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A case series using famciclovir in stem cell transplant recipients with valacyclovir hypersensitivity reactions

Shreya A Shah¹, Alison Gulbis² and Kaci Wilhelm²

Abstract

Background: Herpes simplex virus and varicella zoster virus reactivation can occur in up to 32% and 40% of patients, respectively in the first year post-transplant without prophylaxis. Antiviral therapy consisting of acyclovir or valacyclovir is recommended for at least 1 year post stem cell transplant per evidence-based guidelines.

Objective: In the event of a contraindication or hypersensitivity reaction to either drug, an alternative is essential based on the proven efficacy in reducing clinically significant herpes simplex virus and varicella zoster virus reactivations. We report two cases of successful initiation of famciclovir in stem cell transplant recipients experiencing hypersensitivity to valacyclovir or acyclovir.

Discussion: In both cases, there were no hypersensitivity reactions or breakthrough viral infections after famciclovir initiation but this observation is limited by a small patient population.

Conclusion: Due to the limited data available, famciclovir appears to be a reasonable option in immunocompromised patients with a mild valacyclovir or acyclovir hypersensitivity reaction.

Keywords

Valacyclovir hypersensitivity, acyclovir hypersensitivity, famciclovir, hematopoietic stem cell transplant, viral reactivations, herpes simplex virus, varicella zoster virus

Introduction

Infection is reported as the primary cause of death in 8% of autologous hematopoietic stem cell transplant (autoHSCT) recipients and in around 20% of allogeneic hematopoietic stem cell transplant (alloHSCT) recipients.¹ For at least 1 year following transplantation, patients remain at risk for infections from encapsulated bacteria and viruses.¹ Herpes simplex virus (HSV) and varicella zoster virus (VZV) reactivation can occur in up to 32% and 40% of patients, respectively in the first year post-transplant without prophylaxis.² VZV infectious complications could include scarring, postherpetic neuralgia, myelitis, small vessel encephalitis, and bacterial superinfection.³ In addition, HSV typically presents as oral and mucocutaneous lesions that can progress to esophagitis, pneumonitis, and rarely, hepatitis.⁴ Thus, antiviral therapy is essential to reduce morbidity associated with viral infections. Antiviral therapy has been proven to be effective in

reducing the rate of HSV and VZV reactivations in HSCT recipients. The incidence of HSV lesions is significantly reduced to 2.7% with valacyclovir and 2% with acyclovir.^{5,6} Furthermore, in a cohort of 1117 patients that received acyclovir or valacyclovir for 1 year post alloHSCT or autoHSCT, VZV reactivation occurred in less than or equal to 9% of patients.^{7,8} Therefore, antiviral therapy consisting of acyclovir or valacyclovir is recommended for at least 1 year post SCT.¹

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In the event of a contraindication to acyclovir or valacyclovir, alternatives are limited but essential based on the proven efficacy in reducing clinically significant HSV and VZV reactivations. Recommended alternatives to acyclovir or valacyclovir in the setting of resistance, include foscarnet or cidofovir.¹ Foscarnet is a pyrophosphate analog that non-competitively inhibits viral RNA and DNA polymerases and HIV reverse transcriptase.⁹ It has the propensity to cause major electrolyte abnormalities (i.e. hypocalcemia, hypomagnesemia, hypokalemia), renal impairment, infusion-related toxicities, only available as an intravenous (IV) formulation, and is costly to the patient.⁹ The other recommended alternative, cidofovir, is converted into an active intracellular metabolite (cidofovir diphosphate) that is incorporated into viral DNA, thus reducing DNA synthesis.¹⁰ It is associated with dose-dependent nephrotoxicity, potential bone marrow impairment, and is available as an IV formulation only.^{10,11} In the presence of an acyclovir or valacyclovir hypersensitivity reaction, a practical alternative is essential. Due to potential toxicities and undesirable routes of administration foscarnet and cidofovir are not preferred.

Famciclovir has demonstrated potent activity against VZV, HSV-1, and HSV-2, and has a labeled indication for herpes zoster, herpes labialis, and genital herpes in immunocompetent or HIV-infected adult patients.^{12,13} Data in the SCT population is limited. Famciclovir is rapidly converted to penciclovir, which is then phosphorylated by viral thymidine kinase in HSV-1, HSV-2, and VZV-infected cells to penciclovir monophosphate. Ultimately, it is converted to penciclovir triphosphate (active metabolite), which competes with guanosine during viral DNA synthesis and results in inhibition of DNA synthesis and replication.¹³⁻¹⁵ Famciclovir is rapidly and extensively absorbed following oral administration and only requires periodic monitoring of blood counts.¹³ The most common adverse events reported in greater than 10% of adult patients were headache and nausea with post-marketing reports of thrombocytopenia, abnormal liver function tests, dizziness, and skin disorders.¹³

Structurally, famciclovir has not been recommended as a potential alternative in the setting of valacyclovir hypersensitivity due to their close chemical structures. The 2-aminopurine nucleus common to acyclovir, valacyclovir, ganciclovir, valganciclovir, and famciclovir is thought to provoke both a contact allergy and systemic reactions.¹⁶ Currently, there are three published reports of cross-reactivity and one report of successful use with famciclovir post valacyclovir or acyclovir hypersensitivity.¹⁶⁻¹⁸ We report two cases of successful initiation of famciclovir in two SCT recipients experiencing hypersensitivity to valacyclovir or acyclovir.

