

Use of Leflunomide in Renal Transplant Recipients with Ganciclovir-Resistant/Refractory Cytomegalovirus Infection: A Case Series from the University of Chicago

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Key Words

Renal transplant recipients · Leflunomide · Cytomegalovirus infection

Abstract

Introduction: Although antiviral prophylaxis for cytomegalovirus (CMV) is widely used, CMV infection remains common in renal transplant recipients with adverse consequences. **Methods:** We report 5 cases of renal transplant recipients with resistant CMV infection who were successfully managed with leflunomide at the University of Chicago Medical Center. **Results:** Five renal transplant recipients (2 simultaneous pancreas/kidney transplants, 3 deceased donor kidney transplants) were diagnosed with GCV-resistant CMV infection from 2003 to 2011. Of the 4 patients who had resistance genotype testing, 3 showed a UL97 mutation and 1 patient had a clinically resistant CMV infection. All patients received CMV prophylaxis with valganciclovir for 3 months. The number of days from the date of transplant to viremia ranged from 38 to 458 days (median 219). All 5 patients received other antiviral agents (e.g. ganciclovir, foscarnet), and in 4 patients, viremia was cleared before leflunomide was initiated as consolidation (or maintenance) therapy. **Conclusion:** Leflunomide was well tolerated and successful in preventing recurrence of viremia in renal transplant recipients with resistant CMV infection. The beneficial effect of leflunomide in this setting warrants further investigation.

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Introduction

Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus that causes significant morbidity and mortality in immunocompromised patients. It is well known for having both direct (viral syndrome, tissue-invasive disease) and indirect effects (increased risk of other opportunistic infections, increased incidence of acute rejection, increased overall mortality) [1]. A systematic review of randomized controlled trials showed that antiviral therapies to prevent CMV disease in solid-organ transplant recipients also reduced mortality [2].

Over the past two decades, advances such as the introduction of CMV nucleic acid amplification testing and the widespread use of CMV prophylaxis have led to an increasing likelihood of viremia detection and disease prevention. On the other hand, issues such as late-onset CMV infection and ganciclovir (GCV)-resistant CMV have become clinically more common. The incidence of late-onset CMV infection has been estimated at 35–40% when patients are given 3 months of antiviral prophylaxis [3, 4]. The incidence of GCV resistance among high-risk (D+/R-) recipients treated for CMV viremia is in the 5–10% range [5, 6]. Other known risk factors associated with developing GCV resistance include the organ transplant type (e.g. lung transplant), prolonged exposure to GCV, subtherapeutic level of GCV, and more potent immunosuppression (such as antithymocyte globulin or OKT-3) [7].

The outcome of the IMPACT trial has led many transplant physicians to extend the duration of CMV prophylaxis in high-risk transplant recipients [3, 8]. Studies have shown that a 6-month course of prophylaxis is cost-effective [9, 10]. Current guidelines published by the Transplantation Society International CMV Consensus Group recommend that recipients at high risk (D+/R-) receive prophylaxis with 6 months of valganciclovir (VGCV) or are managed with preemptive therapy by monitoring for CMV viremia [11]. Contradictory data and the absence of a large, well-designed head-to-head comparison study make it difficult to draw firm conclusions on the superiority of one regimen over the other [12–17].

Treatments for CMV infection/disease involve a two-pronged approach that includes careful reduction in immunosuppression and the appropriate antiviral medication. However, the risk of acute rejection and side effects of high-dose GCV (e.g. bone marrow suppression) and nephrotoxicity of second-line agents such as foscarnet and cidofovir often limit available options.

Leflunomide is a malononitrileamide whose active metabolite, teriflunomide (formerly known as A77 1726) possesses both antiviral and immunosuppressive properties [18, 19]. Here we describe our successful experience in treating 5 kidney transplant patients with GCV-resistant CMV infection.

