Prophylactic and pre-emptive therapy for cytomegalovirus infection in kidney transplant patients using oral valganciclovir

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SUMMARY

Prophylactic and pre-emptive therapy with oral valganciclovir for cytomegalovirus infection in renal transplant recipients.

Background: *Cytomegalovirus infection is a very important health problem in solid organ transplant recipients (SOT). Once-daily valganciclovir has been shown to be as clinically effective and well tolerated as oral ganciclovir tid in the prevention of CMV infection in high risk SOT recipients.*

Methods: *The aim of the present study was to evaluate the incidence and severity of CMV disease in 150 renal transplant recipients that received either prophylactic [high risk group (HR), N = 66] or pre-emptive [low risk group (LR), N = 84] therapy with oral valganciclovir (900 mg/day vo) for three months according to their basal risk. Patients were monitored for signs and symptoms of CMV disease and CMV plasma viral load was assessed weekly.*

Results: *A total of 31 patients (47%) of the HR and 26 patients (31%) of the LR presented a positive CMV PCR result. Twelve patients (14.3%) in the LR that had a high viral load (CMV PCR > 1,000 copies/mL) but remained asymptomatic received pre-emptive therapy. Four patients (4.7%) in the LR, after an average time of 35 days after transplant and two patients (4.5%) in the HR, after prophylactic treatment was completed, developed CMV disease. The disease was mild-moderate in most of the cases. Those patients that developed CMV disease responded to treatment with iv ganciclovir for 14 days followed by treatment with oral valganciclovir for up to three months.*

Conclusion: *Prophylactic treatment with oral valganciclovir for CMV prevention is only required in high risk solid organ transplant recipients.*

Key words: *Cytomegalovirus. Renal transplant. Oral vanganciclovir. Quantitative PCR.*

RESUMEN

Antecedentes: **La enfermedad por citomegalovirus (CMV) es un problema sanitario muy importante en receptores de trasplante de órgano sólido (TOS). Una dosis diaria de valganciclovir ha demostrado ser tan clínicamente efectiva y bien tolerada como ganciclovir oral dos veces al día en la prevención de la infección por CMV en los receptores de TOS de alto riesgo.**

Métodos: **El objetivo del presente estudio fue evaluar la incidencia y severidad de la enfermedad por CMV en 150 receptores de trasplante renal que recibieron tratamiento profiláctico (grupo de alto riesgo, N = 66) o anticipado (grupo de bajo riesgo, N = 84) con valganciclovir oral (900 mg/día) durante tres meses según el riesgo basal de sufrir la misma. Se hizo un seguimiento de los síntomas clínicos de la enfermedad por CMV en los pacientes y la carga viral de CMV en plasma fue monitorizada semanalmente.**

Resultados: **Un total de 31 pacientes (47%) del grupo de alto riesgo y 26 pacientes (31%) del grupo de riesgo estándar presentaron un resultado de PCR-CMV positivo. Doce pacientes (14,3%) del grupo de riesgo estándard que presentaron una elevada carga viral (PCR-CMV > 1.000 copias/mL) pero que permanecieron asintomáticos recibieron tratamiento anticipado. Cuatro pacientes (4,7%) del grupo de alto riesgo, en un tiempo medio de 35 días después del trasplante y dos pacientes (4,5%) del grupo de alto riesgo, tras completar el tratamiento profiláctico, desarrollaron la enfermedad por CMV, que fue de intensidad media a moderada en la mayoría de los casos. Aquellos pacientes que desarrollaron la enfermedad respondieron al tratamiento con ganciclovir ev durante 14 días seguido de valganciclovir oral hasta tres meses.**

Conclusión: **El tratamiento profiláctico con valganciclovir oral para la prevención de CMV sólo es requerida en receptores de TOS de alto riesgo.**

Palabras clave: Citomegalovirus. Trasplante renal. Valganciclovir oral. PCR-CMV cuantitativa.

INTRODUCTION

Cytomegalovirus infection is common in the general population. Infection is often asymptomatic, and the virus remains latent in the body causing no apparent clinical signs.

