across centers; adherence to virological monitoring protocols in real-life practice may be different; our results refer to KT and cannot be extrapolated to other types of transplants with different risk and immunosuppression protocols; and we enrolled patients at a potentially low risk for CMV replication since only CMV-seropositive patients with positive CMV-CMI were recruited, which may be a limitation for external validation.

In conclusion, in CMV-seropositive KT patients receiving ATG induction, immunoguided prevention is not inferior to standard prophylaxis to prevent CMV complications. Therefore, antiviral prophylaxis can be prematurely discontinued in CMV-seropositive KT patients receiving ATG when CMV-CMI is recovered since no significant increase in the incidence of CMV replication or disease is observed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We are grateful to the patients who participated in the study for their commitment and consideration in providing blood specimens. We are also grateful to Ana Salinas for her technical support.

Financial support. This work was supported by the 2013–2016 National R&D&I Plan and the Carlos III Health Institute (grantPI15/00402 to J.T.C.). It also had the support of The Spanish Society of Nephrology (grant S.E.N. to C.F.), as well as support from the National R&D&I Plan 2013–2016 and the Carlos III Health Institute, General Sub-Directorate of Networks and Cooperative Research Centres, Ministry of Science and Innovation, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/000, RD16/0016/0003, RD16/0016/0007, RD16/0016/0008, RD16/0016/0009 and RD16/0016/0012), co-financed by the European Regional Development Fund "A way to achieve Europe," Operational Programme Intelligent Growth 2014–2020; Spanish Network for Renal Disease Research (RedInRen, RD16/0009/0006, RD16/0009/0008, RD16/0009/0013, RD16/0009/0014, RD16/0009/0019, RD16/0009/0027, RD16/0009/0034); CIBERES (CB06/06/0058); the Spanish Group for the Study of Infection in Transplantation and the Immunosuppressed Host of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and Spanish Clinical Research Network funded by the ISCIII-Subdirectorate General for the Evaluation and Promotion of Research through projects PT13/0002/0010-PT17/0017/0012 and PT13/0002/0014-PT17/0017/0032 integrated in the 2013–2016 National R&D&I Plan and by the National Plan for Scientific and Technical Research and Innovation (2017–2020) and co-financed by the European Regional Development Fund.

Potential conflicts of interest. C. G. A. reports personal fees from Sociedad Madrileña de Trasplante and Sandoz Pharmaceuticals Spain outside the submitted work. A. C. has also received an honorarium/grants for developing educational presentations for Pfizer and Shionogi. S. C. has received payments (research funding and honoraria) from Qiagen for educational activities both during and outside the submitted work. J. T. C. reported receiving grants from Roche Pharma; grants and personal fees from Qiagen for educational activities outside the submitted work; and nonfinancial support from the Spanish Society of Infectious Diseases and Clinical Microbiology. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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