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CMV Prevention and Treatment in Transplantation: What's New in 2019

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Abstract

Purpose of Review Transplant recipients are at risk for cytomegalovirus (CMV) infection and associated morbidity and mortality. We summarize recently introduced or currently investigated modalities for prevention and treatment of CMV infection in hematopoietic cell (HCT) and solid organ transplant (SOT) recipients.

Recent Findings Letermovir was recently approved for CMV prevention in HCT recipients. Data from real world studies support its role to improve outcomes in this population. Letermovir is currently under investigation for broader patient populations and indications. Maribavir is in late stages of development for CMV treatment and may provide a safer alternative to currently available anti-CMV drugs. Promising CMV vaccine candidates and adoptive cell therapy approaches are under evaluation. CMV immune monitoring assays are predicted to play a more central role in our clinical decision making.

Summary In recent years, major advances have been made in CMV prevention and treatment in transplant recipients. Rigorous research is ongoing and is anticipated to further impact our ability to improve outcomes in this population.

Keywords Cytomegalovirus (CMV) · Hematopoietic cell transplant (HCT) · Solid organ transplant (SOT) · Cell-mediated immunity (CMI) · Prophylaxis · Preemptive treatment

Introduction

Cytomegalovirus (CMV) infection is the most significant viral infection in hematopoietic cell and solid organ transplant recipients and is associated with increased mortality [1–4]. In addition to the direct impact of CMV end-organ disease (EOD), CMV is associated with increased incidence of opportunistic infections, graft-versus-host disease (GVHD) in hematopoietic cell transplant (HCT) recipients [5], allograft loss in solid organ transplant (SOT) recipients [6], and immune tolerance in liver transplantation [7].

A major recent advance in the field is the FDA approval of letermovir (Prevymis™) for CMV prevention in HCT recipients in November 2017 [8]. In the therapeutic area, two phase 3 studies of Maribavir for treatment of CMV are more than half accrued. In the diagnostic area, several assays measuring CMV cell mediated immunity are available as an adjunct tool to guide clinical decisions [9]. Progress has also been made in the standardization of the quantitation of CMV viral load [10], and the acceptance of CMV viral load as a surrogate endpoint by the FDA is a milestone for the clinical development of future drugs for the treatment or prevention of CMV [11].

In this review, we summarize these recent advances, their clinical implications, and potential future directions.

Prophylaxis

Universal post-transplant prophylaxis with valganciclovir or ganciclovir ranging from 3 to 12 months is widely adopted for high-risk SOT recipients [12] and has demonstrated a significant reduction in the risk of CMV disease and of all-cause mortality [13]. A meta-analysis comparing prophylaxis with

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preemptive therapy in SOT demonstrated that prophylaxis and preemptive strategies were both effective in reducing the incidence of CMV disease; however, no direct comparison could be made [14]. In a recent multi center randomized control study in donor seropositive/recipient seronegative liver transplant recipients, patients treated preemptively had significantly less CMV disease compared to those receiving prophylactic valganciclovir [15]. In the recently published American Transplant Society guidelines for CMV management in SOT recipient, both prophylaxis and preemptive therapy are given similar grade of recommendation in various scenarios [16].

Studies demonstrating the negative impact of CMV infection on survival after HCT in the era of preemptive therapy [1, 3] provide supportive evidence that prophylaxis should be the preferred strategy in HCT. However, the toxicities of DNA polymerase inhibitors ganciclovir, valganciclovir, foscarnet, and cidofovir preclude their use as prophylaxis in HCT. Ganciclovir and valganciclovir are associated with myelosuppression [17] while foscarnet and cidofovir with nephrotoxicity and electrolyte imbalance [18, 19]. In a randomized trial in HCT, ganciclovir prophylaxis for the first 100 days failed to show a survival benefit and was associated with substantial neutropenia [20].