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At the age of 30, up to 70% of the population has developed antibodies to CMV. However, in immunodepressed patients, such as SOT recipients, the virus may leave its latent state and cause significant morbidity and mortality in the first months after transplant.[1-4] The clinical picture of CMV disease has a widely varying intensity and severity and may range from a flue-like syndrome consisting of fever, malaise, myalgia, and neutropenia to more severe forms with gastrointestinal (colitis, hepatitis, gastritis), respiratory (pneumonitis), and/or neurological involvement (encephalitis).[3] CMV has also been related to harmful effects on the transplanted organ such as decreased graft survival,[5,6] increases in the number of acute rejection episodes and the frequency of chronic rejection,[7] atherosclerosis,[8] lymphoproliferative conditions,[9] healthcare costs,[10] and bacterial and fungal opportunistic infections in the recipient.[11]

Due to the great significance of CMV in transplant patients, many strategies have been developed to date for prevention and treatment of CMV disease. In a recent systematic review, Hodson et al compared the different regimens for prophylaxis and treatment of cytomegalovirus infection and concluded that the antiviral agents ganciclovir, valganciclovir, and acyclovir, used as prophylaxis, improved prognosis in SOT recipients. These agents reduced the risk of CMV mortality by 60%, and disease derived from herpes simplex, herpes zoster, and bacterial infections by 35%-70%.[12] In head-to-head studies, ganciclovir was shown to be more effective than acyclovir for preventing CMV infection and disease. In a trial comparing ganciclovir and its prodrug, valganciclovir, no statistically significant differences were found between them, suggesting that the benefits shown to date by ganciclovir could be extrapolated to valganciclovir.[13]

In our centre, strategies for preventing CMV disease have followed the prevailing guidelines at each transplant era. In the 80s, no prophylaxis for CMV disease was given, and the rate of diagnosed severe CMV disease was 62%. In the 90s, universal prophylaxis was used in all kidney transplants, consisting of oral acyclovir for 3 months according to the regimen recommended by Balfour.[14] Results achieved with such universal prophylaxis were satisfactory and represented a clear improvement over the previous policy of no prophylactic therapy. Incidence of severe disease dropped from 62% to 9%.[15] Universal prophylactic treatment with acyclovir was subsequently abandoned and replaced by pre-emptive therapy of CMV infection with oral ganciclovir. CMV infection was diagnosed based on antigenemia (pp65), and prophylaxis was not administered in patients identified to be at risk for CMV infection or disease. Pre-emptive therapy was not able to prevent the disease because once viral replication had started, early diagnosis using antigenemia did not prevent progression from infection to disease.[16] We therefore decided a new change to a protocol that would include new diagnostic and therapeutic procedures. Real time, quantitative CMV PCR replaced pp65 antigenemia, and oral valganciclovir was substituted for oral ganciclovir. Prophylactic therapy should be general for all risk situations.

Valganciclovir is a valine ester prodrug of ganciclovir that was developed to overcome the limitations of oral and intravenous ganciclovir. A single oral daily dose of ganciclovir 900 mg provide plasma levels similar to those achieved with ganciclovir 5 mg/kg IV. Bioavailability is up to 10 times higher as compared to oral ganciclovir.[13] Such bioavailability helps decrease the cases of ganciclovir resistance that may occur with low drug exposure.[17-19]

The purpose of our study was to assess the incidence and severity of CMV disease in a group of patients undergoing a recent kidney transplant who were to receive prophylactic or pre-emptive therapy for CMV disease depending on their baseline risk to suffer the condition. The drug to be used as the basis for treatment was oral valganciclovir at a dose of 900 mg/day. Results were to be compared with our previously reported historical series and the literature.

MATERIALS AND METHODS

The study lasted from May 2004 to April 2006. One hundred and fifty patients aged 18 years or older with adequate renal and haematological function receiving a kidney transplant at our centre (102 from cadaveric donors and 48 from living donors) were selected for the study. Exclusion criteria included treatment for CMV within the prior 30 days, severe or uncontrolled diarrhea, and evidence of malabsorption.