Materials and Methods

This retrospective chart review was approved by the Institutional Review Board of the University of Chicago (IRB protocol #14-1143). The study included 5 kidney transplant recipients who were treated with leflunomide for CMV infection at the University of Chicago from 2003 to 2011. Patients were informed of the off-label use of leflunomide, and the potential risks, benefits, and alternative options were discussed in detail. The decision to use leflunomide was made by the transplant team and was not a part of a clinical trial.

Standard definitions were used for asymptomatic viremia, CMV syndrome, and tissue-invasive disease [20].

Clinical Data

Clinical data were collected including demographic information, donor and recipient CMV serological status, CMV viral load, GCV resistance genotype testing (UL97, UL54), immunosuppressive drug regimen, and other antiviral agents used to treat CMV viremia before and after leflunomide was added to the patients' treatment regimen. Delayed graft function (DGF) was defined as the need for dialysis treatment during the first week after transplant. Relevant posttransplant hospitalization summaries and clinic visit notes were also reviewed.

Immunosuppression

Patients received either antithymocyte globulin (1.5 mg/kg × 4–5 doses) or basiliximab as induction immunosuppressive regimen depending on their immunological risk. Of the 5 patients, 4 were maintained on tacrolimus, mycophenolate mofetil (MMF), and prednisone, and 1 patient was maintained on sirolimus, MMF, and prednisone. When leflunomide was initiated, MMF was discontinued.

CMV Prophylaxis

All 5 patients were given CMV prophylaxis for at least 3 months. Two patients were given VGCV. For those who received VGCV, the prophylactic dose was 900 mg daily if creatinine clearance (CrCl) was >60 ml/min, 450 mg daily for CrCl of 40–59 ml/min, 450 mg every other day for CrCl of 25–39 ml/min, and 450 mg twice weekly if CrCl was 10–24 ml/min. One patient received intravenous (IV) GCV only. The remaining 2 patients were given IV GCV (first 1–2 weeks) followed by oral GCV or VGCV.

CMV Detection Assays

Until mid-2003, the presence of CMV was detected using CMV DNA hybrid capture assay. Two patients (patients 4 and 5) had parts of their treatment responses monitored in this fashion. The remaining 3 patients had quantitative nucleic acid testing performed when clinically indicated.

Leflunomide Administration

Patients received a loading dose of 100 mg daily on days 1–5 and were placed on a maintenance dose of 40 mg daily. Teriflunomide levels were not routinely checked unless there were adverse effects of leflunomide such as liver dysfunction.

GCV Resistance Testing

GCV resistance was suspected if the CMV viral load did not show a decrease by 10–14 days after IV GCV or VGCV was started. Genetic testing for mutations in UL97 and UL54 was performed when GCV resistance was suspected. The testing was performed using polymerase chain reaction (PCR) amplification of CMV DNA followed by gene sequencing (Viromed Laboratories, Minneapolis, Minn., USA).

Results

Demographic Data

Table 1 shows the demographic characteristics of the 5 patients (3 kidney and 2 kidney/pancreas transplants) who received leflunomide as treatment of GCV-resistant CMV infection. All 5 patients were male and all were African-American except 1 Hispanic patient. CMV serotype matching for 4 transplant recipients was CMV D+/R–, and 1 was CMV D+/R+.

Clinical Data

All 5 patients were considered to be at a high immunological risk for rejection and were given potent immunosuppressive regimens and were at a high risk for opportunistic infections. Patients 2 and 5 were recipients of simultaneous pancreas/kidney transplants (SPK). Patients 3 (third kidney transplant) and 4 were highly sensitized, and patient 4 received a pair of expanded criteria donor (ECD) kidneys. Patient 1 received a retransplanted kidney from a SPK recipient whose postoperative course included treatment for CMV disease with VGCV.

All had received prophylaxis with either IV GCV or oral VGCV for at least 3 months. Two patients (patients 1 and 4) developed CMV viremia while still on VGCV prophylaxis and did not improve when IV GCV was started. IV foscarnet was given until the viral load became undetectable, and then leflunomide was initiated. The remaining patients developed CMV viremia after completion of the viral prophylaxis. The number of days to viremia (from the date of transplant) ranged from 38 to 458 days (median 148 days, mean 219 days).

