VALGANCICLOVIR AS MAINTENANCE THERAPY FOR CYTOMEGALOVIRUS RETINITIS IN A LUNG TRANSPLANTED PATIENT

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Purpose: To report the use of valganciclovir as maintenance therapy for cytomegalovirus (CMV) retinitis in a lung transplanted patient

Method: Case report

Result: A 30-year-old female with underlying pulmonary lymphangioleiomyomatosis received lung transplantation one year ago. Immunosuppressive agents were used after operation. Cytomegalovirus retinitis developed 4 months later but subsided after intravenous ganciclovir treatment. Unfortunately, the CMV retinitis recurred three times in one year while on oral ganciclovir maintenance therapy. To treat the latest relapse, valganciclovir 900 mg once daily was used as maintenance therapy after intravenous ganciclovir induction. With a 6-month follow-up, the fundoscopic examination revealed old atrophic scar and no active CMV retinitis. The patient was able to maintain best-corrected visual acuity of 20/20 in both eyes.

Conclusions: Valganciclovir may be used as maintenance therapy in CMV retinitis.

Key words: cytomegalovirus retinitis, ganciclovir, valganciclovir

INTRODUCTION

Cytomegalovirus (CMV) infections may be important sight- or life-threatening opportunistic infections in immunocompromised subjects.¹ It is estimated that CMV retinitis affects 25% to 40% of people with acquired immunodeficiency syndrome (AIDS).¹,² CMV is also among the most common and severe infections affecting recipients of solid organ and bone marrow allografts. Intravenous ganciclovir is most widely used for the treatment and prevention of CMV disease in human immunodeficiency virus (HIV) and in transplanted recipients.³ An oral form of ganciclovir has also been ap-
proved for maintenance therapy and prevention of CMV retinitis. Daily maintenance oral ganciclovir is usually taken in three-divided doses (up to 12 capsules per day) and has a bioavailability of only 6 to 9 percent. The limited bioavailability and saturable absorption of oral ganciclovir make the drug less than ideal as a choice for maintenance therapy. Valganciclovir is a monovalyl ester prodrug which is rapidly hydrolyzed to the active compound ganciclovir when administered orally. It has been reported to be used as induction and maintenance therapy in CMV retinitis. Herein, we report the use of valganciclovir as maintenance therapy for CMV retinitis in a lung transplanted patient.

CASE REPORT

A 30-years-old female was initially seen in March, 2002, and presented with exercise intolerance for three months. Her chest x-ray showed diffuse interstitial pulmonary lesion at both lung fields. Pathological exam of specimens from wedge resection of pulmonary lesion confirmed the diagnosis of lymphangioleiomyomatosis. Her pulmonary function deteriorated and she received lung transplantation in May, 2002. After transplantation, immunosuppressive agents (FK 506, imuran, and prednisolone) were given. In Nov. 2002, she was referred to the ophthalmological clinic with complaint of floaters and decreased visual acuity for one week. Her best-corrected visual acuity was 20/20 in both eyes. Slit-lamp examination demonstrated no abnormalities in the anterior segment in both eyes. The vitreous had moderate reaction in both eyes. Fundus examination revealed fluffy, yellowish-white exudates accompanied by intraretinal hemorrhage and edema at temporal lower part of the retina in the right eye and retinal opacification of granular appearance at temporal lower part in the left eye. Fluorescein angiography showed fluorescein dye leakage of temporal lower vessels in the right eye. Active CMV retinitis was impressed. Hemogram revealed white blood cell counts 3,700/μl. Intravenous ganciclovir (5mg/kg) twice daily for induction was given. After a 32-day full course of intravenous ganciclovir induction, the retinal lesions quieted down and became atrophic. She then took oral ganciclovir 1000 mg three times per day for maintenance therapy. However, in January and March 2003, two relapses of CMV retinitis with symptoms of increasing floaters were noted. The prominent new active lesions appeared in the nasal lower part in

Figure 1

1A: The fundus examination revealed frosted angiitis-like lesions with white granular areas of retinal necrosis and hemorrhage at temporal lower part in her right eye.
1B: Fluorescein angiography demonstrated prominent dye leakage from vessels.
the left eye. Hemogram revealed white blood cell counts 4,300/μl. She received the complete 32-day course intravenous ganciclovir (5mg/kg) twice daily for both relapses. Maintenance therapy with oral ganciclovir continued after intravenous induction therapy. During this period, immunosuppressive agents (FK 506, imuran, and prednisolone) were given simultaneously. The attempt to decrease the FK 506 dose to improve her immunity was not carried out because the blood level of FK 506 had already been at the lower limit required. CMV retinitis relapsed again in July, 2003. Hemogram revealed white blood cell counts 4,700/μl. The fundus examination revealed frosted angiitis-like lesions with white granular areas of retinal necrosis and hemorrhage at temporal lower part in her right eye. (Figure 1) Fundus examination of left eye also revealed granular

![Figure 2](image1)

2A: The fundus examination revealed granular lesions at nasal lower part of the retina in her left eye.
2B: Fluorescein angiography demonstrated prominent dye leakage from vessels.