The initial standard immunosuppression regimen consisted of three drugs (oral tacrolimus 0.1 mg/kg/12 hours, oral mycophenolate mofetil 1 g/12 hours, and oral prednisone 1 mg/kg/day, to be gradually tapered). In patients with early graft dysfunction, tacrolimus was transiently discontinued and thymoglobulin (rabbit polyclonal antilymphocyte serum) 1.25 mg/kg/day was administered until graft dysfunction resolved. Thymoglobulin doses were adjusted daily based on lymphocyte count, and treatment was limited to a maximum duration of 10 days or a total cumulative dose of 10 mg/kg. Tacrolimus was gradually restarted overlapped with thymoglobulin withdrawal.

Patients were monitored since the time of graft implantation for symptoms of CMV disease (previously described), treatment received, occurrence of opportunistic infections, acute rejection episodes, and graft survival. Between one and four months after transplant, a real time, quantitative CMV PCR was performed weekly using the Cobas Amplicor CMV Monitor® Test (Roche Diagnostics, Branchburg, NJ, USA), and all clinical events related to a potential CMV disease were recorded by severity and type of involvement as detailed in Table I. the pseudomononucleosis syndrome was defined as viraemia with > 38ºC occurring ≥ two times over ≥ 24 h in a 7-day period, laboratory results positive for CMV, and at least one of the following: fatigue, two consecutive events of leukopenia (defined as a leukocyte count < 3,500/mL or a 20% decrease in the count if the count prior to occurrence of clinical symptoms was < 4,000/mL) in an interval ≥ 24 h, atypical lymphocytosis > 5%, thrombocytopenia, or liver enzyme elevation to ≥ 2 times above the upper normal limit.

Patients were divided into two groups based on their risk of experiencing CMV infection or disease.

High-risk group: This group comprised transplant recipients with prior negative serology for CMV who received

grafts from positive donors (D+/R-), those requiring treatment with antilymphocyte serum (ALS), and those who required increases in their baseline immunosuppression as a result of one or more episodes of acute rejection (AR). Some patients met more than one of these risk criteria. This whole patient group received treatment with oral valganciclovir for 3 months for prophylactic purposes. Doses were adjusted to kidney function.

Standard risk group: This group comprised all transplant patients not meeting any of the above criteria. When CMV viral load was higher than 1,000 copies/mL, oral valganciclovir was given as pre-emptive therapy for 3 months at the doses detailed in table II. If disease symptoms preceded CMV detection in blood using PCR, ganciclovir IV was administered for 14 days, and oral valganciclovir was subsequently given until 3 months of treatment were completed.

The primary efficacy objective was to assess the proportion of patients who developed CMV disease during the first three months after transplant.

Descriptive statistics (mean, median, standard deviation, and proportions) were used to analyse patient characteristics, treatment groups, and events occurring during the study.

RESULTS

High-risk group. Prophylactic therapy

Sixty-six patients (44.29% of all patients) were considered to be at a high risk for CMV disease and received prophylactic therapy with oral valganciclovir adjusted to kidney function for 3 months. The clinical and laboratory criteria for starting prophylactic treatment were previously described. As shown in Figure I, patients at risk were distributed into the groups as follows:

D+/R- group, 24 patients who were administered oral valganciclovir since the start of oral tolerance after transplant.

ALS group, 40 patients, some of whom had already started prophylaxis because they belonged to the D+/R- risk group. In all other patients in this group, prophylaxis was started at the same time as treatment with antilymphocyte serum.

AR group, 22 patients who started valganciclovir together with corticosteroid boluses if they had not received it before for any of the two previous reasons.

Among the 66 patients in the risk group, 35 (53%) always had a negative result in CMV PCR throughout the follow-up period and showed no disease at any time. Some positive CMV PCR measurement was found in the remaining 31 patients (47%). Three of the 66 patients (4.5%) met criteria for CMV disease, that was defined in two cases (3%) as mild to moderate in severity (pseudomononucleosis syndrome) and in the remaining patient (3%) as severe because of pulmonary and gastrointestinal involvement. In all 3 cases, disease occurred after discontinuation of prophylactic therapy. Mean time from treatment discontinuation to disease occurrence was 20 days. No disease occurred during prophylactic therapy (table II). Use of ganciclovir resulted in a positive course leading to cur in two of the patients, while in the remaining patient foscarnet had to be added to ganciclovir due to clinical resistance to the latter. Mean CMV viral load of the whole risk group is given in figure II. An increase in viral load is seen after discontinuation of prophylactic therapy as a result of disease development in 3 patients. The 24 D+/R- patients had a similar course to the rest of the risk group, with a positive CMV PCR in 11 of them (45.8%).