Fig. 1 shows the response of the viral load to the start of antiviral therapy for the 5 individual patients. All of them had received between 1 and 3 antiviral agents for 2–5 months before leflunomide was started. In all 5 patients, viremia was successfully cleared. Patient 5 died of a myocardial infarction with a functioning allograft. Of the remaining 4 patients, 3 still have functioning renal grafts, while 1 patient who received a paired ECD kidney transplant went back on dialysis 18 months after transplant.

Patient 1

A 42-year-old African-American male with a history of (h/o) end-stage renal disease (ESRD) of unknown etiology, hypertension (HTN), who was on hemodialysis for 7 years, received a deceased donor renal transplant in July 2005 (fig. 1a). The renal allograft was procured from a 38 year-old Caucasian female who had received a SPK 3 months before (D-/R+) and died of intracranial bleed [21]. Her posttransplant course was notable for fever and diarrhea and she was treated with IV GCV for presumed CMV colitis. At the time of the kidney procurement from the first transplant recipient, she was noted to be CMV IgM negative. The second recipient was induced with antithymocyte globulin and received a total of 7 doses in the setting of DGF. His maintenance immunosuppression consisted of tacrolimus, MMF, and prednisone. For CMV prophylaxis, he was given IV GCV (50 mg IV daily for 2 weeks) followed by VGCV (450 mg daily). However, he was found to have leukopenia and CMV viremia on postoperative day (POD) 38 (307,000 copies/ml) while he was still on VGCV. He was switched to IV GCV but his viral load continued to rise, and IV foscarnet (3 gm BID) was started on POD 51. The genetic mutation study was notable for UL97 mutation. Viremia was cleared on POD 72, and IV foscarnet was continued until POD 179. Leflunomide was started on POD 185, and he still remains on it. His renal allograft is still functioning (serum creatinine, Scr 1.7–2.1 mg/dl) 10 years later, and he has not had a recurrence of CMV viremia/disease.

Patient 2

A 34-year-old Hispanic male with h/o ESRD, type 1 diabetes mellitus, HTN, and hyperlipidemia, who was on hemodialysis for 3.5 years, underwent a SPK (D+/R-) in August 2008 (fig. 1b). His induction treatment consisted of daclizumab. He was on tacrolimus, MMF, and prednisone, and there was no DGF. He was given a 3-month course of VGCV for CMV prophylaxis. He developed CMV viremia (67,000 copies/ml) on POD 373 and was symptomatic with malaise and diarrhea. Although he was started on IV GCV treatment, the CMV viral load continued to rise, and IV foscarnet was started on POD 378. The CMV viral load peaked at

214,000 copies/ml on POD 383, and the virus became undetectable on POD 401. IV foscarnet was discontinued on POD 436. Leflunomide was started on POD 528 and discontinued on POD 1,106 when his liver function tests were found to be elevated [AST 118 (normal range 15–37) and ALT 248 (normal range 8–35)]. A liver biopsy showed steatohepatitis (grade 1, stage 1). A normalization of the liver enzymes was seen 10 weeks after leflunomide was discontinued. The patient has remained free of CMV viremia/disease, and his renal allograft is still functioning (Scr 2.8–3.0 mg/dl).

Patient 3

A 43-year-old, highly sensitized (PRA: Class I 56%, Class II 85%) African-American male with h/o of ESRD secondary to posterior urethral valve syndrome, s/p DDRT (06/1987), s/p LRRT (10/1987) underwent a third renal transplant (D+/R–) with an ileal conduit on January 27, 2011 (fig. 1c). He was induced with antithymocyte globulin (100 mg × 4 doses). He received a 100-day course of VGCV (900 mg daily) for CMV prophylaxis. His posttransplant course was complicated by an intra-abdominal abscess requiring surgical drainage and prolonged bowel rest except for his medications. CMV was first detected on POD 146 when the patient presented with diarrhea and weakness. He was treated with VCGV (900 mg BID) but continued to have low-grade viremia for the next 5 months. UL97 mutation was detected, and leflunomide was started on POD 297. An investigational oral analogue of cidofovir (CMX001, now known as brincidofovir) obtained from Chimerix for compassionate use was added on POD 322 and discontinued on POD 439. The patient's renal allograft function remains stable (Scr of 1.3–1.4 mg/dl), and he continues on leflunomide.

