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Review Article

Scientific Review of the Knowledge Gap in the Efficacy of Antiviral Therapy to a Low-Risk Kidney Transplant Population Cohort

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Abstract

Opportunistic infection with cytomegalovirus (CMV) is a major cause of patient morbidity and mortality after renal and other solid organ transplantation [1]. De facto standard of care is choice of either prophylactic or preemptive therapy [2]. There is a knowledge gap in the efficacy of antiviral therapy to a low-risk kidney transplant population. I searched the PubMed and clinicaltrials.gov databases with strategic keywords. Although the final search yielded 52 results (PubMed) and 25 (clinicaltrials.gov), I only included 14 articles particular to the main topic of this review. There is limited data specific to this population, therefore, healthcare defaults to the de facto standard of care of choice.

Introduction

End Stage Renal Disease is an end organ diagnosis where the kidneys lose optimal functioning. Two treatment options for this disease are dialysis or kidney transplantation. Dialysis is a process of removing or filtering waste, via a machine, from the blood. Although it is effective, it is not without harmful side effects. The latest studies reveal a significant decrease in mortality with kidney transplant compared to dialysis. This is a reason why most providers encourage their patients to pursue kidney transplantation. Once a patient is transplanted, there is an expected recovery phase. Typically, the first 3 months post-operation is a high-risk period. The patient would have endured significant immunosuppression therapy, which puts the patient at risk for opportunistic infections (viral, bacterial, and/or fungal). This is the reason why antivirals, antibiotics, and antifungals are a staple regimen alongside immunotherapy.

This systematic review will focus on the antiviral regimen. Antivirals are for protection from viruses such as herpes and cytomegalovirus. Cytomegalovirus (CMV) is a major infection that can be very harmful to the donor kidney organ. CMV is a pervasive post-transplant infection, which is how it earned the nickname, the transplantation troll (Kotton, 2018). A post-transplant patient could get infected from a CMV seropositive organ or from the community. Latest research showed that 20%-60% of kidney transplant recipients developed CMV within first 3 months post-transplant [3]. Various post-transplant CMV risk factors include serostatus, rejection history, host factors, and net state of immunosuppression [4]. CMV infections typically lead to febrile illness, opportunistic infections, acute graft rejection and potentially graft failure [1]. The antiviral medication of choice is high dose valacyclovir and research has explored various treatment regimen strategies, prophylaxis *vs* preemption or a hybrid of both (Kotton, 2018).

In the transplant community, universal prophylaxis has been accepted as the standard. Universal prophylaxis is treating all post-transplant patients, within 10 days post operation, and continuing for 3-6 months [4]. Transplant recipients that are CMV

seronegative and receive donor CMV seropositive organs (D+/R-) are considered high risk for CMV. The guidelines uniformly suggest six months of valganciclovir prophylaxis [4]. Transplant recipients that are CMV seropositive (R+), regardless of donor serostatus, are considered intermediate risk and recommended to receive three months of valganciclovir prophylaxis [4]. Prophylaxis disadvantages are drug toxicity, cost, antiviral resistance, delayed T cell response recovery, and late onset CMV. Preemption therapy (PET) takes a reactive approach to immunotherapy. The regimen consists of serial blood tests, symptoms monitoring, then medication treatment only if symptoms meet infection criteria [3]. However, PET doesn't protect against herpes simplex and is logistically difficult to coordinate and monitor (Kotton, 2018). Numerous research studies concentrate on comparing the two therapy philosophies to discover the superior therapy. On the other hand, this review will focus on the efficacy of using antivirals for low-risk kidney transplant population, defined as CMV negative, hepatitis C virus (HCV) negative, and Epstein Barr virus (EBV) negative. These patients are designated as donor seronegative/recipient seronegative (D-/R-).

Background

It is understood that post-transplant patients need protection from CMV. D+/R- patients are considered high risk for CMV as it occurs in 70% of these cases [5]. However, for patients that are not exposed to CMV, and receive an organ that isn't exposed to CMV, there begs the question if antiviral therapy is indicated. In reviewing the latest studies, there is limited data on the efficacy of using antivirals for the low-risk kidney transplant population (D-/R-). One thing to consider is the increased risk for side effects. Another consideration is the increased risk for CMV or other viral resistance. Antiviral, though effective options, can be limited in their effectiveness and adequateness. Acyclovir, though safe and inexpensive, is inferior to cytomegalovirus replication. Ganciclovir, another compelling option, is also susceptible to antiviral resistance [6]. Valganciclovir is costly and with significant side effects [4]. In reference to the preemption vs prophylaxis discussion, CMV DNAemia is more common with preemptive therapy, whereas late-onset CMV DNAemia or disease and neutropenia is more common with prophylaxis (Kotton, 2018).