Table I. Severity of CMV disease

Severity defined as:

1. **Mild to moderate**: Documented CMV infection with poorly relevant clinical signs. Pseudomononucleosis syndrome.
2. **Severe**: Documented CMV infection with severe neutropenia and/or significant liver enzyme elevation and/or documented gastrointestinal and/or respiratory and/or CNS involvement.
3. **Death**: Documented CMV infection at the time of death, responsible for the fatal outcome.

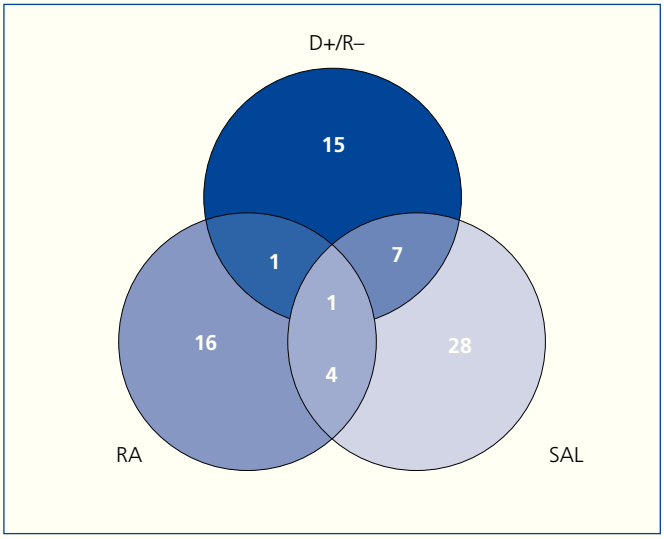

Figure 1. Distribution of patients in the risk group receiving prophylactic therapy.

Table II. Viral load at disease onset in the risk group and mean time to negativization of CMV PCR

CMV disease	Time after prophylaxis (days)	Type of disease	Viral load at onset (copies/mL)	Negativization after treatment (days)
Patient 1	30	Pseudomononucleosis s.	206,000	40
Patient 2	7	Pseudomononucleosis s.	34,300	30
Patient 3	21	Respiratory and gastrointestinal	105,000	90

Standar risk group. Pre-emptive therapy

The remaining patients (low-risk group) were monitored for 12 weeks by weekly CMV PCR from one month after transplant. When viral load ranged from 100 and 1,000 copies, follow-up was intensified (twice weekly), but treatment was not started. Oral valganciclovir (900 mg/day, adjusted to kidney function) was given to patients having > 1,000 copies/mL of CMV but no signs or symptoms of disease (pre-emptive therapy). When patients had a positive CMV PCR and disease signs or symptoms, ganciclovir IV was administered for 14 days, followed by oral valganciclovir until three months of treatment were completed.

Eighty-four of the 150 patients (56%) were considered as having a low risk for CMV disease. Among the 84 patients, 58 (70%) always had a negative result in CMV PCR throughout the follow-up period and showed no disease at any time. Some positive CMV PCR measurement was found in the remaining 26 patients (30%), but most of these (85%) experienced no symptoms. Ten of these 26 patients had at all times a CMV viral load less than 1000 copies/mL and were never treated (fig. III). The remaining 16 patients were treated for different reasons. Twelve of them were given pre-emptive therapy for a viral load > 1,000 copies/mL. Figure IV shows the change over time in the mean viral load of these patients until negativisation during treatment with oral valganciclovir. The mean number of copies was approximately 3,000/mL at the first positive CMV PCR. All patients remained free of symptoms and relapse. The remaining 4 patients met disease criteria. This represents a disease incidence of 4.7% (4/84 patients) in the low-risk group. CMV disease was mild to moderate in all patients. Mean time to disease onset was 35 days after transplant (31-40 days), and more than 100,000 copies/mL of CMV were usually already found at the first measurement (table III). Progression to disease occurred in one out of the 4 above patients after no treatment was started when an initial viral load < 1,000 copies/mL was detected. The other 3 patients started as disease. Combined treatment with ganciclovir IV for 14 days followed by oral valganciclovir to complete 2 months of treatment solved all cases without difficulty.

