

Antiviral agents for preventing cytomegalovirus infection in pediatric renal transplant recipients: A systematic review

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Abstract

Background and Objective: Cytomegalovirus (CMV) infections are associated with severe morbidity and mortality in patients, especially pediatric renal transplantation patients. The use of immunosuppressive agents places these patients at the risk of viral infections. As cytomegalovirus infection influences the graft outcome, adopting useful strategies for limiting this virus after transplantation seems necessary.

Methods: This systematic review evaluates all articles about the prophylactic treatment in pediatric renal graft recipients.

Results: There are several anti-viral agents that are used alone or in combination for preventing CMV infection. The prophylactic agents that are used in pediatric recipients include CMV-Ig, IVIG, acyclovir/valacyclovir, and ganciclovir/valganciclovir. CMV-Ig is an adjuvant agent and it is less effective if used alone. Although performed studies in children are not sufficient to determine valacyclovir effect in preventing reactivation of cytomegalovirus, valacyclovir is used in moderate risk recipients for CMV infection. It seems that valacyclovir is less effective than valganciclovir.

Conclusion: Nowadays oral valganciclovir is the most appropriate prophylactic agent used in most transplant centers for children and adults. However it appears that valganciclovir prevents cytomegalovirus infection only during prophylaxis period. The incidence of late CMV infection does not reduce by this drug. Some trials in adults and a retrospective study in children recommend that longer duration of prophylaxis with valganciclovir lowers the incidence of CMV infection in late stage.

Keywords: Cytomegalovirus, Infection, transplantation, Pediatric, Valganciclovir

Introduction

Cytomegalovirus is the most frequent viral infection in children who underwent renal transplantation. This infection can result in remarkable morbidity and mortality. The effects of this infection on patient and graft survival, number of acute rejection episodes and graft function have been proven by a series of studies in adults and children. There are two strategies to prevent CMV infection after renal transplantation: preemptive therapy and universal prophylaxis. Preemptive therapy has some benefits such as minimization exposure to antiviral agents and their side effects

decreased CMV resistance, economy and prevention of late onset CMV infection. Although there is no trial comparing preemptive treatment with prophylaxis in pediatric renal transplant recipients, in a recent systematic review in adults, the superiority of prophylactic approach over preemptive approach was shown (1). Regarding the use of prophylaxis, the effect of different antiviral agents has been evaluated in pediatric articles. As most of these articles are observational and retrospective and because of the absence of any controlled and randomized trial in children, the specialists could not provide an ideal prophylaxis

Table 1. Reviewed studies.

Study Year	No. of Cases/loss of follow up	Year of study	Prospective study	Age Median (range) Mean (\pm SD)	Male/Female	Living/Deceased donor	Follow up (months)	Immunosuppressive Protocol	CMV monitoring post-transplant	CMV infection definition
Kranz 2008	109/6	1998-2005	No	10.9 (1.6-22) 10.6 \pm 5.3	64/39	30/73	3.9 \pm 2.1 yr (0.8-8.1)	Basiliximab (99%) Prednisolone in all, CsA (79), MMF(9), TAC (11), TAC+MMF (1), CsA+Everolimus (4)	CMV PP65 every week for 6-8 wk and then monthly	Positive PP65
Jongsma 2013	221/62	1999-2010	No	12.1 (2.7-17.6)		65/94	12	Basiliximab since 2002 Pred+MMF+CsA	Quantitative PCR every 2 wk until 4 mo and next at 5,6,9,12 mo	PCR>50geq/ml
Hiliniski 2011	130/29	2004-2008	No	14.5 (1.4-20.4)	62/39	67/34	21.8 (1.5-24)	Basiliximab in all Pred+MMF+TAC for 3mo and then Pred+MMF+sirolimus	Quatitative PCR monthly for the first 6 mo and then every 3 mo	Any level of detection
Randall 1994	151	1987-1992	No	14.5 (1.4-20.4)		102/49	33 \pm 21.7	ATG Pred+AZA+CNi	Viral culture, Rapid antigen test with an unknown schedule	Positive culture seroconversion
Renoult 2007	31	2000-2005	No	14 \pm 3.25	15/16	5/26	43.7 \pm 19.8 (11-82)	ATG (5), Basiliximab (24) pred+CNi+MMF or AZA	qualitative PP67 NASBA weekly till 3 mo, bi-weekly till 6 mo	Positive PCR
Fijo 2013	257/18	2005-2009	No	6 mo-19 yr	160/97		12	Anti CD25 (180), ATG (57), OKT3 (1) Pred+CNi+MMF	CMV PP65 or qualitative PCR every 2 wk during the first 2 months, every 3 wk in 3-4 th mo and then every month	Positive PCR or Positive PP65
Jodi 2010	61/6	2000-2005	yes	11.2 \pm 5.8	25/30	21/34	24	ATG or IL2 antagonist CNi+Pred+MMF/sirolimus	Quantitative PCR monthly for the first 2 year	Any level of detection
Flynn 1997	175	1982-1991	yes	11.6 \pm 4.9 (0.9-20.8)	118/57	46/129	46/129	ATG in some patients CNi+AZA+Pred	CMV titers weekly and then every 2-3 months during the first year	Fourfold or greater in CMV titers
Evans	192	1991-2010	No					not mentioned	qualitative PCR with unknown intervals	Positive PCR