Methods

In PubMed, I used search terms "cytomegalovirus antiviral prophylaxis transplant" (Table 1). The search yielded 2269 results. I was able to find some articles that pertained to my research questions, but I noticed the extensive dating. I adjusted the date filter to "2010-2022' and retrieved 1043 results. As I reviewed articles, I noticed I didn't have access to many articles of interest. I adjusted the search filter to only include "free full text" articles. The results yielded 424 articles. I chose a few articles that specifically reviewed cytomegalovirus, as an antiviral treatment for post-transplant recipients. I excluded articles that didn't pertain to kidney or liver transplant because they share the same standard antiviral regimen. I excluded articles that reviewed antivirals other than valganciclovir because this is standard antiviral medication. The articles ranged from the American Journal of Transplantation, Current Opinion in Infectious Diseases, the Transplantation Journal, Current Hematologic Malignancy Reports. I specifically sought articles that focused on or at least mentioned CMV seronegative donors and recipients.

("cytomegalovirus"[MeSH Terms] OR "cytomegalovirus"[All Fields] OR "cytomegaloviruses"[All Fields]) AND ("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms] OR ("antiviral"[All Fields] AND "agents"[All Fields]) OR "antiviral agents"[All Fields] OR "antivirals"[All Fields] OR "antiviral"[All Fields] OR "antivirally"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields] OR "prophylaxies"[All Fields] OR "prophylaxy"[All Fields]) AND ("transplantability"[All Fields] OR "transplantable"[All Fields] OR "transplantated"[All Fields] OR "transplantating"[All Fields] OR "transplantation"[MeSH Terms] OR "transplantation"[All Fields] OR "transplantations"[All Fields] OR "transplanted"[All Fields] OR "transplanting"[All Fields] OR "transplantation"[MeSH Subheading] OR "transplantation s"[All Fields] OR "transplanter"[All Fields] OR "transplanters"[All Fields] OR "transplantion"[All Fields] OR "transplants"[MeSH Terms] OR "transplants"[All Fields] OR "transplant"[All Fields])

Table 1: Initial Search Terms.

Although I came across articles that helped me frame the research introduction and background, most of the articles focused on CMV seropositive donors and seronegative recipients. Therefore, I did an additional PubMed search with terms "antiviral seronegative donor seronegative recipient transplant" (Table 2). Also, I included "free full text" and "2015- 2022" as filters. My updated search yielded 52 results. To find more information specific to the D-/R- cohort, I searched the cinicaltrials.gov database for latest data. I used key terms "CMV prophylaxis, kidney transplant" which yielded 44 results (Table 2). I applied an additional filter for completed studies, which reduced my results to 25. I excluded pediatric studies and drug intervention comparison studies. Although it was difficult to find studies specific to the D-/R- cohort, I was able to locate information on pipeline therapies to address CMV infection. The HB-101 vaccine recently completed Phase II and it included the D-/R- cohort as a control (National Library of Medicine [NLM], NCT03629080). What is interesting is that this article did not identify the D-/R- cohort as a high-risk population. Hoffmann-La Roche completed a study that looked at the effects of Ganciclovir on cohort, D+/R- and an untreated cohort D-/R- (National Library of Medicine [NLM], NCT01663740). The findings were either comparable or the D-/R- cohort showed superior findings. This isn't surprising as they are a low-risk cohort. Figure 1 illustrates a flow chart that illustrates the search methodology.

(("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms] OR ("antiviral"[All Fields] AND "agents"[All Fields]) OR "antiviral agents"[All Fields] OR "antivirals"[All Fields] OR "antiviral"[All Fields] OR "antivirally"[All Fields]) AND ("seronegative"[All Fields] OR "seronegatives"[All Fields] OR "seronegativity"[All Fields]) AND ("donor s"[All Fields] OR "tissue donors"[MeSH Terms] OR ("tissue"[All Fields] AND "donors"[All Fields]) OR "tissue donors"[All Fields] OR "donor"[All Fields] OR "donors"[All Fields]) AND ("seronegative"[All Fields] OR "seronegatives"[All Fields] OR "seronegativity"[All Fields]) AND ("transplant recipients"[MeSH Terms] OR ("transplant"[All Fields] AND "recipients"[All Fields]) OR "transplant recipients"[All Fields] OR ("recipient"[All Fields] AND "transplant"[All Fields]) OR "recipient transplant"[All Fields])) AND ((ffrft[Filter]) AND (2015:2022[pdat]))

Table 2: Second set of Search Terms.

