Title

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Ocular outcomes after treatment of cytomegalovirus (CMV) retinitis using adoptive immunotherapy with CMV-specific cytotoxic T-lymphocytes

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Abstract

Objective: To describe ocular outcomes in eyes with CMV retinitis treated with adoptive immunotherapy using systemic administration of CMV-specific cytotoxic T-lymphocytes (CMV-CTLs)

Design: Retrospective cohort study

Subjects: Patients with active CMV retinitis evaluated at a tertiary care academic center

Methods: Treatment of CMV retinitis with either CMV-CTLs or standard-of-care therapy with systemic and/or intravitreal antiviral therapy.

Main Outcome Measures: The electronic medical record was reviewed to determine baseline characteristics, treatment course, and ocular outcomes, including: best-corrected visual acuity (BCVA), treatments administered (CMV-CTLs, systemic antivirals, intravitreal antivirals),

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resolution of CMV retinitis, any occurrence of immune recovery uveitis, cystoid macular edema, and/or retinal detachment.

Results: Seven patients (of which 3 had bilateral disease; i.e. 10 eyes) were treated with CMV-CTLs, while 20 patients (of which 6 had bilateral disease; ie. 26 eyes) were treated with standard-of-care. Indications for CMV-CTL therapy included: persistent or progressive CMV retinitis (71.4% of patients), CMV *UL54* or *UL97* antiviral resistance mutations (42.9%), side effects or toxicity from antiviral agents (57.1%), and/or patient intolerance to longstanding, frequent antiviral therapy for persistent retinitis (28.6%). Two patients (28.6%, 4 eyes (40%))) received CMV-CTL therapy without concurrent systemic and/or intravitreal antiviral therapy for active CMV retinitis, while 5 patients (71.4%; 6 eyes (60%)) continued to receive concurrent antiviral therapies. Resolution of CMV-retinitis was achieved in 9 (90%) eyes treated with CMV-CTLs, with BCVA stabilizing (4 eyes, 40%) or improving (4 eyes, 40%) in 80% of eyes over an average follow-up of 33.4 months. Rates of immune recovery uveitis, new onset cystoid macular edema, and retinal detachment were 0%, 10% (1 eye), and 20% (2 eyes). These outcomes compared favorably to a non-randomized cohort of eyes treated with standard-of-care therapy alone, despite potentially worse baseline characteristics.

Conclusion: CMV-CTL therapy may represent a novel monotherapy and/or adjunctive therapy for CMV retinitis, especially in eyes that are resistant, refractory, or intolerant of standard-of-care antiviral therapies. More generally, there may be a role for adoptive cell transfer and adoptive immunotherapy in refractory CMV retinitis. Larger, prospective, randomized trials are necessary.

Precis:

This small, retrospective, observational study provides support for further study of adoptive immunotherapy with systemic administration of CMV-specific cytotoxic T-lymphocytes as monotherapy and/or adjunctive therapy for CMV retinitis.

Cytomegalovirus (CMV) retinitis remains the number one opportunistic ocular infection, and the major cause of vision loss in patients with Human Immunodeficiency Virus (HIV) / Acquired Immune Deficiency Syndrome (AIDS) despite tremendous advances in the treatment of HIV.[1–3] Widespread use of combined antiretroviral therapy (cART) for HIV/AIDS has shifted the epidemiology of CMV retinitis such that non-HIV patientsrepresent an increasing share of those afflicted with CMV retinitis.[2–4] Causes of CMV retinitis amongst patients without HIV include: advanced age, underlying malignancy, autoimmune disorder or organ/bone marrow transplantation requiring systemic immunosuppression, administration of local corticosteroids, diabetes mellitus, or immune disorders such as Good syndrome.[5] In patients with a history of bone marrow or solid organ transplant, insufficient stem cell engraftment or use of immunosuppressive therapies for treatment or prophylaxis of graft rejection or graft-versus-host disease results in T-cell immunosuppression that predisposes to CMV retinitis. Recent studies suggest that despite tremendous improvements in outcomes, CMV retinitis continues to be a sight-threatening condition with the potential for significant visual loss and blindness.[6–7]

CMV retinitis treatment centers upon both antiviral therapy and immune reconstitution, when possible. Antiviral therapies include systemic ganciclovir, valganciclovir, foscarnet, cidofovir, letermovir, and/or off-label leflunomide and intravitreal ganciclovir, foscarnet,

and/or cidofovir. Though effective, each of these agents has side effects and dose-limiting toxicities that can limit their utility in certain patients. Moreover, mutations in the virus, such as *UL54* or *UL97*, can render the virus resistant to one or most of these therapies. Resistance has been reported in 25 – 30% of patients at 9 months of therapy.[1,3–4]

Patients who are either intolerant of or refractory to standard-of-care therapy with systemic and/or intravitreal antivirals are thus left with limited options to manage their sight-threatening infections. Here, we present findings from 10 eyes of 7 patients treated with a novel immunotherapy for CMV retinitis: CMV-specific cytotoxic T-lymphocytes (CMV-CTLs) developed at Memorial Sloan Kettering Cancer Center (MSKCC). CMV-CTLs represent adoptive cell transfer, i.e. the transfer of donor cells into a patient, in this case with the objective of providing a CMV-specific immune response to clear the infection. CMV-CTLs have been reported to be effective in treating allogenic stem cell transplant patients with refractory CMV viremia.[8–10] We have previously reported the case of a single patient with CMV retinitis treated with CMV-CTLs. In that report, we described the use of CMV-CTLs, *without concurrent antiviral treatment*, to manage a patient with multi-drug-resistant CMV retinitis, resulting in resolution of his CMV retinitis and CMV viremia.[11] This paper presents the ocular outcomes of an expanded cohort of 10 eyes of 7 patients that underwent treatment of CMV retinitis using CMV-CTLs at MSKCC, with ophthalmologic evaluation and management at Weill Cornell Medical College (WCMC) Department of Ophthalmology. To our knowledge, this manuscript represents the first case series of adoptive cell transfer or immunotherapy for ocular disease.

Methods

This study was a retrospective chart review of patients with active CMV retinitis who were evaluated at the WCMC Department of Ophthalmology from 2007–2019. This study was approved by the WCMC Institutional Review Board (IRB) and was performed in a fashion compliant with the Health Insurance Portability and Accountability Act and the tenets put forth in the Declaration of Helsinki. The CMV retinitis patients in the CMV-CTL group reported herein are amongst a larger population of patients in a prospective study of CMT-CTL treatment for CMV infection (the vast majority of which did not have retinitis) at MSKCC, and thus MSKCC had obtained IRB approval for such a prospective study at their institution. Moreover, MSKCC obtained an Investigational New Drug (IND) approval was obtained from the United States Food and Drug Administration (FDA) for each patient treated with CMV-CTLs, including those with CMV retinitis. WCMC common provides care for patients with non-oncologic retinal conditions at MSKCC, and thus, patients with CMV retinitis (with or without CMV-CTL therapy) were referred to WCMC for ophthalmologic care. The study herein is an unplanned retrospective analysis of patients with CMV retinitis evaluated at WCMC, and approval for the study was obtained from the IRB at WCMC.

