

# Ganciclovir–tenofovir interaction leading to tenofovir-induced nephrotoxicity

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## ABSTRACT

Viral enteritis is an important gastrointestinal disorder in human immunodeficiency virus (HIV)-infected patients. *Cytomegalovirus* (CMV) is the most common opportunistic agent in these patients. As ganciclovir and tenofovir are the most commonly used drugs for the treatment of CMV and HIV infection, respectively, this case report showcases the potentiality of drug interaction as well as the safety measures to be taken when using these two drugs together in unavoidable situations.

**Key words:** CMV infection, ganciclovir, nephrotoxicity, tenofovir

## INTRODUCTION

Viral enteritis is a common gastrointestinal (GI) disorder in human immunodeficiency virus (HIV)-infected patients. Several viruses such as *cytomegalovirus* (CMV), *herpes simplex virus* (HSV), *adenovirus* (AdV), *norovirus*, *astrovirus*, and *rotavirus*, have been implicated in the causation of viral enteritis.<sup>[1]</sup>

*Cytomegalovirus* is the most common opportunistic agent in HIV-infected patients. Although it can affect the entire GI tract, it frequently involves the esophagus and colon. Here, we present a case of a female patient, on tenofovir-based antiretroviral therapy,

who was started on ganciclovir for suspected CMV infection. She presented with vomiting, anorexia, altered sensorium, and later there was gradual deterioration in her renal function, implicating a drug interaction between tenofovir and ganciclovir. To the best of our knowledge, this is the first case report in which the interaction between ganciclovir and tenofovir is reported.

## CASE REPORT

A woman of age 51 years was diagnosed with HIV 1 infection, five years ago, and since then was under antiretroviral therapy (ART) with tenofovir 300 mg, emtricitabine 200 mg, and efavirenz 600 mg, once daily. Ganciclovir 250 mg orally and fluconazole 150 mg orally once daily were started 14 days prior, at an outside hospital, for loss of appetite and dysphagia. She presented to the Emergency Department of our hospital with complaints of vomiting and decreased food intake of 10 days' duration, with altered sensorium of one-day duration. There was no history of fever, dyspnea, chest pain or palpitations, diarrhea or decreased urine output. The patient underwent left nephrectomy in 2003, for unknown reasons and for which records are not available.

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On examination, she was found to have pallor, with no signs of icterus, cyanosis, lymphadenopathy, clubbing and pedal edema. Her pulse rate was 114 per minute and blood pressure was 90/60 mmHg. She was drowsy, but the remainder of the systemic examination was normal. Blood glucose levels were low, so she was started on 25% dextrose and her sensorium improved. She was started on oxygen inhalation, intravenous fluids, infusion of sodium bicarbonate (NaHCO<sub>3</sub>), infusion of potassium chloride (KCl) and Ryle's tube feeding. Routine investigations were done, which revealed, on day 1, a serum creatinine of 1.5 mg/dl, blood urea of 49 mg/dl, and arterial blood gas (ABG) showed metabolic acidosis. On the second day, her serum creatinine was 1.9 mg/dl, blood urea was 68 mg/dl, serum electrolytes were Na<sup>-</sup> 165 meq/l, K<sup>-</sup> 2.4 meq/l, and Cl<sup>-</sup> 123 meq/l. An ultrasound abdomen done on the third day revealed post left nephrectomy and grade II renal parenchymal changes in the right kidney. Magnetic resonance imaging (MRI) showed diffuse cerebral atrophy and her CD4 count was 99 cells/microliter. Tablet co-trimoxazole (160 mg/800 mg), one tablet, once daily, was added for prevention of opportunistic infection. Serum creatinine and blood urea gradually increased to 2 mg/dl and 69 mg/dl respectively on the fourth day.

On the fourth day, the case was referred to a clinical pharmacologist, for dosage adjustment of the drugs the patient was taking, as acute kidney injury was diagnosed, with a rise in the renal function parameters. After reviewing the case details, a drug interaction was suspected between tenofovir and ganciclovir, which might have caused a rise in the tenofovir concentrations and led to acute kidney injury. Therefore, taking into account this drug interaction, on the fourth day, ART and ganciclovir were withheld. On the fifth day, the patient was symptomatically better and was conscious and coherent. Serum creatinine decreased from 2 mg/dl to 1.7 mg/dl and blood urea decreased from 69 mg/dl to 51 mg/dl. On the fifth day, the patient was discharged at request.

## DISCUSSION

Gastroenteritis is one of the most common and debilitating conditions that affect individuals with acquired immunodeficiency syndrome (AIDS)/HIV. The most significant GI symptoms of gastroenteritis are diarrhea, abdominal pain and fever. Gastroenteritis can be caused by bacteria, protozoa and viruses. Several viruses have been implicated in the causation of gastroenteritis, of which, CMV is the most common opportunistic agent in HIV-infected patients. Although it can infect the entire gastrointestinal tract (GIT), it frequently involves the esophagus and colon.<sup>[2]</sup>

In a study done on HIV-positive patients on ART, 22 out of the 26 virus-positive patients were infected with CMV

which included 11 single infections, two coinfections with adenovirus or *Herpes Simplex Virus-2* and five coinfections with parasites.<sup>[3]</sup>

Despite the widespread use of highly active antiretroviral therapy (HAART) in HIV infection, the GI tract is still frequently affected by HIV-associated disease processes. HIV-infected patients often present with non-specific GI symptoms.<sup>[2]</sup> In this case, the patient was started on oral ganciclovir empirically for suspected CMV infection, by a private practitioner. However, when routine investigations were done for evaluating the patient's condition, it was observed that there was a persistent rise in the serum creatinine and blood urea levels during the first three days of admission. On the third day, grade II renal parenchymal changes were noticed on an ultrasound of the abdomen, which prompted a call to the clinical pharmacologist for dosage adjustment of the antiretroviral drugs and ganciclovir, in this patient.