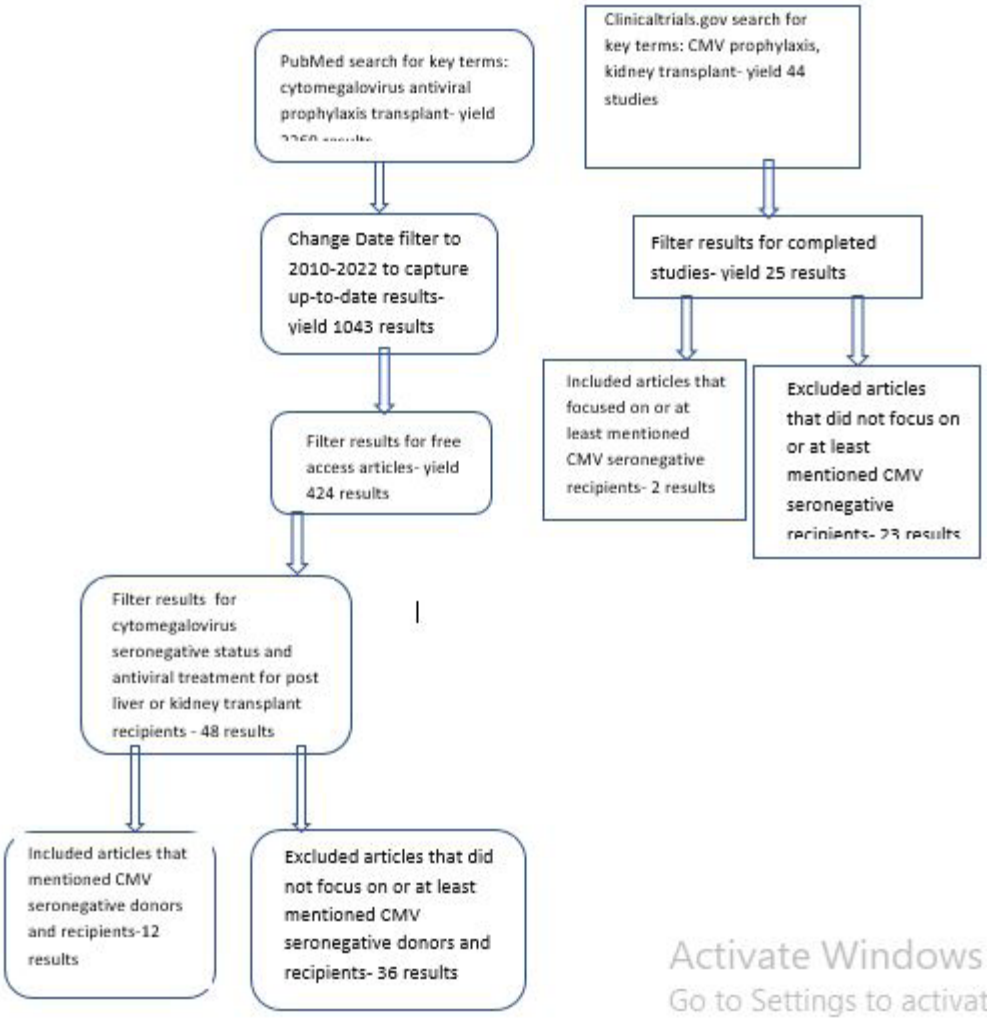

Figure 1: Flowchart of search methodology.

The following table includes the evaluation of resources included.

