First Face Composite-Tissue Transplant Recipient Successfully Treated for Cytomegalovirus Infection with Preemptive Valganciclovir Treatment

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Little is known about cytomegalovirus (CMV) infection after face transplantation, since only two of the 11 cases of face transplantation reported worldwide have documented a CMV infection after transplantation. Herein, we present the first report of a composite-tissue face allotransplant recipient at high risk for CMV infection (D+/-R- [CMV seropositive donor positive/CMV seronegative receptor]) undergoing preemptive treatment. Preemptive treatment was safe and effective for controlling CMV infection and thus promoting early acquisition of a CMV-specific immune response that protected the patient from late-onset CMV disease.

Despite significant clinical advances in recent years, cytomegalovirus (CMV) infection continues to be the main infectious complication after solid organ transplantation (SOT) (3). Due to the heterogeneity of tissues transplanted during face transplantation, the administration of immunosuppressive therapies similar to those administered for SOT is required. Thus, these patients are at high risk for developing opportunistic infections that may also be caused by the accompanying flora of the graft (11). Recently published guidelines recommend the administration of prophylaxis for CMV infection in SOT patients at high risk for CMV infection (CMV-seronegative recipients that receive a seropositive graft, D+/-R-) and those undergoing lung or intestine transplantation (8).

Little is known about the kinetics of CMV infection after face transplantation, since of the 11 worldwide face transplant recipients reported, only two had documented CMV replication after transplantation (2, 5, 9–11). Both patients were at high risk for developing CMV infection (D+/-R-) and received ganciclovir prophylaxis for 6 months, which inhibited CMV replication. However, both presented recurrent episodes of CMV replication after the end of treatment. One of the patients was not able to complete the 6-month treatment due to severe neutropenia (11), while in the other patient a ganciclovir-resistant strain emerged (9). These adverse effects have been associated with the prophylactic administration of ganciclovir.

We have recently reported that the administration of preemptive therapy in SOT patients at high risk for CMV infection was advantageous, since it promoted the acquisition of a CMV-specific T-cell immune response that protected patients from later CMV disease (1). Based on these results, preemptive therapy was administered to a patient who received a partial face transplantation and was at high risk for CMV infection (D+/-R-). The patient was prospectively monitored to study CMV infection and the development of a CMV-specific immune response that would protect him from CMV disease.

On 26 January 2010, a 35-year-old Caucasian male underwent a monobloc tumoral resection from the superficial skin to the periosteum, including bilateral facial, bilateral mental, and bilateral infraorbital nerves from their main trunks, due to type 1 neurofibromatosis. The patient received a face transplantation to repair a severe defect from massive plexiform neurofibromas, consisting of a composite-tissue allograft of the lower two-thirds of the face. An osteomyocutaneous allograft of the lower face comprising skin, subcutaneous tissue, upper and lower lips, mouth, partial oral mucosa (including Stensen’s ducts), perioral muscles (including facial mimic muscles—orbicularis oris, zygomaticus, and levators), bilateral cheeks, bilateral parotid glands, bilateral facial nerves, bilateral mental nerves, bilateral infraorbital nerves, bilateral common carotid arteries, bilateral internal jugular veins, and an osseous chin segment attached to the overlying soft tissues was transplanted (4). The patient was seronegative for CMV and herpes simplex virus (HSV) and was seropositive for varicella-zoster virus (VZV) and Epstein-Barr virus, and he was vaccinated against 2009 influenza A H1N1 and hepatitis A and B virus. The graft proceeded from a 18-year-old donor deceased due to heart failure who was seropositive for CMV, HSV, and VZV. The immunosuppressive regimen consisted of basiliximab (two
doses of 20 mg each), with maintenance tacrolimus, mycophenolate mofetil, and steroids.

The patient needed the transfusion of 24 units of packed red blood cells, 1,500 ml of fresh plasma, one pool of platelets, and 7 g of fibrinogen. The postoperative course in the ICU was for 47 days, and during this time the patient developed an *Acinetobacter baumannii* infection at the surgical site, tracheobronchitis, and an *Enterobacter cloacae* bacteremia, all of which were cured with antimicrobial therapy.

For monitoring CMV infection and CMV-specific T-cell immune response, samples were collected weekly from 15 days after transplantation until 100 days, every 2 weeks from 100 to 180 days, and monthly thereafter. In cases of rejection treated with a corticosteroid bolus, the CMV viral load was determined weekly for 1 month. Cytomegalovirus viral load (VL) was determined in plasma by real-time PCR by using an Affi-gene CMV Trender diagnostic assay (Cepheid AB, Bromma, Sweden) and performing the amplification on an MX3000P QPCR system (Stratagene, La Jolla, CA) following the manufacturer’s instructions. The study was approved by the University Hospital Virgen del Rocío Ethics Committee for Clinical Research, and patient gave written informed consent.