Electronic medical records of patients seen by our Department of Ophthalmology between 2007 and 2019 with diagnoses of chorioretinal inflammation or CMV disease (as defined by the relevant ICD9/ICD10 codes) were reviewed to identify those patients who met the following inclusion criteria: (1) age 18 years or older, (2) active CMV retinitis, as

determined by clinical evaluation by a retina specialist (MPG, SK, RVPC, AO, DJD), and (3) at least 1 month of ophthalmic follow-up. Given CMV retinitis is a clinical diagnosis, the treating retina specialist's assessment was employed both for inclusion criteria for CMV retinitis as well as study outcome criteria (such as resolution, recurrence, etc. of retinitis). Clinical diagnosis of CMV retinitis was made based upon characteristic clinical findings of full-thickness necrotizing retinitis in the setting of immunocompromise, with supporting evidence from ophthalmic imaging and/or aqueous fluid viral polymerase chain reaction (PCR), as available. Given the retrospective nature of this study, imaging was not consistently available for inclusion in this study. The control group included eyes treated with standard-of-care therapies (e.g. intravitreal and/or systemic antiviral therapies and, when relevant, immune reconstitution), and the study group included eyes treated with CMV-CTLs at MSKCC.

Patients who had underwent treatment with CMV-CTLs had been treated at MSKCC as follows. A library of CMV-CTLs was generated at MSKCC as previously described.[10] Briefly, CMV specific T-cells were generated under GMP condition from blood samples obtained from consenting CMV-seropositive, extensively vetted, healthy marrow transplant donors by *in vitro* sensitization with a pool of pentadecapeptides encoding the entire sequence of the CMV pp65 protein and overlapping by 11 amino acids. Each CMV CTL line was HLA by DNA sequencing at high resolution and further characterized to determine the CMV pp65 peptide epitope(s) to which it responds as well as the HLA allele presenting that epitope. Each CMV CTL line was also tested to ascertain its depletion of allo-reactive T-cells, its microbiological sterility, and its lack of mycoplasma or endotoxin, and then cryopreserved.[10]

A large library of CMV-CTLs was thus generated from a number of donors to enable "off-the-shelf" selection of the appropriate CMV-CTL line for each patient referred for CMV-CTL therapy. For each patient with CMV retinitis referred for CMV-CTL therapy, HLA genotyping was performed. The library of CMV-CTLs was then searched to identify an appropriately matched CMV-CTL line, defined as (a) matching the patient at 2 or more HLA alleles and (b) matching the patient ta the specific HLA allele determined to present the CMV pp65 epitope to which the CMV-CTL line responds (i.e. the HLA alleles by which the CMV-CTL is said to be restricted). Peripheral intravenous infusions of CMV-CTLs were administered at a dose of 1×10^6 CMV-CTLs per kilogram under close monitoring at the MSKCC infusion center weekly for three weeks.[10] Logistically, the appropriate CMV-CTL line for a given patient may be selected from MSKCC's CMV-CTL library and then shipped to infusion centers elsewhere for administration to patients. However, this study included only those who underwent ophthalmic evaluation at WCMC. Thus, all patients had received CMV-CTL treatment at MSKCC.

Because the ophthalmic care at WCMC was rendered as medical care and not part of a predetermined study, there were no protocols for ophthalmic evaluation or retinitis treatment for any patients in this study. Ophthalmologic examination and additional treatments such as systemic antivirals or intravitreal antivirals was therefore performed as per the treating clinician's discretion. For patients who responded to the CMV-CTLs and experienced no adverse reactions but still had active CMV retinitis, the series of 3 weekly infusions was

repeated after a two-week break. All patients continue to be followed regularly at the discretion of the clinician. All patients had provided informed consent for each therapy rendered.

In this retrospective study, the electronic medical records were reviewed to collect the following baseline characteristics: age, medical cause of immunosuppression, factors limiting CMV retinitis treatment and indication for referral for CMV-CTLs (e.g., systemic side effects associated with antiviral therapy, resistance to antiviral therapy as determined by labs or clinic notes, progressive CMV retinitis despite maximal systemic/intravitreal antiviral therapy), best-corrected visual acuity (BCVA) with logMAR conversion of Snellen visual acuity, and CD4 count (for patients with HIV/AIDS). The baseline was defined as the last available ophthalmic evaluation prior to CMV-CTL therapy, and the study period was defined as the time period from the baseline visit to the last available follow-up evaluation. The electronic medical records were reviewed to collect the following outcome measures: number of CMV-CTL cycles received, concurrent antiviral therapies given during the study period, resolution of CMV retinitis at final follow-up, recurrence of CMV retinitis (new CMV retinitis activity ≥ 3 months after clinical diagnosis of resolved CMV retinitis), BCVA at final follow-up, and occurrence of any of the following events during the study period: immune recovery uveitis, retinal detachment, fovea-involving cystoid macular edema (CME), and/or death. Statistical analyses included Student's two-tailed t-test for continuous, parametric variables, and Chi-squared or Fisher's exact tests for categorical variables, with $p < 0.05$ taken to be significant.

Results

Twenty seven patients (36 eyes) met inclusion criteria: 7 patients (10 eyes) were treated with CMV-CTLs and 20 patients (26 eyes) were treated with standard-of-care therapies (Figure 1).

Baseline characteristics of patients with CMV retinitis treated with CMV-CTLs.

Seven patients (of which 3 had bilateral retinitis; i.e. 10 eyes) treated with CMV-CTLs met inclusion criteria. The average age was 53.0 years (ranging 26–68 years). All subjects were male. The etiology of immunosuppression was hematologic malignancy with history of stem cell transplant (with ongoing immunosuppressant therapy) in 57.1% of patients (n=4 patients; 5 eyes (50%)), AIDS in 28.6% (n=2 patients; 3 eyes (30%); one of these patients was also receiving chemotherapy for malignancy), and solid organ transplant on immunosuppressive therapy in 14.3% (n=1 patient; 2 eyes (20%)). All patients(n=7 patients; 10 eyes (100%)) had undergone treatment with systemic antiviral agents prior to CMV-CTL treatment. All eyes (and thus all patients)had undergone treatment with one or more intravitreal antiviral agent prior to CMV-CTL therapy. Indications for CMV-CTL therapy included: persistent or progressive CMV retinitis despite systemic and intravitreal antiviral therapy (n=5 patients (71.4%); 7 eyes (70.0%)), persistent CMV viremia despite systemic antiviral therapy with new onset CMV retinitis (n=2 patients (28.6%); 3 eyes(30.0%)), CMV *UL54* or *UL97* mutations rendering resistance to antiviral agents (n=3 patients (42.9%); 6 eyes (60.0%)), side effects or toxicity limiting use of one or more systemic antiviral

agent (n=4 patients (57.1%); 5 eyes (50.0%)), and patient intolerance to longstanding, frequent intravitreal antiviral therapy for persistent retinitis (n=2 patients (28.6%); 4 eyes (40.0%)). All patients had more than one such indication for CMV-CTL therapy. Average baseline BCVA prior to CMV-CTL therapy was logMAR 0.66 (Snellen 20/91), ranging from logMAR 0 (Snellen 20/20) to 2.0 (count fingers). No eyes were light perception or no light perception at baseline. Five eyes (50.0%) had BCVA 20/40 or better, while 4 eyes (40.0%) had BCVA 20/200 or worse (Table 1).