Title/Author with Full Citation	Study Aims and or Hypothesis	Study Design	Study Population	Key Findings
Legendre, C. M., Norman, D. J., Keating, M. R., Maclaine, G. D., & Grant, D. M. (2000). Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation. Transplantation, 70(10), 1463–1468. https://doi.org/10.1097/00007890-200011270-00012	A cost-effectiveness analysis of treatment with valaciclovir versus placebo was performed, assessing the mean total cost for the number of cases of CMV avoided at 6 months in the two groups	multicenter multinational randomized, placebo-controlled, double-blind trial of valaciclovir CMV prophylaxis. Patients were stratified into donor seropositive/recipient sero-negative (D+R-) and recipient seropositive (R+) groups. Patients were followed up 6 months posttransplant for clinical efficacy and 1 year for patient/allograft survival	15 to late 70's Even Male/Female ratio	*CMV disease incidence at 6 months posttransplant were 16% for the valaciclovir group and 45% for placebo controls in the D+R- stratum and 1 and 6% for the valaciclovir group and placebo controls *The 6-month incidence of biopsy-proven acute rejection was 26% for valaciclovir patients versus 55% for controls, and 39 vs. 63% for clinical acute rejection *D+/R- patients who were administered valaciclovir prophylaxis used significantly fewer inpatient resources in several categories: number of hospital admissions, total number of hospital days, number of special procedures, and number of laboratory tests * In D+R- cohort, there were no significant differences in outpatient resource use between the valaciclovir and placebo groups *R+ patients had fewer ER admissions and fewer antiviral use days *Patients who developed CMV disease used significantly more inpatient and outpatient resources than patients without CMV disease, regardless of treatment group *for both cohorts, the cost of valaciclovir was offset by saving expenditures therefore proven economically superior strategy compared to placebo
Couchoud, C., Cucherat, M., Haugh, M., Pouteil-Noble, C. Cytomegalovirus Prophylaxis with Antiviral Agents in Solid Organ Transplantation: A Meta-Analysis. Transplantation: March 15, 1998 - Volume 65 - Issue 5 - p 641-647	The aim of this meta-analysis was to assess the efficacy of antiviral agents to prevent, in solid organ transplant recipients, CMV infection and symptomatic disease and to decrease the incidence of acute rejection, graft loss, and death	prospective randomized study, where one group in the study received a prophylactic treatment with acyclovir and/or ganciclovir (GCV) begun before the CMV infection, and a control group was not treated or receive placebo	adults or pediatric recipients of a solid organ transplant	Significant decrease in CMV infection, however, no decrease in graft loss, acute rejection, or death
Puius, Y. A. & Snydman, D. R. (2007). Prophylaxis and treatment of cytomegalovirus disease in recipients of solid organ transplants: current approach and future challenges. Current Opinion in Infectious Diseases, 20 (4), 419-424. doi: 10.1097/QCO.0b013e32821f6026.	Reviewing the risks and benefits of differing strategies	Metanalysis of randomized controlled trials	D+/R- CMV recipients	*Hodson et al metanalysis, prophylaxis- CMV risk reduced by 60%, mortality reduced by 40% and preemptive therapy was inconclusive *Strippoli et al metanalysis preemption yielded no statistical significance. *Small et al metanalysis preemption yielded no statistical difference in CMV disease, graft loss, or mortality *French Model CEA showed oral valganciclovir prophylaxis as most cost effective when compared to preemptive IV ganciclovir and standard therapy *Khoury et al showed no significant difference between prophylaxis or preemption *Limaye et al. retrospective analysis is most reflective of current practice, however it does not answer question of causality between mortality and CMV disease *Diaz-Pedroche trial focused on preemption with R- CMV cohort (high risk population). * The study results support VGCV needed by average of 58 days after transplant *Doyle et al provided Kaplan-Meier curve that show long term benefit for 24-week prophylaxis *Singh et al trial did not show emergence of CMV resistance with preemptive VGCV *Boivin et al showed low incidence of CMV resistance with prophylactic GCV and VGCV

Boillat Blanco, N., Pascual, M., Venetz, J., Nseir, G., Meylan, P., Manuel, O. Impact of a Preemptive Strategy After 3 Months of Valganciclovir Cytomegalovirus Prophylaxis in Kidney Transplant Recipients. Transplantation: January 27, 2011. Volume 91(2),p 251-255 doi: 10.1097/TP.0b013e318200b9f0	Assess impact of preemptive strategy, after discontinuing antiviral prophylaxis, in prevention of late onset CMV; primary endpoint was incidence of late-onset CMV	Prospective, non-controlled, single center All patients receive 3 mos prophylaxis VGCV, then monitor for CMV by PCR Q15days for 3 mos. VGCV restarted if PCR positive	86 kidney transplant recipients, average age 48 years, 60Male 26Female 30 D+/R- 56 R+	*CMV occurred in 36% recipients; 43% in D+/R- 32% in R+ *None from the R+ group developed late onset CMV, and their PCR results were below threshold *Preemption strategy seems to have a limited impact on the prevention of late-onset CMV disease, particularly in group of seropositive CMV patients
van der Beek, M., Berger, S., Vossen, A., van der Blij-de Brouwer, C., Press, R., de Fijter, J., Claas, E., Kroes, A., loys, C. Preemptive Versus Sequential Prophylactic-Preemptive Treatment Regimens for Cytomegalovirus in Renal Transplantation: Comparison of Treatment Failure and Antiviral Resistance. Transplantation: February 15, 2010 - Volume 89 - Issue 3 - p 320-326 doi: 10.1097/TP.0b013e3181bc0301	Compare the incidence and course of CMV infections, frequency of treatment failure of CMV infections, and role of antiviral resistance	*Retrospective Single center *42 treated preemptive and 29 treated prophylactic *Prior to 2006, preemptive regimen started, guided by CMV DNA load. *Treatment started once CMV load threshold reached. From 2006, prophylaxis regimen started x90 days, followed by preemption.	*78 D+/R- kidney-pancreas transplant recipients *Mean age Prophylaxisn49; preemptionn46 *Males Prophylaxis n24; Preemption n18	*Incidence of CMV was similar for both cohorts *Preemption cohort had significantly higher CMV 69% vs 45% *No CMV end organ disease occurred in any cohort *No significant difference in # of rejection episodes or renal function between the cohorts *Treatment failure, defined by DNA load, was higher in preemption group 71% vs 14% & duration of preemption treatment was longer with preemption cohort 45 days vs 29 days *Sequential prophylaxis-preemptive approach proved practical *CMV infections with a slow response to preemptive antiviral treatment occurred less frequently in patients who had received prophylactic treatment than in patients on a strictly preemptive regimen. *CMV infections with resistant virus were eventually cleared without switching antiviral therapy