Over the last decade, three anti-CMV antivirals (maribavir, brincidofovir, and letermovir) have been evaluated for CMV prevention in HCT. Maribavir, an inhibitor of UL97/threonine kinase, failed to demonstrated a benefit over placebo at a dose of 100 mg BID in phase 3 trials in HCT [21] and liver transplant recipients [22]. Brincidofovir (CMX001), an orally bioavailable conjugated nucleotide analog of cidofovir also failed to show an advantage over placebo through week 24 post-HCT and was associated with unacceptable gastrointestinal toxicity [23]. Consequently, further development of brincidofovir for CMV prophylaxis or treatment was terminated.

A major advance in CMV prevention has been the approval of letermovir in November 2017. Letermovir is a first in class, highly potent, CMV-specific terminase enzyme inhibitor which inhibits CMV replication by binding to components of the terminase complex (UL51, UL56, or both) [24]. Since there is no human analogue of the CMV terminase complex, no human toxicity is predicted. In a phase 3 randomized, double blind placebo-controlled trial of CMV-seropositive HCT recipients, letermovir prophylaxis significantly reduced the risk of clinically significant CMV infection defined as initiation of preemptive therapy for viremia or CMV end-organ disease (37.5% in letermovir arm versus 60.6% in placebo arm, $p < 0.001$).All-cause mortality at week 24 was lower in letermovir recipients (10.2%) versus placebo (15.9%, $p < 0.03$). At week 48, a persistent numerical survival advantage was found for letermovir recipients (20.9%) compared to placebo recipients (25.5%) though the difference was not significant. Letermovir was not associated with myelosuppression, making it feasible to start prior to neutrophil engraftment. Side effects were mild and included mainly vomiting, edema, and mild cardiac arrhythmias [25]. In a post-hoc analysis, letermovir recipients who developed clinically significant CMV infection had improved survival compared to placebo recipients [26].

In our center, adoption of letermovir prophylaxis has drastically reduced the need for preemptive therapy for CMV even in high-risk patients such as recipients of cord blood or T cell depleted allografts. Patients on letermovir require the addition of acyclovir for prevention of herpes simplex virus and Varicella zoster virus. Letermovir is an inducer of cytochrome P450 (CYP)3A, and an inhibitor of CYP2C8 and organic anion transporting polypeptide (OATP)1B and therefore increases the levels of calcineurin inhibitors (CNI) [27]. Dose modification is established for patients receiving cyclosporin A. In our clinical experience, the increase in CNI levels is mild and compensated for by adjusting doses of CNI based on levels, which is the standard of care.

Emergence of resistance during letermovir prophylaxis was rare in the phase 3 study and mapped on codons 231 to 369 of the UL56 gene [28]. The mutation C325Y has been reported in clinical isolates [29]. These mutations are not associated with cross-resistance to other CMV-antivirals. Genotypic assays for detection of letermovir resistance have become available, and continued vigilance is required to assess the frequency and circumstances under which resistance emerges in the real-world setting.

In the phase 3 study, patients that developed CMV infection after discontinuing letermovir had baseline risk factors such as HLA-mismatched donor, umbilical cord blood or T cell-depleted allograft or graft versus host disease (GVHD) requiring immunosuppression [30] providing supportive evidence that prolonged prophylaxis may be beneficial for these patients. A randomized study is currently accruing to evaluate the benefit of letermovir prophylaxis for 3 versus 6 months in high-risk patients (NCT03930615). Letermovir prophylaxis is also currently being evaluated in other populations including a phase 2 open label study in pediatric HCT (NCT03940586), and a phase 3 randomized study with valganciclovir as comparator in kidney transplant recipients (NCT03443869).

Another potential use of letermovir is in secondary prophylaxis for patients that require CMV suppression after completing preemptive therapy. A small observational study of 35 high-risk patients showed promising results [31]. We are currently conducting a single-center phase 2 study of letermovir as secondary prophylaxis at our institution.