CMV replication was first detected at week 3 after transplantation (Fig. 1A), and valganciclovir therapy was administered (VL/H11005 1,010 copies/ml) for 17 days. After 1 week of valganciclovir administration, CMV replication became undetectable. Afterwards, at week 7 posttransplantation, a second replication episode was registered (VL/H11005 1,260 copies/ml), requiring a second round of valganciclovir therapy for 17 days. The viral load decreased to undetectable levels within the first week of treatment.

A CMV-specific immune response was determined by flow cytometry, as previously reported (1). The patient presented undetectable levels of CMV-specific T cells at the time of enrolment in the study (week 2 after transplantation). After the first CMV replication episode, a progressive increase of IFN-γ-secreting T cells was observed, with positive values for IFN-γ CD4+ T cells (0.4%) at week 7 posttransplantation (Fig. 1B). The CMV-specific immune response was considered positive at week 8 when IFN-γ CD8+ T cells reached a positive value (0.4%) (Fig. 1B). At week 51 after transplantation, the patient developed one replication episode that reached 820 copies/ml, concurrently with a decrease of CMV-specific CD4+ and CD8+ T cells, which may be explained by migration of the memory T cells to the infection site. The viral load decreased to undetectable levels without valganciclovir administration (Fig. 1A), while CMV-specific CD4+ and CD8+ T cells experienced a clonal expansion (Fig. 1B), probably due to the immune response mediated by the memory cells. To rule out the possibility of the selection of a resistant strain during the treatment periods, viral DNA was extracted from 200 µl of the patient’s plasma at week 51 using the Affigene DNA extraction assay (Cepheid AB, Bromma, Sweden) according to the manufacturer’s instructions. The UL97 gene was amplified by PCR in a 50-µl reaction mixture containing 250 ng viral DNA template, 0.2 µM each forward and reverse primers (Forward-UL97, 5'-ACCCTTTGACCACCCTGAG-3'; Reverse-UL97, 5'-GTGCATGTACCAGTGACGTGTG-3'); 200 µM deoxynucleoside triphosphate; 2.6 U Expand high-fidelity PCR enzyme mix (Roche Diagnostics, Mannheim Germany), 10 mM Tris-HCl, 1.5 mM MgCl2, and 50 mM KCl (pH 8.3). The PCR product was sequenced, and results confirmed no resistance mutations. No symptoms of
CMV infection or CMV disease or further complications were developed during the first 70 weeks of follow-up.

Cytomegalovirus infection is still the main infectious cause of disease among SOT patients, which is associated with a large number of complications after transplantation (3). In addition, CMV is associated with a large number of indirect effects, including rejection episodes, immunosenescence, and atherosclerosis. Although current guidelines recommend the use of prophylaxis in patients at high risk for CMV infection (D^+/R^−) (8), some authors support the administration of preemptive treatment because of the benefit of preventing the acquisition of an early CMV-specific immune response that would protect patients from late-onset CMV disease (1, 12).

Here we describe the first report of a face transplant recipient undergoing preemptive treatment for the management of CMV infection. We demonstrate that preemptive therapy was safe and effective for the prevention of CMV disease in a face transplant recipient at high risk for infection. Additional studies using a similar approach are warranted for further characterizing this treatment strategy. No CMV-associated symptoms or rejection episodes were developed during the first 70 weeks after the transplant. The evolution of the CMV infection after D^+/R^− face transplantation was similar to what we recently described for a D^+/R^− SOT (liver, heart, and kidney) recipient, with two episodes of CMV replication early after transplantation that required valganciclovir treatment (1). After two replication episodes, the patient was able to develop a CMV-specific immune response early after transplantation that controlled later CMV replication episodes and protected him from CMV disease. Our results showing a satisfactory clinical outcome for a face transplant recipient receiving preemptive therapy is particularly important, since due to the high immunogenicity of the tissues transplanted and to the high intensity of immunosuppression that recipients of composite-tissue face allotransplantation receive during the transplantation process, these patients are considered at high risk for CMV infection, similar to lung transplants or D^+/R^− SOT recipients. Thus, previously reported transplant patients underwent prophylaxis for at least 6 months, and the treatment was extended to 1 year in the last documented patient (2, 5, 9–11).

Recently published data from the IMPACT study (7), in addition to other previously published reports (6), have shown that the extension of the prophylactic period up to 200 days results in lower rates of CMV disease after transplantation in SOT recipients at high risk for CMV infection. However, despite these important improvements to disease rates, other factors, such as neutropenia episodes or the emergence of ganciclovir-resistant strains, have been shown to significantly increase during extended prophylaxis, compared to a prophylactic period of 100 days (6). These risk factors are not associated with preemptive therapy.

In conclusion, this is the first report of a face transplant recipient at high risk for CMV infection (D^+/R^−) undergoing preemptive treatment. This study demonstrates that preemptive therapy was a safe and effective strategy for the control of CMV infection in this high-risk face transplant recipient and promoted early acquisition of a CMV-specific immune response that protected the patient from CMV late onset disease.

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