Khoury, J. A. , Storch, G. A. , Bohl, D. L. , Schuessler, R. M. , Torrence, S. M. , Lockwood, M. , Gaudreault-Keener, M. , Koch, M. J. , Miller, B. W. , Hardinger, K. L. , Schnitzler, M. A. & Brennan, D. C. (2006). Prophylactic Versus Preemptive Oral Valganciclovir for the Management of Cytomegalovirus Infection in Adult Renal Transplant Recipients. American Journal of Transplantation, 6 (9), 2134-2143.	*Our study compares outcomes and costs of adult renal transplant recipients randomized to receive prophylactic or preemptive oral valganciclovir for the clinical management of CMV infection *The primary outcome for the purpose of powering the study was an economic comparison between the prophylactic and preemptive groups. Secondary outcomes included occurrence of CMV infection and disease, clearance of CMV DNAemia, incidence of acute rejection, allograft survival, allograft dysfunction, death, and incidence of neutropenia.	*Randomized single center *Prophylaxis cohort (n50), preemption cohort (n49) with VGCV ,1:1 block design stratified by CMV serostatus *Monitored by PCR before transplant then weekly for 16 wks post-transplant, then at months 5, 6, 9, 12 *Prophylaxis group received VGCV for 100 days post-transplant while preemption only received if PCR detected *Prophylaxis group (age 52 years, male 51%, white 80%) Preemption group (age 49, male 23%, white 90%)	*CMV risk population D+/R+, D+/R-, D-/R+ *D-/R- (n20) were included, but only to monitor (control) *144 adult patients	*No deaths occurred *99% overall allograft survival rate *Rejection (proph n1, preemp n4) *No relationship observed between CMV and acute rejection *No difference in serum creatinine between cohorts *Prophylaxis reduced occurrence of CMV by 90% during first 100 days and by 52% for entire study compared to preemption *In preemption cohort, CMV onset occurred only in first 100 days (avg by 39 days post txp) *Recurrent CMV higher in preemptive cohort (n34 vs n14) *This randomized study found that prophylaxis or preemptive treatment with valganciclovir were each associated with low rates of symptomatic CMV (5%) in kidney transplant recipients *No evidence of CMV recurrence *Symptoms in CMV-proph group (n4) after 100 days treatment; preemption (n1) by 61 days post-transplant *D-/R- cohort only had n2 (10%) with CMV DNAemia *Costs were favorable to preemption (VGCV, hospitalization) but favorable to proph (provider time, CMV PCR testing) *Preemption results suggests correlation with low risk of CMV recurrence in D+/R- group *3 suggested therapies based on results: (1) preemptive, since in this study the overall incidence of CMV DNAemia was similar, but symptomatic CMV was less than with prophylaxis; (2) extended prophylaxis to 6–12 months (26, 27) or (3) prophylaxis to approximate 100 days followed by monitoring and preemptive therapy. *Prophylaxis more effective in reducing CMV occurrence, however less effective in preventing symptomatic disease in D+/R- patients
Hibberd, P. L., Tolkoff-Rubin, N. E., Cosimi, A. B., Schooley, R. T., Isaacson, D., Doran, M., Delvecchio, A., Delmonico, F. L., Auchincloss, H., Jr, & Rubin, R. H. (1992). Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. Transplantation, 53(1), 68–72. https://doi.org/10.1097/00007890-199201000-00013	Define particularly high-risk groups	*Prospective, single center *Cohorts with differing immunosuppressive regimens	*n94 renal transplant recipients *Age >18 years	*D-/R- (N37) were at no risk for CMV *Antivirals are necessary to prevent CMV in CMV seropositive recipients *Antiviral strategies are necessary in CMV seropositive patient; however a preemptive strategy would be more cost effective and logistically feasible approach
Hakki M. (2020). Moving Past Ganciclovir and Foscarnet: Advances in CMV Therapy. Current hematologic malignancy reports, 15(2), 90–102. https://doi.org/10.1007/s11899-020-00557-6	This review will discuss recent developments in CMV antiviral agents and non-pharmacologic interventions that may augment the ability to prevent and treat CMV infections in recipients			*Adoptive therapy entails reconstitution of CMV specific T cells by transfusion of donor T cells *IVIG not effective in CMV therapy -*Monoclonal antibody therapy still in development