Ocular outcomes for patients with CMV retinitis treated with CMV-CTLs.

Average length of follow-up was 30.0 months (median 20.0 months; range 6.0 – 76.0 months). Four eyes received no additional systemic or intravitreal antiviral therapy while receiving CMV-CTLs (40.0%). Specifically, two eyes (20.0%) received no concurrent systemic or antiviral therapies from the time of CMV-CTL therapy onwards, and two eyes (20.0%) initially received concurrent intravitreal antiviral therapy that was promptly stopped (in the setting of still very active CMV retinitis) due to patient intolerance and refusal. Treatment with third-party-derived CMV-CTLs was well tolerated by all patients. At the last available follow-up visit, 90.0% of eyes (n=9) had achieved resolution of CMV retinitis. The average time to quiescence was 3.6 months. The average durability of the resolution among eyes achieving resolution was 33.4 months (range 3.0 – 74.0 months). Mean BCVA at final follow-up was logMAR 0.59 (Snellen ~20/78) (range 0 (Snellen 20/20) to no light perception). Of note, no eyes were light perception only (0%), while one eye (10%) was no light perception. Four eyes (40.0%) had BCVA 20/40 or better, while 3 eyes (30.0%) had BCVA 20/200 or worse. During the study period, BCVA stabilized or improved in 80% (n=8) of eyes: 40.0% (n=4) were stable, 40.0% (n=4) improved, while 20.0% (n=2) worsened, one in the setting of a retinal detachment. Ocular complications related to CMV retinitis and/or CMV-CTL were infrequently noted throughout the follow-up period, with 2 eyes (20.0%) suffering a retinal detachment and no eyes (0.0%) experiencing immune recovery uveitis. Two eyes (20.0%) developed fovea-involving CME. One eye developed fovea-involving CME after initiation of CMV-CTL therapy, which was managed with topical corticosteroids alone. Another patient had history of CME associated with CMV retinitis which was present prior to CMV-CTLs, likely related to perifoveal CMV retinitis which resolved as the CMV retinitis resolved. For both eyes with CME, there were no associated uveitic features (new or worsening anterior chamber or vitreous cells, vasculitis other than that present in areas of active CMV retinitis, etc.). Over the course of follow-up, 1 patient died due to complications related to his malignancy and its treatment (Table 2–3).

Baseline characteristics and ocular outcomes of patients with CMV retinitis treated with standard-of-care antiviral therapies.

Although extensive studies exist regarding outcomes in patients with CMV retinitis treated with standard of care therapies, the control group of CMV retinitis was included because it was felt to more closely resemble the study population. For example, while the vast majority of data in the literature centers upon CMV retinitis in the HIV population, HIV infection was less commonly encountered in both the CMV-CTL and control groups in this study.Twenty patients (of which 6 had bilateral retinitis; i.e. 26 eyes) were treated with standard-of-care therapies. The average age was 46.2 years (ranging 22–71 years).

The etiology of immunosuppression was hematologic malignancy with history of stem cell transplant (with ongoing immunosuppressive therapy) in 35% of patients (n=7; 10 eyes (38.5%)), hematologic malignancy (without stem cell transplant) in 5% (n=1 patients; 1 eye (3.8%)), AIDS in 55% (n=11 patients; 14 eyes (53.8%)), and solid organ transplant on immunosuppressive therapy in 5% (n=1 patient; 1 eye (3.8%)). Baseline BCVA was on average logMAR 0.46 (Snellen 20/58), with range logMAR −0.12 (Snellen 20/15) to 3.0 (hand motion). No eyes were light perception or no light perception at baseline. Sixteen eyes (38.5%) had BCVA of 20/40 or better, while 3 eyes (11.5%) had BCVA 20/200 or worse. All patients (n=20; 26 eyes (100%)) were treated with systemic antiviral agents. Twenty eyes (76.9%) of 16 patients (80%) were also treated with one or more intravitreal antiviral agents. Average length of follow-up was 34.2 months (range 2–143 months). At final-follow, mean BCVA was logMAR 0.56 (Snellen ~20/73), with range 0 (Snellen 20/20) to no light perception. Of note, one eye (3.8%) was light perception only and one eye (3.8%) was no light perception. Thirteen eyes (50%) had BCVA of logMar 20/40 or better, while 8 eyes (30.8%) had vision 20/200 or worse. Compared to baseline BCVA, final BCVA was stable or improved in 46.1% of eyes (n=12): 15.4% (n=4) were stable, 30.8% (n=8) were improved, and 53.8% (n=14) were worse. At final follow-up, CMV retinitis was resolved in 69.2% of eyes (n=18). Ocular complications related to CMV retinitis included 8 eyes (30.8%) suffering a retinal detachment, 3 eyes (11.5%) experiencing immune recovery uveitis, and 4 eyes (15.4%) developing fovea-involving CME (Table 3).

Representative CMV-CTL case 1.

The patient (ID #2) is a 68-year-old man, previously CMV seronegative, with a history of Wegener's granulomatosis nephropathy status post renal transplant from a CMV seropositive donor, who was on immunosuppression for graft rejection prophylaxis with prednisone, tacrolimus, and mycophenolate. Approximately one year after the transplant, he developed CMV viremia, and by, 2.5 years post-transplant, serum CMV viral load became undetectable. Six months later, i.e. 3 years post-transplant, the patient developed CMV retinitis OU. For over 2 years thereafter, he exhibited persistent and progressive CMV retinitis, despite systemic and intravitreal antiviral therapies. His treatment course included ganciclovir and valganciclovir, the effectiveness of which was limited by presence of the *UL97* CMV mutation conferring resistance to these drugs. Foscarnet and cidofovir were not administered given renal toxicity risk in the setting of prior renal transplant. Leflunomide treatment was limited by the development of peripheral neuropathy. Frequent bilateral intravitreal injections with ganciclovir and foscarnet slowed progression but failed to achieve resolution of CMV retinitis OU. The patient's ophthalmologic course was also complicated by glaucoma that required tube shunt surgery OD, tube shunt revision and cataract extraction OD, tube shunt surgery with cataract extraction OS, a second tube shunt surgery OS, and diode laser cyclophotocoagulation OD. Due to persistent active CMV retinitis for over two years, coupled with CMV antiviral resistance and dose-limiting side-effects and toxicities limiting use of antiviral therapies, the patient was referred for treatment with CMV-CTLs. Visual acuity prior to CMV-CTL therapy was CF OD and 20/300 OS, and there were large area of active CMV retinitis OU (Figure 2A–B). The patient underwent two rounds of 3 weekly infusions of CMV pp65 CTLs. During the first round of infusions, the patient continued to receive once weekly intravitreal injections of

foscarnet and ganciclovir OU. There was noted to be marked improvement in the retinitis OU (Figure 3C–D), though still with large areas of active retinitis. Aqueous CMV PCR was performed OS and improved from 287,000 copies/cc to 29,600 copies/cc. The patient declined further intravitreal antiviral therapy but underwent a second round of CMV-CTLs (i.e. treatment with CMV-CTLs alone). The CMV retinitis continued to consolidate OU (Figure 3E-F), ultimately with resolution of retinitis (including undetectable aqueous CMV PCR), which remained durable at the last available follow-up visit six months later (Figure 3G-H). There were no identified changes to the patient's immunosuppressive therapies for kidney transplant nor overall health which might have contributed to the improvement in his previously longstanding CMV retinitis. There were no episodes of uveitis, cystoid macular edema, or retinal detachment. Visual acuity at final follow-up was stable compared to pre-CMV-CTL therapy OD at CF and improved OS at 20/150 from 20/300.