Figure V details the course of all patients.

DISCUSSION

High-risk group

Prophylactic therapy with oral valganciclovir was shown to be greatly effective for preventing CMV disease in the group of patients at a high risk of suffering it. Among all 66 high-risk patients, only 3 (4.5%) developed the disease, that was considered mild to moderate in severity in two of them and severe in the other (1.5%). Our experience[15,16] with risk patients at the beginning of the 90s had showed higher disease rates. The historical series of risk patients receiving no prophylaxis against CMV showed CMV disease in 62.5% of cases. The condition was mild to moderate in 37% of cases and severe in 25%. Thirty-eight percent of patients remained asymptomatic.

Prophylaxis with oral acyclovir for 3 months according to the scheme devised by Balfour[14] subsequently reduced from 62.5% to 28% our percentages of CMV disease in the risk group, with a statistically significant difference ($p < 0.05$) as compared to the group receiving no prophylaxis. The convenience of prophylactic therapy in the risk group had already been widely shown in the literature by many authors. In a recent meta-analysis covering a large number of studies on the subject, Kalil et al[20] concluded that universal prophylactic therapy with either oral acyclovir or ganciclovir decreases both the incidence and severity of CMV infection and the number and severity of acute rejection episodes, though a head-to-head comparison of both drugs could not be made in such meta-analysis. Prophylactic therapy also provides benefits in terms of number of bacterial and fungal infections, and also for decreasing the chance of patient death. In our centre, universal prophylaxis with acyclovir in at risk patients was replaced in 1997, when oral ganciclovir was introduced, by pre-emptive therapy with

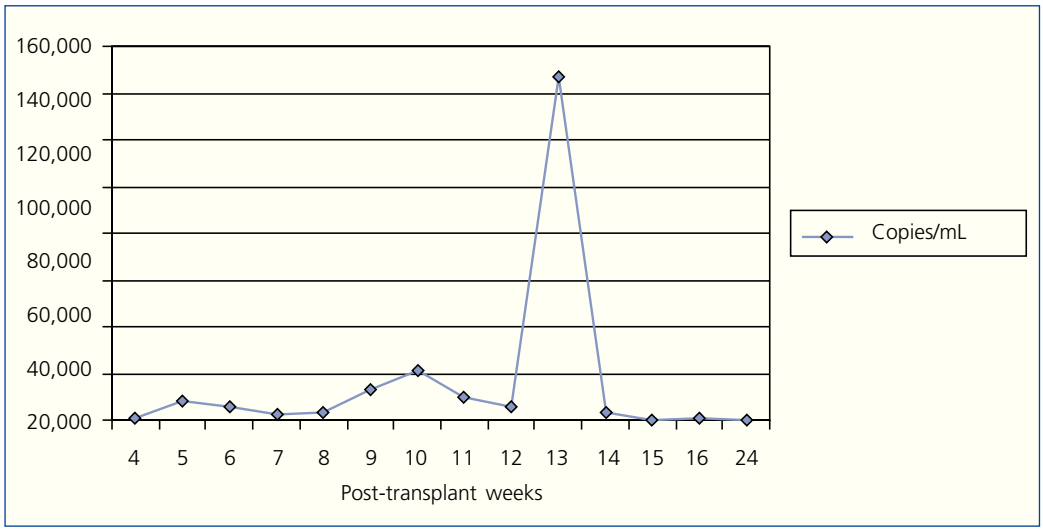

Figure 2. Post-transplant change over time in mean viral load in the risk group.