![Figure 3](image2)

After maintenance therapy with valganciclovir, the fundoscopic examination revealed some fibrotic change and old atrophic scar at previous active retinitis site (3A: od; 3B: os) No active CMV retinitis noted. The patient had corrected visual acuity of 20/20 in her both eyes.
retinal lesions with yellowish-white exudates at nasal lower part. (Figure 2) Fluorescein angiography demonstrated prominent dye leakage from vessels. Induction therapy of intravenous ganciclovir was given immediately. After a complete course, we decided to use the ganciclovir as maintenance therapy. The drug was given in a dose of 900 mg once daily. After a 6-month follow-up period, her best-corrected visual acuity remained 20/20 in both eyes. There were no more symptoms of floaters. The fundus revealed fibrotic change at temporal lower in the right eye and atrophic scar in the left eyes at previous active lesions. (Figure 3)

DISCUSSION

Ganciclovir is commonly used in the treatment of CMV disease in patients who are immunocompromised and for the prevention of CMV disease in solid organ transplant recipients. The standard intravenous ganciclovir regimen for CMV retinitis consists of induction with 5 mg/kg administered intravenously twice daily for 14-21 days, followed by maintenance therapy at 5 mg/kg/day. Induction therapy with intravenous ganciclovir usually results in stabilization of fundus lesions within 2 weeks, and a full response in 1 month. Although intravenous ganciclovir is extremely effective, it is inconvenient for long term use and may be associated with the risk of catheter-related sepsis.

Oral ganciclovir is approved for maintenance therapy, although its efficacy is limited somewhat by its poor absorption. The approved dosage for maintenance is 1000 mg three times per day (up to 12 capsules per day, total 3000 mg), but the bioavailability of only 6 to 9 percent. However, the requirement of up to 12 capsules a day taken on a three-times daily schedule compromised patient compliance significantly.

Valganciclovir (Figure 4) is a valyl ester prodrug of ganciclovir that has an absolute bioavailability approximately 10-fold higher than that of oral ganciclovir. Pharmacokinetically, the absolute bioavailability of ganciclovir from valganciclovir is 60 percent, and a dose of 900 mg (two 450-mg tablets) results in ganciclovir blood levels similar to those obtained with the dose of 5 mg of intravenous ganciclovir per kilogram of body weight. In the AIDS patients with CMV retinitis, orally administered valganciclovir (900 mg twice daily) had been proved to be as effective as intravenous ganciclovir (5 mg/kg twice daily) for induction treatment. As maintenance therapy, oral valganciclovir (900 mg once daily) is also equally as effective as intravenous ganciclovir (5 mg/kg once daily).

During the maintenance therapy with valganciclovir, the most commonly reported adverse events included neutropenia, anemia, thrombocytopenia, gastrointestinal complaints, fever, headache, peripheral neuropathy, and retinal detachment.
After lung transplantation, patients usually need lifelong immunosuppressant and or would thus be in an immunocompromised status. In our patient, CMV retinitis developed after lung transplantation for pulmonary lymphangioleiomyomatosis. Three relapses were recorded. Her symptoms and the lesions of her fundus improved after induction therapy. However, the maintenance therapy with oral ganciclovir could not avoid relapse in both eyes. It might be due to the poor bioavailability of oral ganciclovir or poor compliance due to large-dose regimen.

Although in the AIDS patients with CMV retinitis, CD4+ count may increase after highly active antiretroviral therapy (HAART), and virus load could decrease due to immune recovery. The situation in the lung transplant patient is quite different. The patient may have adequate white blood cell and CD4+ cell counts, but the functions of the cells were suppressed by immunosuppressive agents. One way to decrease the relapse is to decrease the dosage of immunosuppressant. However, it is difficult to taper immunosuppressive agents. Ciardella et al. once reported successfully treated CMV retinitis with systemic ganciclovir and minimal dose of FK 506 in a renal transplant patient. However, the patient after lung transplantation required higher blood FK 506 level. In our patient, the patient had adequate white blood cell counts at each relapse, and the blood FK 506 level was lowered to the minimal therapeutic level. Therefore, we could not adjust the FK 506 dose anymore.

At the last relapse, we used valganciclovir (900mg once daily) as maintenance therapy after induction therapy with intravenous ganciclovir. The patient could maintain her best visual acuity, and repeated examinations of the fundus didn't demonstrate any sign of recurrence during a 6-month follow-up period. No adverse effects such as neutropenia, anemia, thrombocytopenia, nausea, and vomiting were noted.

This case showed good response to valganciclovir as maintenance therapy for CMV retinitis in a period of follow-up for 6 months. Although valganciclovir has high bioavailability, the treatment of CMV retinitis in immunocompromised patients still requires careful surveillance for progression throughout treatment. In the future, we believed using valganciclovir in the CMV retinitis could benefit immunocompromised patients after organ transplantation.

REFERENCES

以 Valganciclovir 在淋巴管平滑肌瘤症
接受肺臟移植後併發巨細胞病毒視網膜炎
中做為維持療法

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徐紹勛 2  李元麒 2  方啓泰 3

目的：以 Valganciclovir 在淋巴管平滑肌瘤症接受肺臟移植後併發巨細胞病毒視網膜炎中做為維持療法，同時回顧過去的相關文獻
方法：病例報告
結果：病例為三十歲女性，在一年前被診斷為肺部淋巴管平滑肌瘤症，同年接受肺臟移植手術，術後病人長期服用免疫抑制劑治療，病人於術後四個月併發巨細胞視網膜炎，於是住院接受靜脈注射 Valganciclovir 治療，但巨細胞病毒視網膜炎仍於一年內陸續復發三次，每日 900 毫克的 valganciclovir 被使用於最後一次復發後的維持療法，在之後六個月的追蹤，眼底檢查發現舊萎縮斑痕，並無巨細胞病毒視網膜炎復發的情形，病人兩眼最佳矯正視力皆可達壹點零。
結論：由我們的經驗發現，valganciclovir 可以在巨細胞病毒視網膜炎中做為維持療法。