Representative CMV-CTL case 2.

This previously reported case[11] now with long-term follow-up (ID #6) is a 26-year-old man with a history of pre-B-cell acute lymphoblastic leukemia (ALL) status post allogeneic hematopoietic cell transplant, complicated by graft-versus-host disease requiring immunosuppressant therapy. Several months after the transplant he developed CMV viremia, with the CMV mutation *UL54* mutation conferring resistance to valganciclovir, foscarnet, and cidofovir. Due to persistent systemic CMV infection including esophagitis, stomatitis and vision threatening retinitis despite antiviral therapy, he was referred for CMV-CTL therapy. He developed CMV retinitis in both eyes, which was treated with biweekly intravitreal ganciclovir injections, with modest response OS and no significant response OD. Just prior to CMV-CTL therapy, BCVA was 20/40 OU, and there was active CMV retinitis OU (Figure 3A–B). The patient underwent 2 cycles of CMV-CTL therapy. No intravitreal nor systemic antivirals were administered after initiation of CTL infusions. CMV retinitis gradually consolidated and resolved by 3 months after initiation of CMV-CTL therapy. No changes to the patient's systemic medication regimen nor overall health were identified which may have contributed to the resolution of the patient's previously persistent and longstanding systemic CMV infection nor his CMV retinitis. On last follow-up 76 months after initiation of CMV-CTL therapy, the retinitis remains resolved with no recurrences, and BCVA was 20/20 OU (Figure 3C–D). The patient experienced no immune recovery uveitis, cystoid macular edema, nor retinal detachment during the CMV-CTL course or thereafter.

Discussion

Cytomegalovirus (CMV) is an enveloped, double-stranded DNA virus belonging to the herpes virus family.[3–4] While primary CMV infection may be asymptomatic in an immunocompetent host, CMV causes significant morbidity among the immunocompromised, as these individuals are unable to mount an effective T-cell response against the virus. CMV retinitis is a potentially blinding infection characterized by a full-thickness, necrotizing retinitis.[1–4] Historically, in the pre-cART era, CMV retinitis was primarily encountered among patients with HIV/AIDS, with such patients demonstrating a lifetime CMV retinitis risk of ~30%. The advent and widespread use of cART led to a significant decrease in the rate of CMV retinitis, although patients with a late diagnosis of

HIV or poorly-controlled HIV, especially with CD4 counts < 50 cells/microliter, continue to be afflicted.[2,12] CMV retinitis is also encountered in the non-HIV/AIDS population among other patients with impaired T-cell immunity, especially those with a hematologic malignancy and/or stem cell transplant. The risk of CMV retinitis is further increased in these patients and in patients with solid organ transplants due to the need for potent immunosuppressant therapy for graft-versus-host disease or to prevent graft rejection, respectively.[2] Among allogeneic stem cell transplant recipients, the greatest risk of CMV retinitis is in CMV-positive hosts receiving transplants from CMV-seronegative donors, while the reverse is true for solid organ transplants.[1–4]

Treatment of CMV retinitis centers upon (1) immune reconstitution and (2) antiviral therapy. Systemic antiviral therapies for CMV retinitis include intravenous ganciclovir, oral valganiclovir (the prodrug of ganciclovir), intravenous foscarnet, intravenous cidofovir, and/or intravenous leflunomide (currently not FDA approved for this indication). The use of each of these may be limited by side effects or toxicities, such as myelosuppression from ganciclovir and valganclovir (neutropenia 16%, thrombocytopenia 5%), dose-limiting renal toxicity from foscarnet (10–23%) and cidofovir (24%), and/or peripheral neuropathy from leflunomide. Moreover, intravenous administration can be a limiting factor for patients requiring months or years of antiviral therapy to keep the CMV infection at bay. In addition, mutations in two viral genes of the CMV virus itself confer resistance to antiviral therapy: a mutation in the *UL54* gene confers resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir, while the *UL97* mutation confers resistance to ganciclovir and valganciclovir.[1,3–4]

We previously reported a case of a patient with CMV retinitis and CMV viremia who underwent treatment with CMV-CTLs, without concurrent antiviral therapies. There was a dramatic consolidation and resolution of the both the CMV retinitis and the viremia.[11] This response has remained durable for at least 76 months of follow-up (representative case 2 reported herein). Since that initial patient, an additional small cohort of patients have received CMV-CTL therapy for CMV retinitis that is refractory or intolerant to standard-of-care systemic and/or intravitreal antiviral therapy. These patients with retinitis were treated through a larger, longer-term IRB-approved study at MSKCC of CMV-CTL therapy for CMV infection (of which a very small minority were treated for CMV retinitis), and an IND approval was obtained from the FDA for each patient by MSKCC prior to treatment. Patients with CMV retinitis (with or without CMV-CTL therapy) were frequently sent to WCMC for non-oncologic retinal care. The study reported herein is an unplanned retrospective analysis of patient with CMV retinitis who were evaluated at the Department of Ophthalmology at WCMC. This study aimed to describe the ocular outcomes in this cohort and represents, to our knowledge, the first case series of adoptive cell therapy or adoptive immunotherapy for ocular disease. Our key findings were (1) patients with CMV retinitis treated with CMV-CTL therapy, with or without additional antiviral therapies, achieved resolution of CMV retinitis and (2) rates of ocular adverse events in CMV retinitis treated with CMV-CTLs were similar to those in patients treated with standard-of-care therapy.

Here, we demonstrate that patients treated with CMV-CTLs, with or without additional antiviral therapies, achieved resolution of retinitis and stabilization or improvement in vision. In this small series, 90.0% of eyes achieved resolution and 80.0% maintained or

improved visual acuity. Four eyes (40%; 2 patients (28.6%)) received no other antiviral therapies during all or part of the active CMV retinitis course treated with CMV-CTLs, suggesting that the CMV-CTL therapy itself led to resolution of retinitis in at least some patients. On the other hand, since 6 eyes (60%; 5 patients (71.4%)) were treated concurrently with systemic and/or intravitreal antiviral therapies, it is impossible to parse out whether the standard antiviral therapies, theCMV-CTLs, or bothcontributed to resolution of the retinitis. Chart reviews indicate that systemic and/or intravitreal agents were administered not due to failure of CMV-CTL therapy, but rather they were continued in all patients who agreed and/or were able to continue such therapies. Thus, while some patients achieved CMV retinitis resolution with CMV-CTL therapy alone, prospective, randomized, controlled trials are needed to clarify the efficacy of CMV-CTLs, if any, as compared to standard of care. Moreover, studies are necessary to determine whether adding CMV-CTL therapy as an adjunctive therapy on top of systemic and/or intravitreal antiviral therapies can improve outcomes. Overall, 40% of eyes treated with CMV-CTLs achieved stability in vision, while 40% achieved an improvement, with mean BCVA improving slightly (0.66 logMAR prior to CMV-CTL therapy versus 0.59 logMAR at final follow-up).