Stamps, H., Linder, K., O'Sullivan, D. M., Serrano, O. K., Rochon, C., Ebcioglu, Z., Singh, J., Ye, X., Tremaglio, J., Sheiner, P., Cheema, F., & Kutzler, H. L. (2021). Evaluation of cytomegalovirus prophylaxis in low and intermediate risk kidney transplant recipients receiving lymphocyte-depleting induction. Transplant infectious disease: an official journal of the Transplantation Society, 23(4), e13573. https://doi.org/10.1111/tid.13573	*Evaluate if this recently implemented change in CMV prophylaxis strategy based on serostatus has resulted in a change in incidence of post-transplant CMV *Viremia in D-/R- and R+ cohort who received lymphocyte-depleting induction therapy. *Primary outcome was incidence of CMV viremia within first year post transplant. *Secondary outcome includes CMV syndrome incidence (fevers, myalgias, fatigue etc.), biopsy proven CMV, leukopenia or neutropenia, CMV related hospitalization, and biopsy-proven rejection	*Retrospective *pre-post intervention *Single site Cohort: R+ (historic)- received 120 days prophylaxis R+ (experiment)- received less than 120 days prophylaxis D-/R- (historic) received valganciclovir D-/R- (experimental) received valacyclovir	*Adult kidney recipient *Age >18 years *205 patients	*No viremia for D/R- cohort *No significant difference in CMV viremia in R+ groups *No significant difference of CMV syndrome between the groups *No significant difference in cohorts which validates 3 mos CMV prophylaxis as an effective strategy *Results that there is no increased risk of rejection or disease despite a shorter duration of VGCV use *No correlation that aggressive VGCV prophylaxis strategy reduces the incidence of CMV viremia in D-/R- or R+ cohort who received lymphocyte-depleting induction
Kotton, C. N., Kumar, D., Caliendo, A. M., Huprikar, S., Chou, S., Danziger-Isakov, L., Humar, A., & The Transplantation Society International CMV Consensus Group (2018). The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation, 102(6), 900–931. https://doi.org/10.1097/TP.0000000000002191				*Regarding D-/R-, there is minimal risk of CMV infection, and routine prevention of CMV is not necessary *Antiviral prophylaxis against other herpes infections (especially disseminated varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered
David-Neto, Elias (2011, November - 2013, July). Definition of Cut Off for PCR - Quantitative and Antigenemia in the Diagnosis of Cytomegalovirus (CMV) Disease in Serum-positive Kidney Transplant Recipients. Identifier NCT01573039. https://clinicaltrials.gov/ct2/show/NCT01573039?term=CMV+prophylaxis&recrs=e&cond=kidney+transplant&draw=2&rank=2	*Establish a cutoff for viremia, antigenemia detected by PCR and quantitative-to event for CMV disease	*Observational prospective *Randomized parallel	*120 participants *Age 14-75 years *non-probability kidney transplant recipient sample *CMV seropositive	*Seronegative patients receive 90-day GCV prophylaxis *Seropositive patients undergo surveillance for early viremia detection

Schwendinger, M., Thiry, G., De Vos, B., Leroux-Roels, G., Bruhwyler, J, Huygens, A., Ganeff, C., Buchinger, H., Orlinger, K., Pinschewer, D., Monath, T., Lilja, A. A Randomized Dose-Escalating Phase I Trial of a Replication-Deficient Lymphocytic Choriomeningitis Virus Vector-Based Vaccine Against Human Cytomegalovirus, The Journal of Infectious Diseases, Volume 225, Issue 8, 15 April 2022, Pages 1399–1410, https://doi.org/10.1093/infdis/jiaa121	*First in-human Phase I trial to assess the safety and immunogenicity of 3 administrations of the candidate vaccine at ascending doses in healthy seronegative adult volunteers.	*Randomized, double-blind, sequential *Dose-escalation Phase I study *Parallel cohorts	*CMV seronegative *Age 18-45yrs	*Vaccine associated with mild-moderate adverse events *Vaccine was otherwise well tolerated and produced the preferred outcomes
Hookipa Biotech GmbH. (2018, December 12 - 2022, June 22). A Study of CMV Vaccine (HB-101) in Kidney Transplant Patients. Identifier NCT03629080. https://clinicaltrials.gov/ct2/show/study/NCT03629080?term=CMV+prophylaxis&recrs=e&cond=kidney+transplant&draw=2&rank=16	to assess the safety, reactogenicity, immunogenicity, and efficacy of HB-101 in adult patients	*Phase II *Randomized double-blind Interventional parallel	*83 participants *CMV seronegative	
Hoffmann-La Roche. (2012, January 30 - 2016, December 30). A Study on Spermatogenesis in Male Renal Transplant Recipients Receiving Valganciclovir (Valcyte®) Versus Untreated Matched Controls. Identifier NCT01663740. https://clinicaltrials.gov/ct2/show/study/NCT01663740?term=CMV+prophylaxis&recrs=e&cond=kidney+transplant&draw=2&rank=19	*To compare spermatogenesis in male adult renal transplant recipients receiving valganciclovir versus untreated matched controls	*Randomized multicenter prospective interventional study	*59 participants *Males, age 20-50 years	