Vaccines

While vaccination is an attractive strategy in transplantation, patients who will benefit most from vaccines are those that are

least likely to respond to vaccines (for example recipients of T cell depleted HCT or those with GVHD and immune suppression). Protective immunity may differ between HCT and SOT recipients. Neutralizing antibodies prevent cell to cell CMV transmission and thus, are important in prevention of primary infection and are likely important for CMV protection in donor seropositive/recipient seronegative SOT recipients. The CMV envelope glycoprotein gB plays a role in host cell entry, cell to-cell virus transmission, and fusion of infected cells [32]. In liver and kidney transplant recipients, a gB targeted vaccine showed similar rates of viremia compared to placebo but increased anti-gB levels which were correlated with decreased duration of viremia and shortened treatment duration [33]. The protective effect elicited by the gB vaccine may not be dependent solely on neutralizing antibodies [34].

In HCT, CMV-specific T cells are required for protective immunity [35]. While the exact target repertoire is not well defined, presence of EI- and pp65- specific T cells correlates with protection [36].

The ASP0113, a bivalent plasmid-DNA vaccine composed of two plasmids encoding pp65 and gB failed to show a benefit over placebo in HCT or SOT recipients [37] and has not been developed further.

The CMV PepVax is a chimeric peptid-based vaccine composed of covalently linked pp65 and the helper T cell epitope P2 (from tetanus toxin), adjuvanted with PF03512676 (a Toll-like receptor 9 agonist). In a phase 1b randomized trial of CMV-seropositive HCT recipients, the vaccine was safe and well tolerated and achieved virologic endpoints and relapse-free survival [38]. A larger phase 2 placebo-controlled trial of PepVax in HCT is ongoing (NCT02396134).

The Triplex CMV vaccine is based on a modified vaccinia Ankara (MVA) vector encoding three full-length highly recognized CMV antigens: pp65, IE1-exon4, and IE2-exon5. Safety and tolerability was demonstrated in healthy adults [39] and clinical trials are ongoing in HCT recipients and donors.

The HB-101 vaccine is based on a recombinant lymphocytic choriomeningitis virus (rLCMV) vector expressing pp65 and a truncated isoform of gB. A randomized, placebo-controlled phase 2 trial in donor seropositive/recipient seronegative kidney transplant candidates is currently ongoing (NCT03629080). Ongoing vaccine studies are summarized on Table 1.

Treatment

Preemptive therapy (PET) has been the most common approach to CMV management in HCT and has effectively reduced rates of CMV end-organ disease and associated mortality [40, 41]. CMV viral load thresholds for initiation of PET are not well established; however, most centers use a risk-adapted approach where PET is initiated at lower viral loads for high-risk patients (mismatched donors or receipt of T cell depleting agents). Although currently available antivirals are effective for CMV treatment, safer alternatives are needed.

Maribavir is currently in clinical trials for CMV treatment. Maribavir, a CMV selective inhibitor of UL97 threonine kinase, interferes with viral synthesis, packaging, and egress of virions from the nucleus [42]. Maribavir has an excellent oral bioavailability and is not associated with myelosuppression or nephrotoxicity [43]. Two recently completed studies of maribavir (dosing from 400 to 1200 mg BID) have shown promising results for treatment of CMV in HCT and SOT. For preemptive treatment, maribavir had comparable efficacy with valganciclovir. Twenty-two percent (22/98) of those in the maribavir arm versus 18% (5/28) in the valganciclovir arm developed CMV recurrence. There were more GI adverse events (23%) and dysgeusia (40%) in the maribavir arm compared with valganciclovir (10–15% and 3%, respectively). In contrast, neutropenia was less common in the maribavir (5%) versus valganciclovir arm (18%) [44]. A phase 3 study in HCT recipients is currently ongoing (NCT02927067).