These findings are particularly compelling when compared to a non-randomized, retrospective control cohort of eyes with CMV retinitis treated with standard-of-care systemic and/or intravitreal antivirals at our institution (Table 3). Because CMV-CTL therapy was offered as a “rescue” therapy for CMV retinitis refractory, resistant, or intolerant to antiviral therapies, the CMV-CTL group was expected to have more severe disease at baseline. Insufficient imaging was available to retrospectively evaluate baseline disease severity in a systematic fashion. However, several baseline characteristics support the presence of potentially more severe disease in the CMV-CTL cohort: eyes treated with CMV-CTLs exhibited baseline BCVA of logMAR 0.66 (Snellen 20/91) versus logMAR 0.46 (Snellen 20/58) in the control group. Despite the small samples sizes, there was a trend toward higher rates of baseline BCVA of 20/200 or worse in eyes treated with CMV-CTLs (40.0% vs. 11.5%, $p = 0.07$). All patients receiving CMV-CTLs had been treated with both intravitreal and systemic antiviral therapies prior to CTL therapy, while only 80% of patients (76.9% of eyes) in the control group received intravitreal antiviral therapy (all received systemic antiviral therapy), potentially due to adequate control with systemic therapy alone. Moreover, patients in the CMV-CTL group had significant limitations in their ability to receive effective therapy with existing antivirals alone. Overall, there were no signals suggesting poorer ocular outcomes in the CMV-CTL group compared to the control group, despite potentially more severe disease at baseline. A larger percentage of eyes in the CMV-CTL group maintained or improved vision (80%, vs. 56.2%), although statistical significance was not achieved, perhaps owing to the small sample sizes involved. These findings suggest the need for larger, randomized, prospective trials of CMV-CTL therapy for CMV retinitis.

Ocular adverse events for CMV retinitis treated with CMV-CTLs were similar to retinitis treated with standard-of-care therapy. As an adoptive immunotherapy aimed at re-establishing immune cell activity against CMV retinitis, CMV-CTLs pose a potential risk of inducing immune recovery uveitis. We noted no cases of immune recovery uveitis in this small cohort. There were two eyes that developed fovea-involving CME during

the CMV-CTL treatment course. Notably, one eye exhibited CME even before CMV-CTL therapy was introduced, in the setting of perifoveal CMV retinitis. The CME recurred during CTL therapy and resolved without additional treatment as the retinitis itself resolved. There were no other features consistent with immune recovery uveitis (e.g. new or worsening anterior chamber or vitreous cells, vasculitis outside the area of retinitis, etc.). Thus, it was felt that the CME in this case was likely unrelated to CMV-CTL therapy. Another eye developed CME during the course of CMV-CTL therapy, potentially related to immune reconstitution. There were no other immune recovery uveitis features, and the CME resolved with topical therapy alone. Retinal detachment related to CMV retinitis occurred in 20% of eyes treated with CMV-CTLs and 30.8% of controls. Thus, overall, the ocular adverse event rates were comparable to those in the non-randomized, retrospective control cohort of eyes with CMV retinitis treated with standard-of-care systemic and/or intravitreal antivirals. The finding of no concerning safety signals thus support the need for further studies.

This study has several limitations. (1) The study is retrospective in nature and thus subject to all of the inherent limitations of a retrospective study. Moreover, as a retrospective study, the data were collected from evaluations by clinicians who were not blinded to the type of treatment (CMV-CTL versus standard-of-care) at the time of their evaluation. Similarly, because it is not controlled and because the investigators are limited to data available from the chart retrospectively, it is impossible to be certain whether there were unidentified changes to the subjects' overall health or care which might have contributed to resolution of the CMV retinitis. Finally as a retrospective study, there was no randomization to CMV-CTL therapy versus standard-of-care therapy. As a "rescue" treatment through an IND, CMV-CTL patients were likely those with more severe disease or more difficult to control disease (for instance due to resistance or intolerance to available standard-of-care therapies). While acknowledging these limitations, we nonetheless report baseline characteristics and outcomes in eyes with CMV retinitis treated with standard-of-care therapies to serve as a relevant, albeit limited, benchmark against which to compare CMV-CTL therapy. (2) This was a single center study with small sample sizes, owing to both the low overall incidence of CMV retinitis and the novelty and limited widespread availability of CMV-CTL therapy. As described above, if found to be effective, CMV-CTLs could be sent from the MSKCC library to infusion centers elsewhere for administration to patients. (3) There was a lack of quantitative data, such as baseline area of CMV retinitis and rates of progression of CMV retinitis. Due to the retrospective nature of this study, imaging protocols varied significantly among clinicians, and there were insufficient data for retrospective imaging review. (4) Because the CMV retinitis care at WCMC was clinical care and not part of any prespecified clinical trial protocol, and because several clinicians treated the 7 patients treated with CMV-CTLs, there was significant variability in other treatments rendered for CMV retinitis. Since a significant number of eyes treated with CMV-CTLs also underwent treatment with systemic and/or intravitreal antiviral therapy, the relative contribution of each intervention to the reported outcomes in these cases cannot be determined. However, a subset of the CMV-CTL group was treated with CMV-CTLs alone (due to patient inability or refusal to also continue antiviral therapies), and a comparison group treated with systemic and/or intravitreal antiviral therapy is provided.

From a practical standpoint, there may be certain logistical limitations to widespread use of CMV-CTLs. CMV-CTLs are generated from CMV seropositive donors and require extensive and complex laboratory processes in GMP-compliant settings. A large library of such CMV-CTLs must be developed and maintained to enable “off the shelf” use of appropriately matched CTLs for patients, and the selected CMV-CTL line must be expanded to generate sufficient volume for treatment of patient. Thereafter, the CTLs may be infused at MSKCC or shipped to an infusion center elsewhere for administration to patients. The implications regarding cost, resources, and access for widespread use of CMV-CTLs remains to be determined.

In conclusion, we report ocular outcomes in eyes with CMV retinitis treated using adoptive immunotherapy with systemically administered CMV-CTLs. To our knowledge, this is the first report of systemic adoptive cell transfer and of adoptive immunotherapy for ocular disease. It is notable that resolution of CMV retinitis was achieved by CMV-CTL monotherapy in 4 eyes (2 patients), despite the immune privileged status of the ocular tissues. This small, retrospective study suggests that CMV-CTLs demonstrate similar outcomes and similar ocular adverse event profiles, when compared to the standard of care, despite being used in a particularly challenging patient population (i.e., those requiring “rescue” therapy following standard treatment).

Thus, CMV-CTL may represent a novel therapy for CMV retinitis that is refractory or intolerant to available antiviral therapies. As was noted in this series, in some patients, CMV-CTLs alone (i.e. without concurrent systemic and/or intravitreal antiviral therapy) may achieve CMV retinitis resolution. However, caution should be taken in employing this experimental therapy in lieu of standard-of-care therapies supported by larger studies and/or long-term clinical experience. Further studies, ideally prospective, randomized, blinded trials, are necessary to evaluate the safety and efficacy of CMV-CTL immunotherapy for CMV retinitis and to clarify their role, if any, as a monotherapy and/or adjunctive therapy for CMV retinitis. Finally, these findings also suggest that adoptive cell transfer technologies administered systemically can reach and generate a clinically significant response in immune privileged target tissues in the eye.