Table 3: Table of Included Studies.

Title/Author with Full Citation	Strengths and Limitation of Study	Other Comments
Legendre, C. M., Norman, D. J., Keating, M. R., Maclaine, G. D., & Grant, D. M. (2000). Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation. Transplantation, 70(10), 1463–1468. https://doi.org/10.1097/00007890-200011270-00012	*Medical Resource Use (MRU) and costs not standardized across hospital systems *Applicable to French health care context Only analyzed 6month post-transplant period	*Study population did not include D-/R- cohort
Couchoud, C., Cucherat, M., Haugh, M., Pouteil-Noble, C. Cytomegalovirus Prophylaxis with Antiviral Agents in Solid Organ Transplantation: A Meta-Analysis. Transplantation: March 15, 1998 - Volume 65 - Issue 5 - p 641-647	Because not all the authors performed routine viral monitoring, the exact incidence of cytomegalovirus infection could not be assessed for all trials.	To date, there is no evidence to suggest that cytomegalovirus prophylaxis should be prescribed to reduce the incidence of acute or chronic rejection
Puius, Y. A. & Snydman, D. R. (2007). Prophylaxis and treatment of cytomegalovirus disease in recipients of solid organ transplants: current approach and future challenges. Current Opinion in Infectious Diseases, 20 (4), 419-424. doi: 10.1097/QCO.0b013e32821f6026.	*Randomized control study *No clear effect on acute rejection *Sparse data for preemptive therapy *No data on seronegative donor and seronegative recipient	*Strippoli et al. meta analysis, 17.8% patients (64/358) excluded because of early CMV onset (days 0-10) *Endpoints of rejection and mortality not addressed *Prophylaxis relies on costly drugs *Preemption relies on costly testing for CMV monitoring *And the treatments for CMV & rejection are costly *Resistance can occur in the absence of prophylaxis
Boillat Blanco, N., Pascual, M., Venetz, J., Nseir, G., Meylan, P., Manuel, O. Impact of a Preemptive Strategy After 3 Months of Valganciclovir Cytomegalovirus Prophylaxis in Kidney Transplant Recipients. Transplantation: January 27, 2011. Volume 91(2),p 251-255 doi: 10.1097/TP.0b013e318200b9f0	*Data from first period of study collected retrospectively *No control group *Small cohort sample *Strengths were a homogeneous population, prophylactic protocols & follow-up, PCR testing quality, and viral load monitoring schedule	D-/R- patients were excluded

van der Beek, M., Berger, S., Vossen, A., van der Blij-de Brouwer, C., Press, R., de Fijter, J., Claas, E., Kroes, A., loys, C. Preemptive Versus Sequential Prophylactic-Preemptive Treatment Regimens for Cytomegalovirus in Renal Transplantation: Comparison of Treatment Failure and Antiviral Resistance. Transplantation: February 15, 2010 - Volume 89 - Issue 3 - p 320-326 doi: 10.1097/TP.0b013e3181bc0301		The cost effectiveness of both regimens is a relevant aspect in decision making. Costs may vary locally but depend among other things on the number of samples for CMV DNA load measurement, the amount of antiviral medication administered, and the number of admissions for CMV infections
Khoury, J. A. , Storch, G. A. , Bohl, D. L. , Schuessler, R. M. , Torrence, S. M. , Lockwood, M. , Gaudreault-Keener, M. , Koch, M. J. , Miller, B. W. , Hardinger, K. L. , Schnitzler, M. A. & Brennan, D. C. (2006). Prophylactic Versus Preemptive Oral Valganciclovir for the Management of Cytomegalovirus Infection in Adult Renal Transplant Recipients. American Journal of Transplantation, 6 (9), 2134-2143.		*Both options were effective, minimal side effects, and low rates of adverse outcomes *D-/R- & preemption cohorts received acyclovir x100 days post-transplant for herpes prophylaxis *No significant side effects of oral VGCV *No clinical or viral evidence of resistance *Costs evaluation suggests the transplant center may need to absorb the PCR testing and that MCR part D significantly covers VGCV
Hibberd, P. L., Tolkoff-Rubin, N. E., Cosimi, A. B., Schooley, R. T., Isaacson, D., Doran, M., Delvecchio, A., Delmonico, F. L., Auchincloss, H., Jr, & Rubin, R. H. (1992). Symptomatic cytomegalovirus disease in the cytomegalovirus antibody seropositive renal transplant recipient treated with OKT3. Transplantation, 53(1), 68–72. https://doi.org/10.1097/00007890-199201000-00013		*More than 50% of patients transplanted are CMV seropositive *CMV defined as unexplained fever (greater than 38.0 for 3+consecutive days and positive blood or urine sample *Allograft rejection defined as elevation in serum creatinine of at least 0.4mg/dl, usually with reduced urine output and renal biopsy