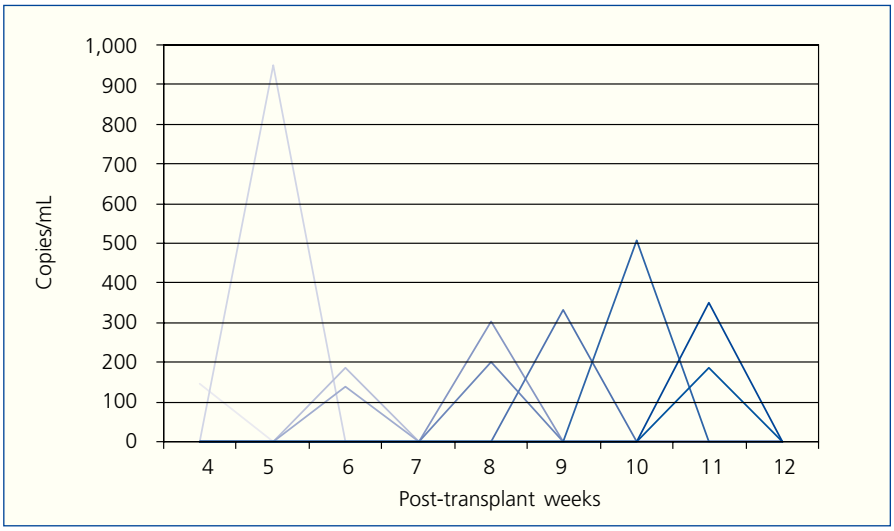

Figure 3. Change over time in the viral load of low-risk patients with values lower than 1,000 copies/mL at all times and receiving no treatment.

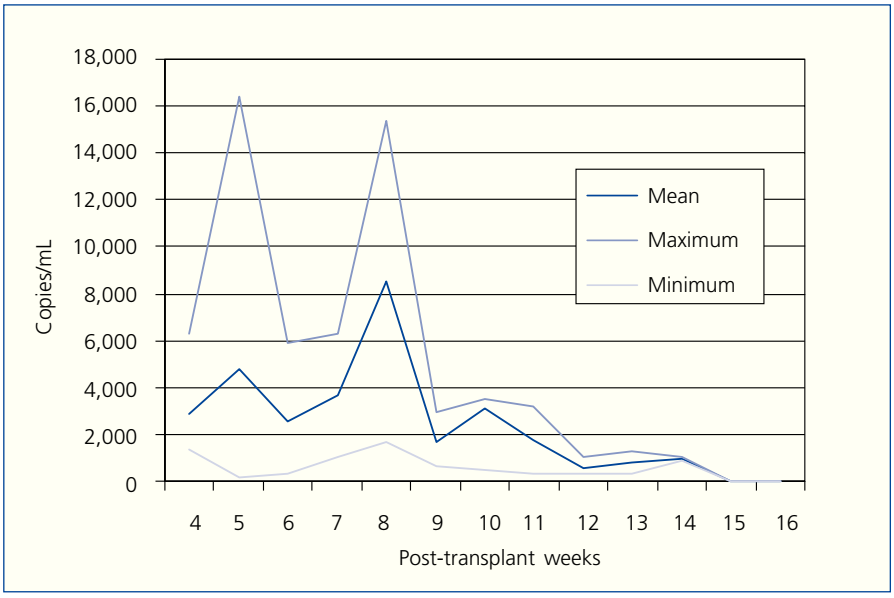

Figure 4. Change over time in viral load in the group of low-risk patients receiving pre-emptive therapy (CMV PCR > 1,000 copies/mL).

Table III. Viral load (copies/mL) at disease onset in patients from the standard risk group

CMV disease	Week 4 PCR	Week 5 PCR	Week 6 PCR	Week 7 PCR	Week 8 PCR
Patient 1	347	167,000	341,000	80,800	4,990
Patient 2	0	103,000	6,000	2,420	980
Patient 3	0	12,500,000	482,000	28,000	2,240
Patient 4	0	5,540	1,130	0	140

this drug when the pp65 antigen was detected.[16] Using this approach, the antigen was detected in 67% of patients in the risk group, but 100% of patients with a positive antigen test developed severe disease. This showed that risk group patients always required anti-CMV prophylactic therapy. Anticipated virus detection did not allow for preventing the disease if no prior prophylaxis was given. Based on these conclusions derived from our own experience, we decided to conduct a clinical study on the risk group based on the following concepts:

a) Prophylaxis was indispensable in this group because the disease could not be avoided if not given.
b) Oral valganciclovir has a high bioavailability and allows for long-term prophylactic therapy that is convenient for the patient, avoiding hospital admissions, day-