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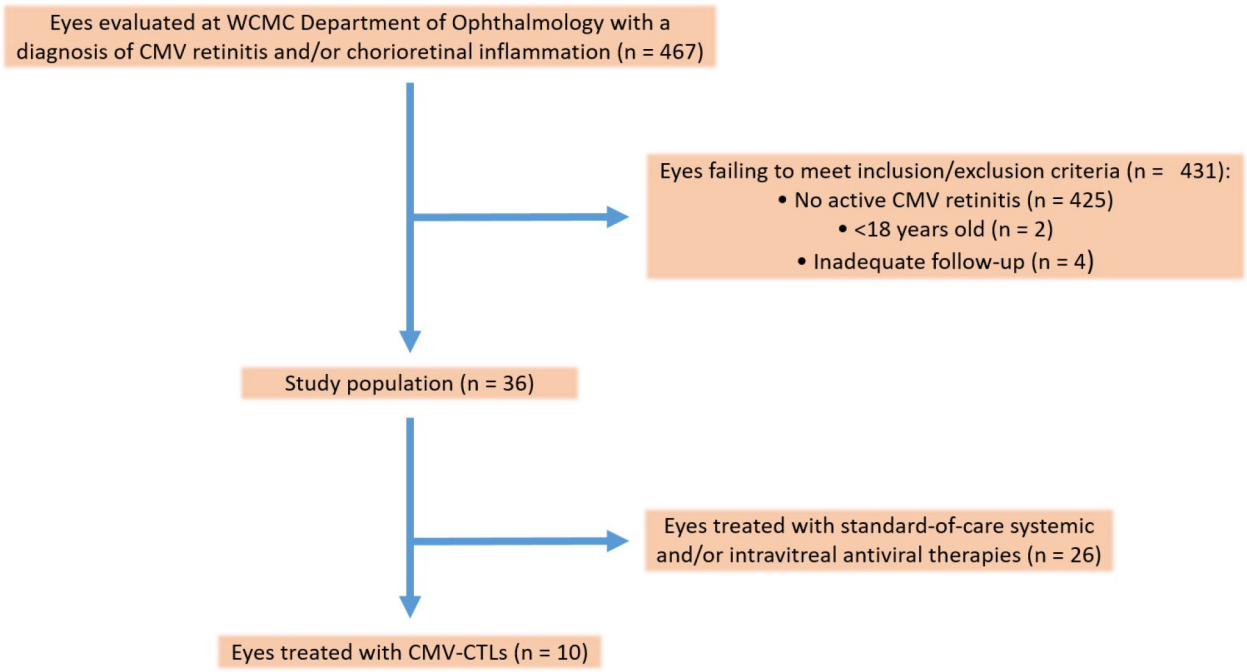

Figure 1. Study population.

Four hundred and sixty-seven eyes were evaluated at Weill Cornell Medical College (WCMC) with a diagnosis of cytomegalovirus (CMV) retinitis or chorioretinal inflammation. Of those, 431 eyes were excluded due to lack of active CMV retinitis (n = 425), age less than 18 years (n = 2), or inadequate length of follow-up (n = 4). Thirty-six eyes were included in this study, including 10 eyes of 7 patients who were treated with CMV-specific cytotoxic T-lymphocytes (CMV-CTL) and 26 eyes of 20 patients treated with standard-of-care therapy using systemic and/or intravitreal antivirals.

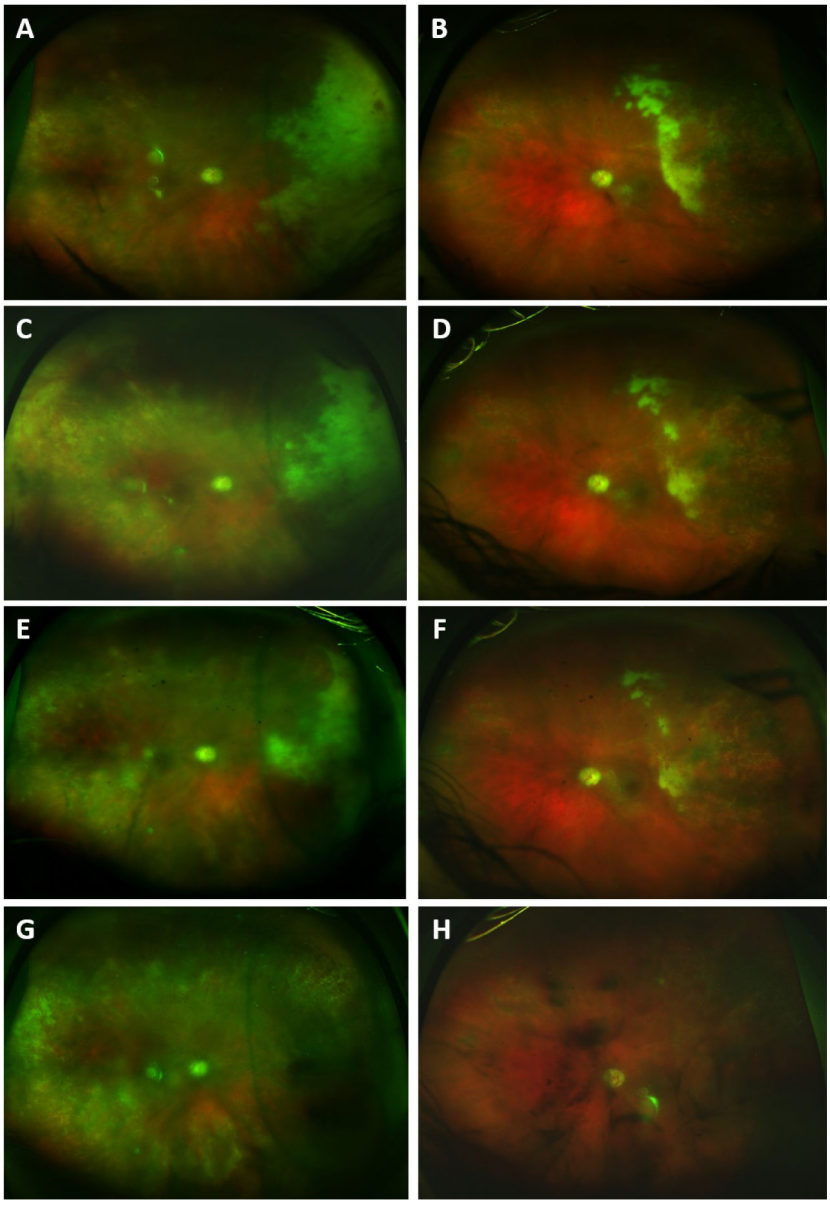

Figure 2: Representative case (ID #2) of cytomegalovirus (CMV) retinitis treated with CMV-specific cytotoxic T-lymphocytes (CMV-CTL).