Patient 4

A 45-year-old, highly sensitized (PRA 88–100%) African-American male with h/o of ESRD of unknown etiology, HTN, who was on hemodialysis for 7 years, received a paired deceased donor kidney transplant from a 67-year-old deceased donor in December 2002 (fig. 1d). He received 1 dose of antithymocyte globulin and 2 doses of basiliximab for induction. His posttransplant course was complicated by DGF. He received VGCV for CMV prophylaxis but developed leukopenia and CMV viremia while still on VGCV prophylaxis on POD 80. He was treated with an increased dose of VGCV and was switched to IV GCV treatment on POD 110 when the CMV DNA hybrid capture test results continued to rise. Foscarnet was started on POD 134, and CMV was undetectable on POD 154, at which time foscarnet was replaced with leflunomide. There was no recurrence of CMV viremia/disease, but the patient had gradually worsening renal allograft function. A renal biopsy on POD 145 showed acute tubulointerstitial nephritis (due to foscarnet), and a subsequent biopsy on POD 318 showed a type 1A rejection and chronic allograft nephropathy with 40% tubular loss. He was restarted on dialysis in July 2004.

Patient 5

A 51-year-old African-American male with h/o of ESRD, type 1 DM, and HTN underwent a SPK in May 2001 (fig. 1e). He was induced with 1 dose of antithymocyte globulin and 2 doses of basiliximab and was maintained on sirolimus/MMF/prednisone. His CMV prophylaxis consisted of 3 months of GCV treatment (mostly IV). His posttransplant course was complicated by DGF and three episodes of acute rejection (two type 1B rejections (on POD 21 and 43) and one type 2A rejection (on POD 184) and required treatment with IV antithymocyte globulin as well as pulse steroids. Viremia, first detected on POD 458, was accompanied by diarrhea and malaise, and the patient was treated with IV GCV. Although his viral load improved as estimated by a CMV hybrid capture study, he was unable to eradicate the

viremia, and a 2-week course of IV foscarnet was started on POD 595 to achieve viral clearance. He had a recurrence of CMV viremia on POD 811 and was treated with IV GCV but without viral clearance. IV foscarnet was started on POD 884, and leflunomide was added on POD 942. His last detectable CMV viremia occurred on POD 1,420. He died on POD 3,359 of a myocardial infarction. His renal allograft function ranged from 1.7–2.0 mg/dl in the last 3 months of his life.

Discussion

Since leflunomide received FDA approval in 1998 for the use in treating rheumatoid arthritis, its potential use as an antiviral agent has been explored by several groups [18, 19]. Its known mechanisms of action include inhibition of the enzyme dihydroorotate dehydrogenase and inhibition of phosphorylation of tyrosine kinases involved in T- and B-cell activity. Leflunomide is unique in that it appears to possess both immunosuppressive and antiviral properties [19].

Unlike other antiviral drugs that inhibit the viral DNA polymerase, leflunomide seems to act by preventing tegument acquisition by viral nucleocapsids. This unique mechanism of action makes it a potentially useful candidate drug in treating GCV-resistant CMV.

Reduction of immunosuppression is an important component of antiviral treatment in renal transplant recipients; however, the concern for precipitating an acute rejection episode often limits this option. Although not tested in the patients described in this series, replacing MMF with a mTOR inhibitor is another potential strategy to be considered. Several observation studies have suggested that sirolimus or everolimus may be associated with a lower incidence of CMV disease [22, 23].