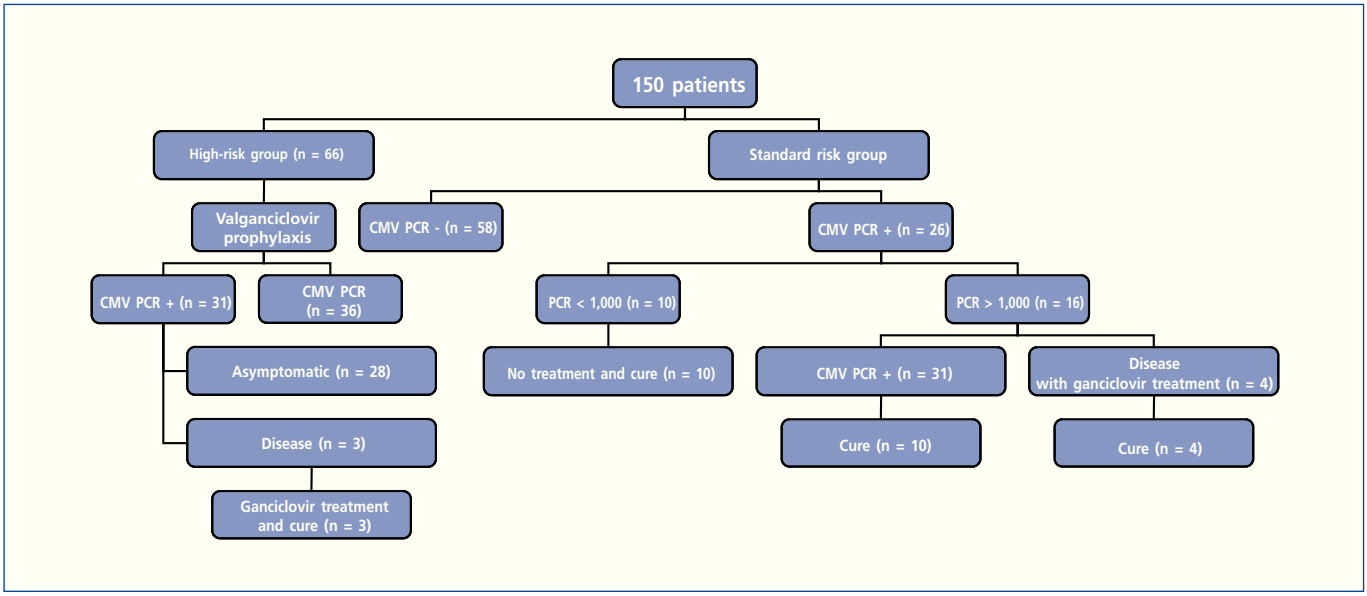

Figura 5. Change over time in all patients by risk group assigned.

care hospital, and intravenous administration of medication.

c) Addition of weekly real time, quantitative CMV PCR could help us achieve a good control of the course of CMV infection in risk patients and indicate us what would be the factors predicting for disease development.

The following observations were made during the patient follow-up period:

a) None of the 66 patients at risk experienced CMV disease during the prophylactic therapy.
b) Fifty-three percent of high-risk patients never had a positive CMV PCR test. This is very important because it shows that treatment with oral valganciclovir is highly effective for controlling the possibility of primary infection and/or viral reactivation in patients in whom, as demonstrated by prior experience, infection rates would otherwise have been very high (62%).
c) Forty-seven percent of high-risk patients had some positive CMV PCR test. However, the control of viral replication achieved with oral valganciclovir allowed that no patient developed disease criteria during prophylaxis. Only 3 patients (4.5%) developed disease on discontinuation of prophylactic therapy (mean time after prophylaxis 20 days, 7-30). CMV disease was totally cured in all these patients, as shown by both clinical criteria and permanent negativisation of CMV PCR.