lactic protocol in this age group (2-4).

The aim of this systematic review is to review all pediatric articles in which various types of prophylactic treatments were assessed for prevention of CMV infection after renal transplantation.

Methods

Search method: We searched the PubMed, MD Consult, Science Direct and Google Scholar for relevant articles between 1980 and 2014. The key words were cytomegalovirus, prophylaxis, renal transplantation and children. In our article we included prospective or retrospective cohort, case-control and cross sectional studies, but not case reports.

Study selection: We reviewed all subjects and

abstracts of searched articles. The full texts of all studies about different methods of CMV prophylaxis in pediatric renal transplantation were found. Two persons reviewed all these full texts separately. All relevant articles in reference list of searched articles were also assessed.

Data extraction: Two persons extracted all data of eligible articles. The extracted data were as follows: study design, publication year, patient number, patient characteristics, details of diagnosis of CMV infection/disease, the type of antiviral agent used for prophylaxis and duration of prophylaxis.

Definitions: CMV infection was defined when there was asymptomatic CMV detection in blood/plasma or tissues. CMV disease was de-

Table 2. Reviewed studies results.

Study Year	Prophylaxis	High risk, Intermediate risk, Low risk patients	CMV infection CMV disease	Rate of CMV infection based on the receiving prophylaxis
Kranz 2008	CMV-Ig for high risk recipients (D+/R-) No prophylaxis for others	27%, 37%, 36%	23/103 (21.1%) 10/103 (9.7%)	High risk group: 50% during prophylaxis
Jongsma 2013	(Val)ganciclovir for high risk group (D+/R-) for 3 mo (Val)acyclovir for intermediate risk group (D-/R+, D+/R+) for 3 mo IV acyclovir+CMV-Ig in both high and intermediate risk group (1999-2003) Low risk (No prophylaxis) for D-/R-	29%, 41%, 30%	61/159 (38.3%) 18/159 (11.3%)	High risk group: 41% after cessation of valganciclovir Intermediate group: 24% 50% during/after CMV-Ig 33% in valganciclovir after cessation of prophylaxis 22% in valacyclovir during / after valacyclovir Low risk: 12% all in the first 3 months 27% CMV infection during or after cessation of prophylaxis Only 2 patients with CMV disease received complete 6 mo prophylaxis
Hilinski 2011	Valganciclovir to all R+ and/or all D+/R- and a few children with serostatus of D-/R- for a mean of 5.9 mo	39.6%, 48.5%, 18.8%	30 (27%) 5 (4.5%)	Only 2 patients with CMV disease received complete 6 mo prophylaxis
Randall 1994	Oral acyclovir to some patients without precise criteria and unknown duration		12/151 (7.9%) 17/151 (11.2%)	
Renoult 2007	CMV-Ig for high risk recipients (D+/R-) 150 mg/kg within the first 72 hr, repeat at 2,4,6,8 wk post-transplant and then 100 mg/kg at 12 and 16 wk after transplantation	42%, 13%, 45%	11/31 (35%) 3/31 (9.6%)	High risk group: 76% during or after renal transplantation Three CMV disease: two patients received incomplete prophylaxis and one of them received complete prophylaxis No death
Fijo 2013	Prophylaxis 80.8% IV ganciclovir 36.3% IV ganciclovir+oral ganciclovir 57.5% IV gammaglobulin+oral cyclovir 5.7% No prophylaxis 19.2%	25.1%, 50%, 23.8%	58/239 (24.2%)	High risk group: 26.6% after cessation of valganciclovir Intermediate group: 19.6% Low risk: 3.5% all in the first 3 months
Jodi 2010	IV ganciclovir and then oral valganciclovir for 3 months or 12 months	45%, 24%, 31%	12/55 (22%)	High risk group: 67% after cessation of valganciclovir Intermediate group: 25% Low risk: 8% No difference of CMV incidence in 3 mo and 12 mo prophylaxis
Flynn 1997	IVIG to some D+/R- weekly during hospitalization and then every 2-3 months	38%, -, 16%	38% in IVIG+ vs 71% in IVIG- 17% in IVIG+ vs 71% in IVIG-	less severe CMV disease in 17% of D+/R- recipients with prophylaxis vs more severe CMV disease in 71% of D+/R- recipients without prophylaxis
Evans	acyclovir to all D+/R- 5 mg/kg loading dose and then 22 mg/day for 200 days	25%, -, -	25% 19.4%	