Most cases of GCV resistance stem from mutations in the phosphotransferase gene (UL97) or in the DNA polymerase gene (UL54). Use of more potent induction and/or maintenance immunosuppressive agents and routine prophylaxis using oral GCV are thought to contribute to the development of a GCV-resistant CMV strain. In addition, underdosing of GCV when using estimated GFR or using the ideal body weight in the Cockcroft-Gault formula when calculating CrCl in obese patients is likely to result in a subtherapeutic level of GCV [24, 25].

We described a series of 5 renal transplant recipients who had GCV-resistant CMV disease (3 of 5 with UL97 mutations) and were successfully managed with leflunomide-based ‘consolidation’ therapy. Our strategy for treating GCV-resistant CMV in renal transplant recipients was to achieve viral clearance with IV foscarnet and maintain suppression of viral replication using leflunomide, which does not cause nephrotoxicity. In four cases, viral clearance was achieved with IV foscarnet and leflunomide was initiated to prevent viral recurrence. In 1 case, the patient had low-level viremia with first-line therapy (IV GCV or VGCV) and leflunomide was given with another oral agent (CMX001/brincidofovir) in order to achieve clearance of viremia.

The efficacy and safety of leflunomide as an antiviral agent have not been studied thoroughly. Farasati et al. [26] considered the antiviral effect of leflunomide against BK virus to be moderate at best based on a low selectivity index value of 3.8. As an anti-CMV agent, leflunomide lacks pharmacodynamic data including 50% effective concentration (EC₅₀) and selectivity index and has a wide interpatient variability in pharmacokinetics [27, 28]. In the clinical setting of high-grade viremia, it has been reported not to be very effective [29]. Taking this into consideration, we decided to achieve viral clearance with foscarnet and prevent viral recurrence with leflunomide. Reported adverse effects include diarrhea, anemia, trans-

aminitis, peripheral neuropathy, and thrombotic microangiopathy. We did not observe any of the known adverse effects except abnormal liver function tests (patient 2). In light of the long half-life of teriflunomide (~15 days), it may take several weeks for liver function tests to return to normal after discontinuation of the drug. In our experience, leflunomide is well tolerated and effective in preventing viral recurrence when used with short-term foscarnet in treating GCV-resistant CMV infection.

A review of the literature on the use of leflunomide in renal transplant recipients with CMV infection revealed only six publications, all of them case reports (table 2). Although the majority of the publications report clinical success, this could be attributed to reporting bias. Recently, a case report of failure of leflunomide to control recurrent CMV in an allogeneic stem cell transplant recipient has been reported [30]. A close look at the report shows that the patient was given leflunomide for only 2 weeks. In light of its long half-life, it is unlikely that the patient would have achieved a reasonable steady state during that time period.

In conclusion, leflunomide is a unique agent that possesses both antiviral and immunosuppressive properties. It may be useful in managing GCV-resistant CMV and deserves further study to confirm our findings and to determine the ideal dose and duration of the treatment.

Disclosure Statement

The authors declare that there are no conflicts of interests regarding the publication of this paper.

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Table 1. Baseline characteristics of patients and CMV treatments before leflunomide therapy

	Patients				
	1	2	3	4	5
Age, years/ gender/race	42/M/AA	34/M/H	43/M/AA	45/M/AA	51/M/AA
Transplant date	07/02/05	08/12/08	01/26/11	12/06/02	05/22/01
Transplant type	DDKT ^a	SPK	DDKT	DDKT	SPK
CMV D/R serostatus	D+/R+	D+/R–	D+/R–	D+/R–	D+/R–
CMV viremia detection date	08/09/05	08/20/09	06/22/11	02/17/03	08/11/03
CMV PPX	GCV (IV), VGCV	GCV (IV), VGCV	VGCV	VGCV	GCV (oral/IV)
LEF initiation date	01/03/06	01/22/10	11/19/11	05/08/03	02/10/04
Antiviral agents before LEF (after PPX)	GCV (IV) FOS	GCV (IV) VGCV FOS	VGCV	GCV (IV) FOS	GCV (oral/IV) FOS
CMV resistance genotype	UL97	None detected	UL97	UL97	Not done

DDKT = Deceased donor kidney transplant; LEF = leflunomide; FOS = foscarnet; PPX = prophylaxis; M = male; F = female; AA = African American; H = Hispanic.