Treatment of resistant CMV

The terms “resistant” or “refractory” CMV infection are used in clinical practice for infections that fail to respond to commercially available antivirals. CMV anti-viral resistance ranges from 1 to14% in certain high-risk HCT recipients [45]. Similar rates have been reported in SOT recipients [46]. Mortality rates are high in patients with resistant CMV [47, 48]. Recently, consensus definitions of resistant and refractory CMV were established [49]. In most patients with ganciclovir resistance, mutations are present on the UL97 kinase clustered at codons 460, 520, and 590 to 607 [50]. CMV that is ganciclovir resistant due to mutations in UL97 remains susceptible to foscarnet and cidofovir. Viral UL54 DNA polymerase gene mutations can confer cross-resistance to the traditional CMV polymerase inhibitors ganciclovir, foscarnet, and cidofovir. UL54 mutations cluster in certain functional domains resulting in distinct resistance phenotypes [50]. In general, mutations conferring ganciclovir and cidofovir cross-resistance map to the exonuclease and thumb domains and do not confer foscarnet cross resistance [51]. In contrast, foscarnet resistance mutations tend to cluster in different structure domains, typically confer 3–5-fold increase in IC50 and may confer a low-grade ganciclovir ± cidofovir cross-resistance [50].

In a phase 2 study, maribavir showed promising results for treatment of resistant or refractory (R/R) CMV in HCT or SOT recipients. Overall, 67% of patients with R/R CMV achieved virologic suppression within 6 weeks of treatment. Of these, 35% had a recurrent CMV infection. UL97 mutations

Table 1 Ongoing clinical trials evaluating CMV therapeutics and laboratory assays

	Trial identifier no.	Sponsor	Product name	Trial description	Trial status
Drugs	NCT03930615	Merck Sharp & Dohme Corp	Letermovir	Phase 3 to evaluate duration of prophylaxis in HCT recipients	Recruiting
	NCT03940586	Merck Sharp & Dohme Corp	Letermovir	Phase 2 to evaluate prophylaxis in pediatric HCT recipients	Recruiting
	NCT03728426	Dana Farber Cancer Center + Merck Sharp & Dohme Corp	Letermovir	Phase 2 to evaluate treatment of refractory or resistant CMV in HCT/SOT/other immune-compromised	Recruiting
	NCT03443869	Merck Sharp & Dohme Corp	Letermovir	Phase 3 to evaluate prophylaxis for kidney transplant recipients	Recruiting
	NCT02927067	Shire	Maribavir	Phase 3 as preemptive treatment for HCT recipients	Recruiting
	NCT02931539	Shire	Maribavir	Phase 3 as treatment for refractory or resistant CMV in HCT/SOT recipients	Recruiting
Vaccines	NCT02396134		CMVPepVax	Phase 2 in R+ HCT recipients	Recruiting
	NCT01877655	Astellas Pharma Global Development, Inc. and Vical	TransVax (ASP0113)	Phase 3 in R+ HCT recipients	Completed, results announced
	NCT02506933	City of Hope Medical Center	Triplex (CMV-MVA)	Phase 2 in R+ HCT recipients	Active, not recruiting
	NCT03560752	City of Hope Medical Center	Triplex (CMV-MVA)	Phase 2 in HCT donors	Recruiting
	NCT03354728	City of Hope Medical Center	Triplex (CMV-MVA)	Phase 1/2 in pediatric R+ HCT recipients	Recruiting
	NCT03383055	Masonic Cancer Center, University of Minnesota	Triplex (CMV-MVA)	Phase 1 in autologous HCT	Recruiting
	NCT03629080	Hookipa Biotech	HB-101	Phase 2 in R-D+ kidney transplant candidates	Recruiting
Adoptive cytotoxic T cell therapy	NCT03266640	New York Medical College	Donor-derived CMV-specific CTL	Phase 2 single arm in pediatric and young adult HCT recipients for treatment of refractory CMV	Recruiting
	NCT00673868	Milton S. Hershey Medical Center	Donor-derived CMV-specific CTL	Phase 1 pediatric and adult recipients of T cell depleted HCT as CMV prophylaxis	Completed not published
	NCT03004261	Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine	Donor-derived CMV-specific CTL	HCT recipients as CMV treatment	Recruiting
	NCT00880789	Baylor College of Medicine	Cord blood-derived CMV + adenovirus CTL	HCT recipients as prophylaxis	Completed
	NCT02210078	M.D. Anderson Cancer Center	Donor-derived CMV-specific CTL	Phase 2 in HCT recipients as CMV treatment	Recruiting
	NCT01945814	Children's Research Institute	Donor-derived CMV + EBV + adenovirus CTL	Phase 1 in HCT as prophylaxis or treatment	Recruiting
	NCT01923766	Children's Research Institute	Cord blood-derived CMV + EBV + adenovirus CTL	Phase 1 in HCT as prophylaxis or treatment	Active, not recruiting
	NCT02210065	M.D. Anderson Cancer Center	Autologous CMV-specific CTL	Phase 2 in HCT as preemptive CMV treatment	Completed
	NCT03665675	Ohio State University Comprehensive Cancer Center	Donor-derived CMV-specific CTL	Phase 1 as treatment in HCT and SOT	Recruiting
	NCT01646645		Donor-derived CMV specific CTL	Phase 2 as treatment in HCT	Recruiting