fined when CMV detection was occurred with symptoms and signs.

Objective: To assess the efficacy of antiviral agents in pediatric renal transplant recipients in the prevention of cytomegalovirus infection and symptomatic disease and in the reduction of the incidence of acute rejection, graft loss and death.

Results

After a thorough search related articles were retrieved, the redundant similar articles removed, and 120 articles remained. The studies were performed between 1987 and 2012. The title and abstract of these articles were evaluated and finally 13 full text articles were assessed. After assessment of full text of these articles, 9 studies were included in this systematic review. Two articles

were prospective whereas others were observational and retrospective. All articles were case series and we did not find any trial in pediatric age group in this regard. The details of these studies are shown in Tables 1 and 2. We found no trial in pediatric age group in this regard.

Discussion

Cytomegalovirus is the most significant viral agent affecting the patients following renal transplantation. CMV infection is a greater problem in children compared to adults due to more seronegativity of pediatric recipients. More than half of CMV seronegative recipients who received a solid organ from a seropositive donor are involved with CMV infection in the absence of prophylaxis (5). The use of suitable prophylactic treatment re-

duces CMV infection in both adults and children after renal transplantation especially during the phase of prophylaxis (6,7). In addition, the effect of anti-viral prophylaxis on the improvement of the graft survival was shown by Bock et al (3). In an adult study performed by Opelz et al, the use of prophylaxis significantly reduced the need to anti-rejection therapy after transplantation (4).

In total, there are controversies regarding the best anti-viral composition as CMV prophylactic treatment in pediatric renal transplant recipients (8-14). Besides, the studies performed in this ground are low in numbers and most of them are observational and retrospective (15-18). To our knowledge there is not any controlled trial in this regard in children. In this systematic review, we reviewed all prophylactic protocols used in the pediatric articles for CMV prevention after transplant. Based on these studies, the following medications were used in prophylaxis in children.

IVIG: Flynn et al in a prospective study gave IVIG to D+/R- recipients and compared the results with D+/R- recipients who received no prophylaxis. CMV disease occurred in 17% of IVIG group and in 71% of recipients without prophylaxis. In addition, the severity of CMV disease in non-prophylaxis group was significantly more than IVIG group (19).

CMV hyperimmune globulin (CMV-Ig) has been prophylactically administered in pediatric renal transplant recipients by some researchers (2,3). Kranz et al followed 103 children with renal transplantation. All recipients with D+/R- serostatus received CMV-Ig in this study, but the duration of prophylaxis was not mentioned. CMV infection was reported in 21.1% of all patients, and in 50% of D+/R- recipients despite prophylactic treatment (2). Bock et al reported a significant decrease in hospitalization due to CMV disease in D+ recipients who received prophylactic treatment with CMV-ig (4). Jongsma et al in a retrospective study followed 22 patients (D+/R-, D+/R+, D-/R+) who received intravenous acyclovir for two weeks and CMV-Ig seven infusions once every two week as prophylactic treatment (8). The clinically important CMV infection (quantitative PCR > 1000geq/ml) was seen in 50% of these patients that was significantly higher than patients who received 3 months valganciclovir or valacyclovir as prophylaxis. In another study by Renoult et al, 76% of high risk patients developed CMV infection despite prophylaxis with CMV-Ig (15). However only 3 patients developed CMV disease, in

two of them, the prophylactic treatment was not completed due to side effects of medicine. Although some adult's studies have shown the preventive effect of CMV-Ig (18), however some recent studies have challenged this preventive strategy. Taken together, it appears that CMV-Ig is better to administer as adjunctive therapy or administer combined with a preemptive approach.