^a Patient 1 had a retransplant of a previously transplanted allograft.

Table 2. Overview of literature on anti-CMV activity of leflunomide in kidney transplant recipients with either CMV infection or disease

Authors [ref.]	Patients, n	CMV viremia or disease (V/D)	Anti-CMV therapy before LEF	Resistance mutations	Follow-up duration, months	Outcome	Time to viral clearance
Avery et al. [29]	17 (3 K, 5 KP)	V (3), D (14)	GCV, FOS, CMVlg	UL97 (7), UL54 (2)	7–36	Viral clearance (9), Transient response (5), Failure (3)	0.4–5 months (median 1.25)
Andrassy et al. [31]	2	V (2)	GCV, FOS	UL97 (2)	15–36 ⁺	Viral clearance (2)	6 weeks
Ciszek et al. [32]	1	V (1)	GCV, FOS, CMVlg	not done	36 ⁺	Viral clearance (1)	6 months
John et al. [33]	4	D (4)	none	not done	3–5	Viral clearance (4)	1 month
John et al. [34]	17	V (7), D (10)	GCV (3)	not done	1–12	Viral clearance (15), Failure (2)	0.5–8 months (median 1.5)
Levi et al. [35] ^a	1	D (colitis, retinitis)	GCV, FOS, CMVlg	UL97 (1), UL54 (1)	12 m	Viral clearance (1)	1 year

LEF = Leflunomide; FOS = foscarnet. ^a No loading dose given. Dose gradually escalated.

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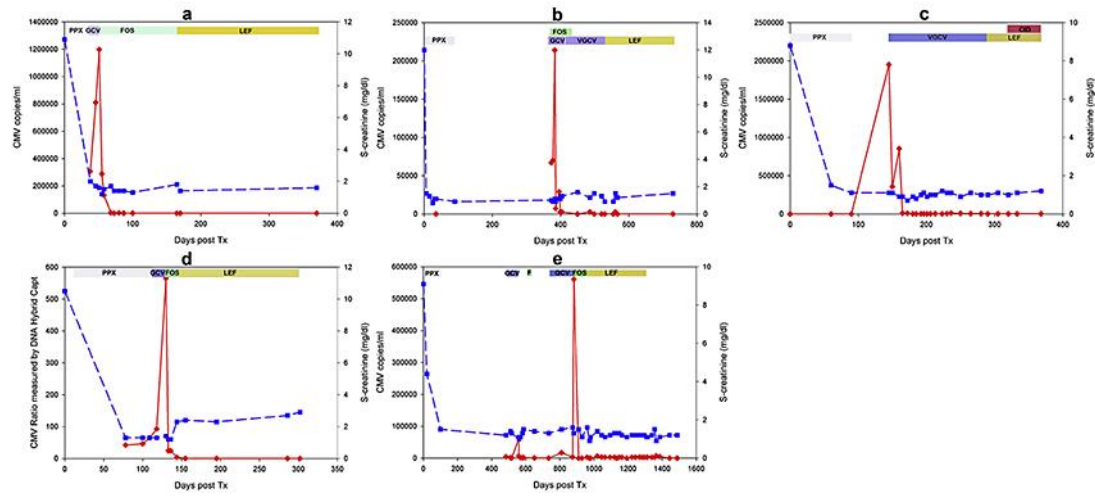


Fig. 1. Kinetics of viral load (red solid line) and Scr (blue dashed line) in 5 patients with CMV viremia after antiviral prophylaxis treated with leflunomide and other antiviral agents. The horizontal axis in each frame shows the time course in days after renal transplant (Tx). The duration of antiviral prophylaxis and therapy with different antiviral agents is indicated by horizontal bars on the top of each frame. PPX = Prophylaxis (gray bars); GCV/VGCV (purple bars); LEF = leflunomide (orange bars); FOS = foscarnet (green bars); CID = brincidofovir (red bar).