Table 1 (continued)

	Trial identifier no.	Sponsor	Product name	Trial description	Trial status
		Atara Biotherapeutics with Memorial Sloan Kettering Cancer Center			
	NCT03594981	Children's Research Institute	Cord blood-derived multi-virus (CMV, EBV, BKV and adenovirus)	Phase1/2 in HCT as prophylaxis or treatment	Recruiting
	NCT01535885	Medical College of Wisconsin	Donor-derived CMV + EBV + adenovirus CTL	Phase 1 in HCT as prophylaxis	Recruiting
	NCT02136797	Atara Biotherapeutics with Memorial Sloan Kettering Cancer Center	Third party CMV-specific CTL	Phase 2 as treatment in HCT	Recruiting
	NCT02985775	Peking University People's Hospital	Donor-derived CMV-specific CTLs	Phase 1/2 as preemptive treatment in HCT	Recruiting
	NCT02510404	Children's Research Institute	Third party CMV + EBV + adenovirus CTL	Phase 1 in patients before HCT with active viral infection	Active, not recruiting
	NCT02510417	Children's Research Institute	Third party CMV + EBV + adenovirus CTL	Phase 1 as treatment in HCT	Recruiting
	NCT02108522	ViraCyte	Third party multi virus (CMV + EBV + adenovirus, + JC virus + BKV + HHV6	Phase 1 as treatment in HCT	Active, not recruiting
	NCT02532452	Children's Hospital Medical Center, Cincinnati	Third party multi virus (CMV, EBV, BKV and Adenovirus)	Phase 2 as treatment in immune-compromised including HCT	Recruiting
	NCT02048332	Children's Hospital Medical Center, Cincinnati	Donor derived multivirus (CMV, EBV, BKV and Adenovirus)	Phase 1/2 as treatment in HCT	Recruiting
Immune-assays	NCT02382211	Oxford Immunotec	T-SPOT	Kidney transplant recipients to assess CMI dynamics (prospective observational)	Completed
	NCT02538172	University of Lausanne Hospitals	T-Track CMV assay	RCT in SOT recipients for d/c of prophylaxis	Recruiting
	NCT02156479	Lophius Biosciences GmbH	T-Track CMV assay	HCT recipients to assess CMI dynamics (prospective observational)	Completed
	NCT02784756	University Health Network, Toronto	Quantiferon-CMV	Prospective interventional in SOT recipients for decision to give prophylaxis	Recruiting
	NCT03924219	Vanderbilt University Medical Center + ViraCor Laboratories	ICS	Pediatric SOT recipients to assess infection risk (prospective observational)	Recruiting
	NCT01558037	Northwestern University + ViraCor Laboratories	ICS	SOT recipients	Completed