Oral acyclovir/valacyclovir and/or intravenous ganciclovir have been used as prophylaxis in some studies (2). CMV is not sensitive to acyclovir *in vitro*, but the efficacy of this drug in prevention of CMV reactivation was shown by some adult studies (1,11). Bock et al have shown the use of oral acyclovir or intravenous ganciclovir did not reduce the incidence of CMV infection but decreased the severity of CMV disease in children. However this study was retrospective and the patients selected for prophylactic agent and the duration of prophylaxis were unclear. In Jongsma's study, valacyclovir was used as prophylaxis in intermediate risk recipients (D+/R+, D-/R+), but CMV infection occurred during and or after receiving valacyclovir in 22% of patients and the authors could not respond to this question whether valacyclovir is effective to prevent CMV infection in intermediate risk patient or not. For proving the effectiveness of this medication, we need controlled trial studies to compare valacyclovir with valganciclovir.

Oral ganciclovir or valganciclovir: Oral ganciclovir preparations are effective for the prevention of CMV infection. Valganciclovir is a prodrug that is converted to ganciclovir after oral use. Valganciclovir was used as CMV prophylaxis in adult patients and was effective in reducing CMV infection/disease in the duration of prophylaxis.

In this systematic review, we found that the incidence of CMV infection/disease varies in these nine studies. This difference can be due to different screening methods for CMV detection, different definitions of CMV infection, different risk profile of studied population, different type and duration of prophylactic treatment and immunosuppressive protocols used by different centers. However, the incidence of CMV infection was between 20-40% in all these studies. This incidence is relatively similar in patients who received prophylaxis and those without prophylaxis. Although the development of new potent antiviral agents has lowered CMV infection, but has not eliminated it and in contrast has increased the in-

cidence of late onset CMV infection. Extended duration of prophylactic treatment from 3 to 6 months is recommended for reducing the incidence of the late CMV infection. In a recent randomized prospective double blinded trial in adults, 3 months administration of valganciclovir was compared to six 6 months regimen. A significant decrease in CMV infection was seen in patients receiving 6 months valganciclovir (8,9). In a retrospective study performed in children, Heliniski et al administered valganciclovir prophylaxis to all D+/R- and a few children with serostatus of D-/R- for a mean of 5.9 months. The CMV infection rate was 27% and CMV disease 4.5% (13). Five patients developed CMV disease in this study; of those only 2 patients completed the 6 month prophylaxis and others discontinued prophylaxis due to side effects of valganciclovir. However there are disadvantages for this extended prophylaxis such as side effects of medications, CMV resistance, low compliance and increased cost. To this reason some other researchers have recommended preemptive treatment after 3 months prophylaxis. To our knowledge there is no trial comparing different durations of prophylaxis with each other in children. Hilniski study was also retrospective, without control group, and the selected recipients for the use of prophylaxis is not completely clear and all patients did not receive 6 months prophylaxis. This article could not respond our question about the best duration of prophylaxis in children. In a recent prospective study in children, 6 months and 12 months prophylaxis did not affect the incidence of CMV infection. For determining a unique protocol for prophylaxis, we need controlled and randomized trials in this age group.

Conclusion

We found that the incidence of CMV infection or disease is high despite prophylactic treatment especially after cessation of prophylaxis. The incidence of CMV in children receiving 3 months valganciclovir was between 20 and 40% in different studies and most of these infections occurred after prophylaxis ended. Longer duration of prophylaxis is recommended to reduce these late forms of CMV infection, but effectiveness, cost, CMV resistance and side effects of drug should be considered in protocols with extended duration of valganciclovir. A controlled trial may help to resolve these controversies.

Conflicts of interest: None declared.

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