In all these patients with a positive CMV PCR at any time during follow-up, except for the 3 patients who developed disease, viral load decreased without adding ganciclovir IV. Treatment wit oral valganciclovir permitted that, despite positivisation of CMV PCR, viral load was not high enough as to cause signs of disease. Figure II shows the mean viral load of patients in the risk group with positive CMV PCR as a function of follow-up time. The periods in which viral load reached maximum frequency and intensity coinciding with discontinuation of prophylactic therapy 12 weeks after the transplant may be seen in the figure. In patients who did not develop CMV viral load definitively disappeared or decreased, while in patients who developed disease viral load rapidly increased to more than 100,000 copies/mL. Disease treatment with ganciclovir IV allowed for symptom improvement and negativisation of viraemia in all cases but one, in which clinical and laboratory resistance to ganciclovir occurred and foscarnet was required for resolution. Despite such treatment, the patient maintained a stable and normal kidney function.

Table IV compares the chance of suffering CMV disease as a function of the different therapeutic options (no treatment, prophylactic therapy, and pre-emptive therapy) and the procedure used for early diagnosis of CMV infection (pp25 antigen levels or quantitative CMV PCR). The table shows a significant decrease in CMV disease in the group of risk patients followed by CMV PCR and receiving prophylactic therapy with oral valganciclovir.

Standard risk group

This group also showed an excellent clinical response to protocol. It was first shown that this group does not require universal prophylactic treatment. All viral load measurements were negative in 70% of patients in this group. The remaining 30% had some positive CMV PCR, but the predefined 1000 copies/mL were not exceeded in a good part of cases (38% of these group and 12% of all patients in this series) and no prophylactic and/or pre-emptive therapy was

required either. Finally, 14% of all patients in this low risk group (12/84 patients) successfully received pre-emptive therapy, and only 4 out of 84 patients (4.75%) experienced mild to moderate disease. No cases of severe disease occurred in this patient group. The low incidence and severity of CMV disease in the standard risk group supports our choice to monitor infection using real time, quantitative CMV PCR, that allows for very early infection diagnosis, and oral valganciclovir is highly effective for outpatient control of this infection, with no severe disease occurring in any patient in our series. Use of CMV PCR helped to limit treatment to only 18.75% of patients (16/84) from the standard risk group (pre-emptive therapy in 14% and treatment for mild to moderate disease in 4.75%).

The experience acquired in our series of kidney transplant patients leads us to the following conclusions:

- The group of patients at risk of CMV disease (D+/R-, treatment with antilymphocyte serum and/or increase in immunosuppression due to acute rejection) requires anti-CMV prophylactic therapy. Otherwise, this group of transplant patients has a very high risk of suffering severe CMV disease.
- Prophylactic therapy with oral valganciclovir for 3 months has been shown to be highly effective for preventing CMV disease. Only 4.5% of patients in the risk group experienced CMV disease, usually of mild to moderate severity, and only one patient had severe disease.
- No patient experienced CMV disease during prophylactic treatment, which helps prevent the condition in early transplant phases.
- Mean time to disease occurrence after discontinuation of prophylactic therapy was 20 days (7-30), and the disease occurred in very few patients (3/66). Mean viral load at disease onset was 115,000 copies/mL (34,300-206,000). This suggests that monitoring with CMV PCR after discontinuation of prophylactic therapy should be continued for at least one month for early detection of signs of viral replication.
- Ganciclovir IV has been effective for treating patients with CMV disease after discontinuation of prophylaxis.
- The standard risk group required no prophylactic therapy. Monitoring of infection by CMV PCR allows for early diagnosis of infection, and oral valganciclovir for effective control, thus preventing development of severe disease in virtually all patients.

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Table IV. Incidence of CMV disease in the risk group by type of treatment and procedure used to detect CMV

Group at risk for CMV disease	No prophylactic of pre-emptive therapy	Universal acyclovir prophylaxis	pp65 antigenemia + pre-emptive therapy	Universal oral valganciclovir prophylaxis and quantitative CMV PCR
N	50	50	72	66
Treatment duration Disease	No treatment 62%	3 months 28%	3 months 67%	3 months 4.5%
% with severe disease	25%	9%	67%	1.5%
Disease treatment	Ganciclovir IV	Ganciclovir IV	Ganciclovir IV	Ganciclovir IV*

*Foscarnet was added in one case due to clinical resistance to ganciclovir.

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