CMV cytomegalovirus, *HCT* hematopoietic cell transplant, *SOT* solid organ transplant, *R* recipient CMV serostatus, *D* donor CMV serostatus, *CTL* cytotoxic T cells, *EBV* Epstein Barr virus, *BKV* BK virus, *HHV6* human herpes virus 6, *CMI* cell-mediated immunity, *ICS* intracellular cytokine staining

conferring maribavir resistance were found in a substantial proportion of patients who developed recurrence while on maribavir. Recurrence was more common in patients with continued immunosuppression underscoring the importance of immune recovery for long-term protection from CMV [52]. A phase 3 study comparing maribavir to the best available treatment in transplant recipients with R/R CMV is approximately 70% accrued at this time (NCT02931539).

The clinical experience with letermovir for treatment is limited. Small proof of concept studies and case reports has shown a virologic effect [53, 54]. A low genetic barrier to resistance was observed in vitro [28] raising concerns about emergence of resistance in a setting of high-grade viral replication. Case series of HCT and SOT recipients with refractory CMV, using variable doses and duration of letermovir, showed mixed virologic and clinical responses and emergence of resistance [55, 56]. A study of letermovir treatment for patients experiencing refractory or resistant CMV infection or disease with concurrent organ dysfunction is ongoing (NCT03728426).

Adoptive Cytotoxic T Cells (CTL) Immune Therapy

Lack of CMV-specific T cells is a risk factor for CMV disease [57], and restoration of CMV T cell immunity correlated with protection against CMV disease [58]. Multiple studies have provided proof of concept that adoptive cell therapy can restore CMV immunity using a variety of cellular products, for different indications (prophylaxis vs. preemptive therapy vs. treatment of CMV disease) in diverse HCT types. The lack of appropriate control groups in these studies preclude comparisons and limit the applicability in the clinical setting. In addition, logistic hurdles and cost of cellular therapy are considerable [59–61]. Ongoing clinical trials are summarized in Table 1.

CMVpp65-specific donor-derived CTLs given for preemptive therapy along with antiviral therapy in high-risk haploidentical HCT recipients reduced the risk of persistent and late CMV infection and improved 1-year overall survival compared to matched controls [62].

An alternative approach to donor-derived CTL is "third party" CTL generated from unrelated donors partially matched to the recipient. A bank of cellular products covering the most common HLA alleles could provide "off the shelf" cellular therapy.

In a small study from our center, 73.3% patients responded to third party CMV-CTL [63]. Unlike donor-derived CTL that may persist in the recipient for up to 10 years, third-party T cells do not achieve durable engraftment and are commonly detected only for about 90 days post administration. Thus, multiple infusions may be required to maintain therapeutic effect [64].

Studies of third party CTL with specificity against multiple viruses (EBV, CMV, adenovirus, HHV-6, and BK) have also showed safety and efficacy in small uncontrolled studies in HCT recipients [65] and several prospective multicenter trials are in progress.

The therapeutic use of CTLs has been less extensively studied in SOT recipients. CMV-specific T cell response is often attenuated due to immunosuppressive therapy, and the importance of CMV immune-reconstitution has been demonstrated in this population [66]. SOT recipients are not tolerant to donor-derived CTL [67]; nevertheless, successful treatment of resistant/refractory CMV infection in SOT recipients with CMV-specific CTLs has been demonstrated in case reports [68–71], and there is increasing interest in "off the shelf" CTLs using HLA-matched third-party banked cells for SOT.

Assessment of CMV Immune Reconstitution

Quantitative assessment of CMV Cell-mediated immunity (CMI) reconstitution may assist in risk stratification and enable an individualized approach for initiation or discontinuation of prophylaxis and preemptive therapy [9]. CMI assays in clinical trials are listed in Table 1.