After taking the detailed history, there were three important suggestions made, one was a suspected drug interaction between tenofovir and ganciclovir, which could have increased the tenofovir concentrations, leading to acute kidney injury, second, to hold back administration of tenofovir and ganciclovir, and third, substitution of oral ganciclovir by valganciclovir, if treatment for CMV infection was unavoidable. In addition, dosage adjustments were recommended for fluconazole, emtricitabine, and trimethoprim-sulfamethoxazole, as the creatinine clearance was approximately 33 ml/minute. It was recommended that fluconazole be administered in a dose of 50 mg once daily, emtricitabine 200 mg every 48 hours, and trimethoprim-sulfamethoxazole at half the usual dose.

In this case, the patient was under treatment with tenofovir since five years, with good tolerability, but there was a persistent rise of serum creatinine during the first three days of admission, from 1.5 to 2 mg/dl, which was most probably due to tenofovir-induced nephrotoxicity. A sudden onset of intolerability with tenofovir, raised suspicion into what factors could have triggered this event.

Risk factors for tenofovir-induced glomerular filtration rate (GFR) reduction include advanced age, low body weight, higher serum creatinine levels before starting tenofovir treatment, comorbidities (diabetes, hypertension, hepatitis C virus (HCV) coinfection), concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS), and male sex according to a multivariate analysis done on postmarketing data.<sup>[4]</sup>

In this case, the factors that need attention include solitary kidney and concomitant medications. The evidence from living donors indicates that renal function, as measured

by GFR, shows an initial decline of 25 - 35% following donation, with a long-term GFR around 10 mL/minute per 1.73 m<sup>2</sup>, less than that expected without nephrectomy. There is no evidence of an accelerated decline when compared with the age-matched controls. The absolute decrement in GFR appears to remain constant with aging. The prognostic implication of reduced GFR in living kidney donors is unknown.<sup>[5]</sup> However, we do not know, the indication for which nephrectomy was done in this case. A review article by Mark A. Perazella, on Renal Vulnerability to Drug Toxicity, that reviewed the factors that increase vulnerability of the kidney to potential toxins, identifies patient-specific factors, kidney-specific factors, and drug-specific factors, among which, a solitary kidney is not listed.<sup>[6]</sup> Therefore, in the light of the available literature it seems that the solitary kidney might not have contributed to acute kidney injury in this case.

Among the concomitant medications prescribed, emtricitabine, trimethoprim-sulfamethoxazole, and fluconazole are excreted by the kidney and therefore dosage adjustments were recommended, but they are not known to cause nephrotoxicity. Although ganciclovir is not nephrotoxic, its interaction with tenofovir was suspected, as the timing at which the events occurred, coincided with the time at which ganciclovir was started.

Tenofovir is primarily excreted by the kidneys, by glomerular filtration and active tubular secretion. Twenty to thirty percent of tenofovir is excreted unchanged in the urine through active secretion by the proximal tubular cells. Organic anion transporter 1 (OAT1) is the main transporter taking tenofovir into the proximal tubular cell. Once inside this mitochondrial rich cell type, tenofovir must be extruded into the tubular lumen by MRP-2 and MRP-4. Therefore, blocking tenofovir extrusion by MRP-2 and MRP-4 by pharmacological interference boosts tenofovir nephrotoxicity. Ganciclovir being a MRP-4 inhibitor, may have raised the concentrations of tenofovir, leading to nephrotoxicity.<sup>[4]</sup>

Treatment of CMV enterocolitis requires parenteral therapy, with either ganciclovir (5 mg/kg twice daily) or foscarnet (90 mg/kg twice daily). In an open-label, randomized study, comparing a two-week course of foscarnet with ganciclovir, no significant difference in clinical response was found between the two therapies. Around 75% of the patients had good clinical and endoscopic responses, with the disappearance of the inclusion bodies, as determined histologically. The use of oral ganciclovir in the maintenance of GI remission has not been evaluated.<sup>[1]</sup>

Most of the experience has been established in transplant recipients and in patients with AIDS, who have CMV retinitis,

for which (oral) valganciclovir is of equal efficacy to intravenous ganciclovir, for treating CMV disease.<sup>[7]</sup>

On account of the poor bioavailability of oral ganciclovir, as the therapeutic effect is uncertain, valganciclovir, a valine ester prodrug of ganciclovir, was suggested. However, as valganciclovir also inhibits MRP-4, its co-administration with tenofovir could raise the concentrations of tenofovir, leading to nephrotoxicity. Therefore, the suggestion of stopping tenofovir was given. Subsequent to the clinician's decision of stopping ganciclovir and ART, the serum creatinine and blood urea showed a decline on the fifth day.

## CONCLUSION

As ganciclovir or valganciclovir are the drugs of choice for *Cytomegalovirus* infections that are commonly encountered opportunistic infections in HIV-infected individuals, in whom tenofovir-based ART is better tolerated (the most commonly employed ART regimen), this interaction assumes clinical relevance. To the best of our knowledge, there is no case report published in this regard, and this would be the first one. Therefore, whenever a patient is on tenofovir-based ART, ganciclovir or valganciclovir co-administration should be avoided. In case ganciclovir or valganciclovir are indicated for treatment of the co-infection, then tenofovir may be substituted with any other appropriate antiretroviral drug, to preserve renal function.

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