A 68 year old previously CMV seronegative male with a history of Wegener's granulomatosis nephropathy status post renal transplant from a CMV seropositive donor on immunosuppressant therapy for graft rejection prophylaxis and over 2 years of active CMV retinitis in both eyes despite treatment with systemic and intravitreal antivirals presented with retinal necrosis consistent with CMV retinitis in both eyes (A, OD; B, OS). Visual acuity was CF OD and 20/300 OS. A UL97 CMV mutation conferred ganciclovir and valganciclovir resistance, renal toxicity limited use of foscarnet and cidofovir, and leflunamide therapy had previously been discontinued due to peripheral neuropathy. During the two years of active CMV retinitis and its treatment, the patient's had developed glaucoma requiring multiple glaucoma surgeries in both eyes. The patient underwent

treatment with a first round of CMV-CTLs along with once weekly intravitreal antiviral injections in both eyes, with some consolidation of retinitis noted three weeks later. However, there was persistent active CMV retinitis as evident from fundus imaging (C, OD; D, OS) and aqueous CMV PCR of 287,000 copies/cc (OS). A second round of CMV-CTLs was administered, with no concurrent systemic or intravitreal antivirals. Subsequently, the CMV retinitis continued to consolidate (E, OD; F, OS) and ultimately resolved (G, OD; H, OS). After the second round of CMV-CTLs, aqueous PCR was noted to decrease 10-fold to 29,600 copies/cc (OS) and then ultimately became undetectable. This response was durable for at least 6 months of follow-up, at which time visual acuity was stable at CF OD and improved to 20/150 OS.

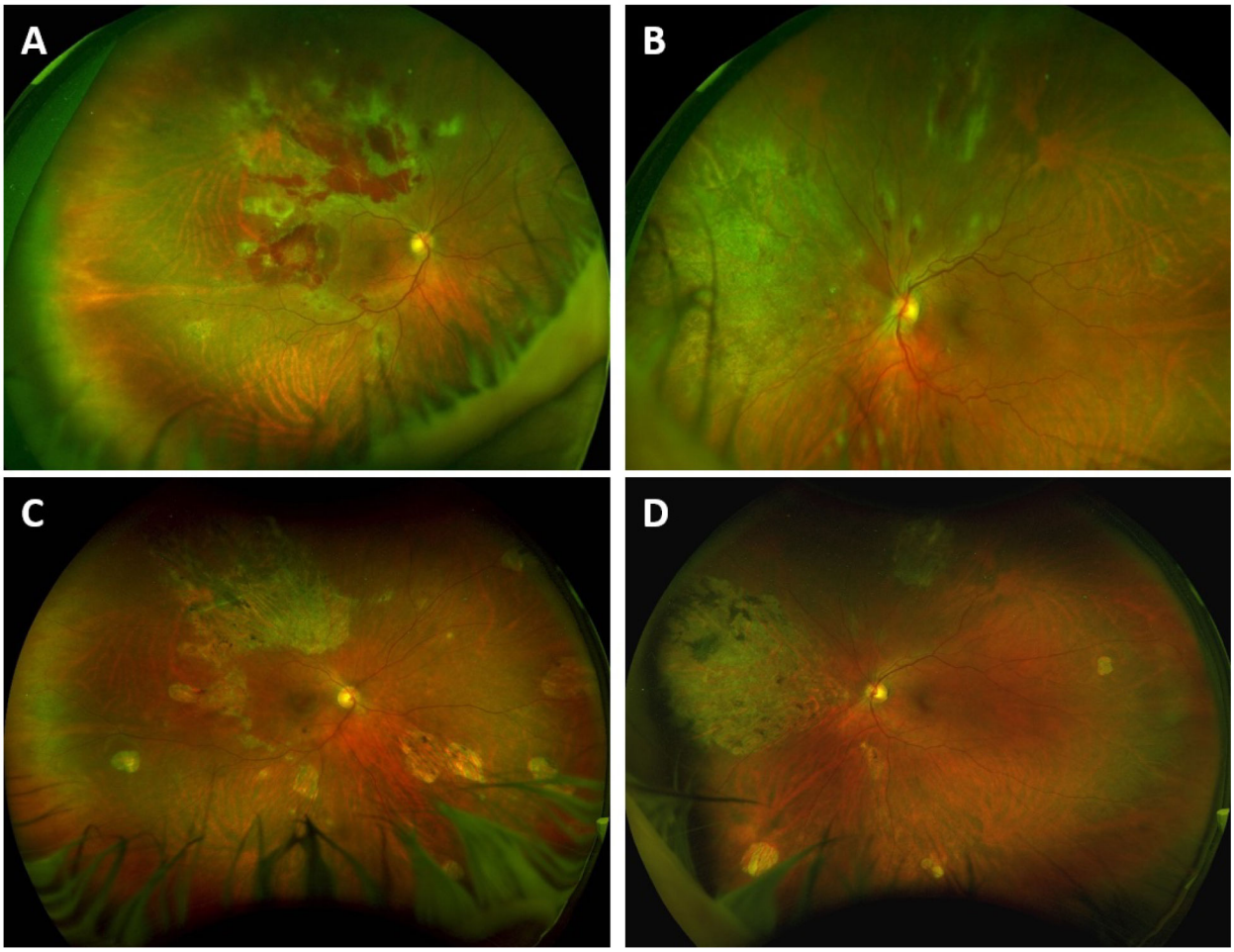

Figure 3: Representative case (ID #6) of cytomegalovirus (CMV) retinitis treated with CMV-specific cytotoxic T-lymphocytes (CMV-CTL).

A 26 year old male with acute lymphocytic leukemia status post allogeneic stem cell transplant complicated by graft-versus-host disease requiring immunosuppressant therapy developed systemic CMV infection refractory to systemic antiviral therapies. He also developed CMV retinitis which was treated with systemic and intravitreal antiviral therapies with modest response. His CMV harbored the UL54 mutation rendering resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir. Due to progressive vision threatening retinitis, he was referred for CMV-CTL therapies. Funduscopic examination revealed full thickness retinal necrosis with hemorrhages consistent with CMV retinitis in both eyes (A-B). Baseline BCVA was 20/40 OU. The patient underwent two rounds of CMV-CTL therapy, during which he received no other systemic and/or intravitreal antiviral therapies. There was dramatic consolidation and then resolution of the retinitis within 3 months of initiating CMV-CTL therapy. This response was durable, as funduscopic evaluation 76 months after CMV-CTLs revealed chorioretinal scarring with no recurrence of retinitis (C-D), nor uveitis, macular edema, or retinal detachment.