The enzyme-linked immunosorbent spot (ELISPOT) assays quantify both CD4+ and CD8+ T cells producing IFN-γ in response to CMV by measuring IFN-γ as spot forming colony (SFC)/cells. Two ELISPOT assays (T-Track ® CMV Lophius Biosciences, Germany, and T-SPOT.CMV ®, Oxford Immunotec, UK) are currently marketed in Europe and used as a laboratory developed test (LDT) in the USA. Several recent studies in kidney transplant recipients support the clinical utility of ELISPOT assays at various time points. A positive CMI response 1 month following transplant was associated with protection against CMV reactivation [72], and a negative response has shown to predict the risk for CMV viremia at 3-month post-transplant [73, 74]. Pre-transplant evaluation of CMI using ELISPOT was highly predictive of post-transplant CMV outcomes in SOT recipients [75, 76].

In a prospective observational trial in HCT recipients, results of the ELISPOT assay correlated with clinically significant CMV infection [77].

The Quantiferon-CMV® assay (Qiagen Ltd) is a commercially available kit that uses enzyme-linked immunosorbent assay (ELISA) to detect IFN-γ secretion by CD8 T cells after peptide stimulation. It is simple and rapid and thus may be easily incorporated in clinical settings. Studies in SOT recipients support the utility of Quantiferon-CMV assay to predict risk for CMV disease [78, 79], assist in decision making for safe discontinuation of antiviral treatment [80], and optimize

duration of prophylaxis in lung transplant recipients [81]. A study is ongoing to evaluate the utility of Quantiferon-CMV as a tool to guide administration of primary prophylaxis (NCT02784756).

Limitations of the IFN-γ-based assays include the difficulty to interpret the results in cases of negative mitogen controls representing T helper cell activity [82], but the utility of these assays in these cases merits further evaluation. IFN-γ-based assays cannot be performed in profoundly lymphopenic patients.

Intracellular cytokine staining (ICS) provides functional immunophenotyping and can detect multiple cytokines and cell surface markers and differentiate T cell phenotypes [83–86]. Until recently, ICS was only available in research setting. Currently an ICS-based assay is offered by Viracor (Eurofins, Lee's Summit, MO, USA), and two clinical trials to evaluate its clinical use in SOT are ongoing (NCT03924219, NCT01558037).

In summary, a growing clinical experience to date supports the clinical utility of CMV monitoring immune assays as an adjunct tool in the management of CMV in transplantation. Controlled studies are critical for validation of these assays, establishing relevant cut offs and determining optimal frequency of monitoring and the type of assay best suited for each patient population.

Summary

It has taken a village of scientists, clinicians, and industry over 30 years to catch up with the "troll of transplantation". The year 2019 is an exciting time for CMV. After more than two decades of no new anti-CMV antivirals, letermovir, a first in class, CMV-terminase inhibitor, was approved for CMV prevention in HCT recipients. Real-world data to date supports the efficacy of letermovir in preventing CMV infection without any new safety concerns. Letermovir provides us a powerful tool to assess the impact of CMV prevention on long-term outcomes such as survival beyond the duration of prophylaxis [26].

Maribavir is in late stages of development for CMV treatment and may provide a safer alternative to DNA polymerase inhibitors for treatment of CMV. Promising CMV vaccine candidates and adoptive cell therapy approaches are under evaluation. The optimal way to incorporate cellular therapies in the era of letermovir remains open. CMV immune monitoring assays are predicted to play a more central role in our clinical decisions. The ultimate challenge will be to close the survival gap of disadvantaged CMV R/D serostatus in transplantation. While there will be challenges along the way, the outlook is clearly positive for CMV in transplantation.

Compliance with Ethical Standards

Conflict of Interest Anat Stern declares that she has no conflict of interest.

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