Hakki M. (2020). Moving Past Ganciclovir and Foscarnet: Advances in CMV Therapy. Current hematologic malignancy reports, 15(2), 90–102. https://doi.org/10.1007/s11899-020-00557-6		*Table 1- anti CMV agents with listed toxicities *Several CMV vaccines are still in Phases I and II pipeline *More randomized studies needed to assess safety & benefit of adoptive immunotherapy and passive immunization as they may be more realistic, viable option *Need to determine if combo therapy is superior to monotherapy
Stamps, H., Linder, K., O'Sullivan, D. M., Serrano, O. K., Rochon, C., Ebcioglu, Z., Singh, J., Ye, X., Tremaglio, J., Sheiner, P., Cheema, F., & Kutzler, H. L. (2021). Evaluation of cytomegalovirus prophylaxis in low and intermediate risk kidney transplant recipients receiving lymphocyte-depleting induction. Transplant infectious disease: an official journal of the Transplantation Society, 23(4), e13573. https://doi.org/10.1111/tid.13573	*Compared to other antivirals, valganciclovir increases neutropenia risk by 263% *Did not evaluate WBC/ANC *R+ cohort had 105 fewer days of exposure which equates to healthcare cost savings *Confounding factors include retrospective design, small sample size, missing data	*Average US cost of 3 mos VGCV prophylaxis costs $3853
David-Neto, Elias (2011, November - 2013, July). Definition of Cut Off for PCR - Quantitative and Antigenemia in the Diagnosis of Cytomegalovirus (CMV) Disease in Serum-positive Kidney Transplant Recipients. Identifier NCT01573039. https://clinicaltrials.gov/ct2/show/NCT01573039?term=CMV+prophylaxis&recrs=e&cond=kidney+transplant&draw=2&rank=2		* Preemptive treatment is suggested

Table 4: Study Evaluation Table.

Results

The results of the integrative review indicate, for cytomegalovirus prophylaxis, there is no common opinion concerning its necessity and efficacy [6]. A search specific to the D-/R- cohort was lacking. Instead, there were far more articles investigating treatment strategies, prophylaxis vs preemption. Though, no strategy proved significantly dominant over the other. Preemption is less costly than prophylaxis, but it requires frequent monitoring and still carries risks of rejection, dysfunction, and infections [7]. Meta-analyses & pooled analyses found no difference in mortality, graft loss, and acute rejection, between prophylaxis vs preemption and none were identified as an independent risk factor of graft loss (Kotton, 2018).

Discussion

The trend in research is primarily focused on high-risk patients, and low risk patients have been insistently lumped into the consensus. It would be beneficial to the patient to avoid unnecessary medications, to minimize the identified risks. That is not to say that other infection risks should not be considered. Antiviral prophylaxis against other herpes infections (especially disseminated varicella and herpes simplex) with acyclovir, famciclovir, or valacyclovir should be considered (Kotton, 2018). It goes without saying that there should be ongoing efforts to investigate the correlation between cell-mediated immunity against CMV and high risk CMV infection [3]. One study estimated that monitoring CMV plasma viral load would have avoided approx. 1/3 of late onset CMV cases, however there are no subsequent

studies that evaluate this in routine clinical practice [8-10,3]. At this point, we can deduce that CMV prevention is not warranted for a low risk CMV seronegative donor/recipient cohort.

Conclusion

All in all, this review makes the case for further exploration into how to achieve this goal. A study can conduct a cost utility analysis to compare QALYs between the generally medicated vs the preemption prophylactic approach. A cost of illness analysis can compare indirect/direct costs. Another option is a cost benefit analysis to investigate the difference in net benefits between both approaches.

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