Table 1:

Baseline characteristics oF patients witH CMV retinitis treated with CMV-CTLs

ID	Eye	Age (years)	Sex	Cause of immunosuppression	Indication for CMV-CTL	BCVA, logMAR (Snellen)
1	OD	56	M	AIDS (27 CD4 cells/ μL); receiving chemotherapy for malignancy (Burkitt lymphoma, Kaposi's sarcoma)	Persistent CMV retinitis proximate to the fovea despite systemic antivirals and biweekly intravitreal foscarnet and ganciclovir antivirals; intolerance to intravitreal injection therapy	0.1 (20/25)
	OS					0.0 (20/20)
2	OD	68	M	s/p solid organ (kidney) transplant on systemic immunosuppressant therapy for graft rejection prophylaxis	Longstanding, progressive retinitis despite systemic and intravitreal antiviral therapy; *UL97* mutation conferring resistance to ganciclovir/ valganciclovir; nephrotoxicity concerns limiting use of foscarnet/cidofovir; peripheral neuropathy with leflunomide; patient intolerance to longstanding and frequent intravitreal antiviral injections	2.0 (CF)
	OS					1.2 (20/300)
3	OS	63	M	Leukemia status-post stem cell transplant, on systemic immunosuppressant therapy for graft-versus-host disease	Longstanding, persistent CMV viremia and retinitis despite systemic and intravitreal antiviral therapy; cytopenia associated with oral therapy (valganciclovir)	0.5 (20/70)
4	OS	66	M	Myelodysplastic syndrome status-post stem cell transplant; periodic treatment with systemic immunosuppressant therapy for complications related to prior transplant	Longstanding, persistent CMV viremia and retinitis with recurrence despite aggressive intravitreal therapy; *UL97* mutation conferring resistance to ganciclovir/valganciclovir; cytopenia associated with systemic oral antivirals (valganciclovir)	0.1 (20/25)
5	OD	42	M	AIDS	Progressive CMV retinitis despite systemic and intravitreal antiviral therapy	1.1 (20/250)
6	OD	26	M	Leukemia status-post stem cell transplant, on systemic immunosuppressant therapy for graft-versus-host disease	*UL54* mutation conferring resistance to ganciclovir/valganciclovir, foscarnet, and cidofovir; persistent CMV viremia despite antiviral therapy	0.3 (20/40)
	OS					0.3 (20/40)
7	OS	59	M	Lymphoma status-post stem cell transplant	Bone marrow suppression limiting use of ganciclovir/valganciclovir; *UL97* mutation conferring resistance to ganciclovir/ valganciclovir; persistent CMV viremia despite antiviral therapy	1.0 (20/200)

Abbreviations: CMV, cytomegalovirus; CMV-CTL: cytomegalovirus retimtis-speciric cytotoxic I-lymphocytes; ID: numerical patient ID number; BCVA, best-corrected visual acuity; OD: right eye; OS: left eye; M: male, F: female; HIV: human immunodeficiency virus; AIDS: Acquired Immune Deficiency Syndrome; CF: count fingers.

Table 2:

Ocular outcomes in patients with CMV retinitis treated with CMV-CTLs

ID	Eye	Number ofCMV-CTL series (3-week infusions)	Concurrent systemic and/or intravitreal antiviral treatment for CMV retinitis during CMV-CTL therapy course	Length of follow-up (months)	Resolution of CMV retinitis at last followup	Recurrence of CMV retinitis after resolution	Final BCVA, logMAR (Snellen)	Immune recovery uveitis	RD	CME
1	OD	1	Yes	16	Yes	No	0.1 (20/25)	No	No	Yes ǂ
	OS	1	Yes	16	Yes	No	0.0 (20/20)	No	No	No
2	OD	2	No	6	Yes	No	2.0 (CF)	No	No	No
	OS	2	No *	6	Yes	No	0.9 (20/150)	No	No	No
3	OS	4	Yes	24	Yes	No	0.5 (20/70)	No	No	No
4	OS	3	Yes	44	Yes	Yes	1.2 (20/300)	No	Yes	No
5	OD	2	Yes	30	No	N/A	NLP	No	No	No
6	OD	2	No	76	Yes	No	0 (20/20)	No	No	No
	OS	2	No	76	Yes	No	0 (20/20)	No	No	No
7	OS	1	Yes	6	Yes	No	0.60 (20/80)	No	Yes	Yes

Abbreviations: ID: numerical patient ID number, CMV: cytomegalovirus retinitis; CMV-CTL: cytomegalovirus retinitis-specific cytotoxic T-lymphocytes;, BCVA, best-corrected visual acuity; RD: retinal detachment; CME: fovea-involving cystoid macular edema; OD: right eye; OS: left eye; CF: count fingers; NA: data not available; NLP: no light perception

ǂ This patient had a history of CME prior to CMV-CTL treatment, likely related to perifoveal CMV retinitis, which then recurred during the CTL treatment course and resolved as the retinitis resolved.

* This patient declined further treatment with intravitreal antivirals partway through the CMV-CTL treatment course, prior to consolidation of CMV retinitis. He never resumed treatment with systemic and/or intravitreal antiviral therapies. Thus, he had active CMV retinitis undergoing treatment with CMV-CTLs only.

Table 3:

Baseline characteristics and ocular outcomes in patients with CMV retinitis treated with CMV-CTLs versus standard-of-care therapy

		CMV-CTL	Control	p-value
Average age (years)		53.0	46.9	0.27
Etiology of immunosuppression, % (n)	**Hematologic malignancy s/p stem cell transplant**	50.0 (5)	38.5 (10)	0.29
	Hematologic malignancy (without stem cell transplant)	0.0 (0)	3.8 (1)	
	AIDS	30.0 (3)	53.8 (14)	
	Solid organ transplant on immunosuppressant therapy	20.0 (2)	3.8 (1)	
Ever treated with systemic antiviral therapies, % (n)		100.0 (10)	100.0 (10)	1.0
Ever treated with intravitreal antiviral therapies, % (n)		100.0 (10)	76.9 (20)	0.16
BCVA at baseline, logMAR (Snellen)		0.66 (20/91)	0.46 (20/58)	0.45
BCVA ≥ 20/40 (Snellen) at baseline, % (n)		50.0 (5)	81.5 (16)	0.53
BCVA ≤ 20/200 (Snellen) at baseline, % (n)		40.0 (4)	11.5 (3)	0.07
Length of follow-up (months)		33.4	34.2	0.74
BCVA at final follow-up, logMAR (Snellen)		0.59 (20/78)	0.56 (20/73)	0.78
BCVA ≥ 20/40 (Snellen) at final follow-up, % (n)		40.0 (4)	50.0 (13)	0.59
BCVA ≤ 20/200 (Snellen) at final follow-up, % (n)		30.0 (3)	30.8 (8)	0.96
Change in vision during study period, % (n)	**Improved**	40.0 (4)	30.8 (8)	0.14
	Stable	40.0 (4)	15.4 (4)	
	Worsened	20.0 (2)	53.8 (14)	
Resolution of CMV retinitis at final follow-up, % (n)		90.0 (9)	69.2 (18)	0.96
Retinal detachment during study period, % (n)		20.0 (2)	30.8 (8)	0.51
Immune recovery uveitis during study period, % (n)		0.0 (0)	11.5 (3)	0.26
Fovea-involving CME during study period, % (n)		20.0 (2)*	15.4 (4)	0.74

All data is presented on a per-eye basis

Abbreviations: s/p: status-post; AIDS: acquired immunodeficiency syndrome; CMV: cytomegalovirus; CMV-CTL: cytomegalovirus-specific cytotoxic-T-lymphocytes; CME: cystoid macular edema

*One eye included here had a history of CME prior to CMV-CTL treatment, likely related to perifoveal CMV retinitis, which then recurred during the CTL treatment course and resolved as the retinitis resolved.