Case 1

A 57-year-old woman presented with progressive cutaneous T cell lymphoma (CTCL) stage IVA (erythematous patches and plaques on her scalp, chest, back, and extremities) and evaluation for an alloHSCT. Her past medical history was significant for melanoma in situ of the left leg, hypertension, hypercholesterolemia, irritable bowel syndrome, atrial fibrillation, perineal HSV, and anxiety. Per patient report her history of perineal HSV consisted of painful lesions that were treated with oral acyclovir initially and then switched to oral valacyclovir. She developed a mild rash thought to be valacyclovir induced due to symptom resolution after drug discontinuation, but the etiology may have been HSV itself or CTCL. Upon presentation, she had a complex history of several drug allergies including amoxicillin (itching), daptomycin (rash), vancomycin (rash, peeling, itching), denileukin diftitox (peeling), bexarotene (rash, swelling of extremities and face), and codeine (rash, peeling, itching).

Almost 1 year later, while planning her matched unrelated donor alloHSCT she developed an HSV reactivation (open blisters and sores on her perineal area), which was confirmed as HSV on biopsy. She was re-challenged with oral acyclovir for 10 days and concomitantly started on azithromycin 500 mg daily for 5 days and levalbuterol 2 puffs twice daily as needed for shortness of breath. Her medications at the time included amiodarone 200 mg three times daily, aspirin 81 mg daily, ferrous sulfate 325 mg three times daily, furosemide 40 mg twice daily, digoxin 0.125 mg daily, levothyroxine 100 mcg daily, escitalopram 10 mg daily, lisinopril 10 mg daily, metoprolol 50 mg three times daily, esomeprazole 40 mg daily, nifedipine 30 mg daily, nystatin 500,000 units every 6 h, pravastatin 40 mg daily, clonazepam 0.5 mg twice daily, morphine sulfate ER 30 mg twice daily, aquaphor topical daily, ciclopirox olamine gel 0.7% topical daily, triamcinolone cream 0.1% transdermal daily as needed for rash, urea 10% lotion apply twice daily as needed for dry skin, morphine IR 15 mg every 6 h as needed for pain, and prochlorperazine 10 mg every 6 h as needed for nausea/vomiting. On day 10 of her HSV treatment, she subsequently developed a rash over 3-4 days, which improved with hibiclens wash, triamcinolone cream, aquaphor ointment, and discontinuation of acyclovir. A biopsy was taken by dermatology, which was proven to be spongiotic dermatitis. Dermatology considered it either a drug-related rash (favored) or manifestations of early CTCL. At next follow up (1 month later), her previous HSV ulcers had completely resolved, but future antiviral options were of concern due to her upcoming alloHSCT. In the interim, she had also failed a one week trial of vorinostat with interferon

due to gastrointestinal toxicities, but continued interferon as monotherapy.

Within 1 week, she presented to the hospital with worsening left lower extremity pain that radiated down to her foot and a recent erythematous maculopapular rash that was now healing. She was eventually admitted for intravenous pain medications and was initiated on gabapentin 300 mg by mouth three times daily. During that hospitalization, dermatology performed a biopsy showing spongiotic and psoriasiform dermatitis, which could represent CTCL disease relapse or be medication induced from the recent initiation of interferon (which had been held upon admission). By discharge her skin had improved and interferon was not resumed. However, during that admission, she was evaluated by infectious diseases for antiviral options post HSCT and consequently underwent successful oral acyclovir desensitization 3 days prior to discharge with only facial flushing occurring and was ultimately discharged on oral valacyclovir 500 mg daily.

Two weeks later at follow up, the patient reported initially experiencing a mild erythema on her skin, which progressed to a whole body rash, peeling and fevers since hospitalization. A skin biopsy revealed spongiotic dermatitis with parakeratosis, due to a possible drug rash, atopic dermatitis, contact dermatitis, or nummular dermatitis, of note no evidence of CTCL as an etiology. Valacyclovir was discontinued. Her fevers resolved and the skin erythema improved over the next 5 days. She was ultimately initiated on famciclovir 500 mg by mouth twice daily 8 days prior to transplantation without any complications. She was noted to have complete resolution of skin manifestations while on famciclovir. She underwent alloHSCT as planned and was maintained on famciclovir without any reported viral reactivations for at least 1 year post HSCT but has since been lost to follow up.

Case 2

A 60-year-old woman presented with a new diagnosis of stage III non-secretory multiple myeloma and a history of hypothyroidism secondary to hashimoto's thyroiditis. She was referred to us for induction chemotherapy and eventual autoHSCT. Her home medications included a compounded thyroid supplement and occasional ibuprofen with no known drug allergies. Her induction chemotherapy consisted of bortezomib, lenalidomide, liposomal doxorubicin, and dexamethasone. Concurrently, she was started on aspirin 81 mg daily, zolpidem 5 mg at bedtime and valacyclovir 500 mg daily on day 1 of chemotherapy. On day 15 of induction chemotherapy, she developed an urticarial-type rash bilaterally on her torso, back and

thighs, which was treated with a 10-day methylprednisolone taper and patient decision to discontinue valacyclovir. At subsequent follow up, about 2 weeks later, her rash had subsided. She was re-challenged with valacyclovir and similar symptoms reappeared, without any other systemic manifestations. These sequences of reactions were attributed to oral valacyclovir. Two months later she returned for stem cell mobilization with filgrastim followed by high dose melphalan (200 mg/m²) and autoHSCT. The day prior to her autoHSCT she was started on levofloxacin 500 mg daily, fluconazole 400 mg daily and famciclovir 500 mg daily for prophylaxis. By day 11 post HSCT, she stopped anti-fungal and bacterial prophylaxis and continued anti-viral prophylaxis without any reported issues. In addition, pneumocystis pneumonia prophylaxis was eventually added and at last follow up (6 months post HSCT) famciclovir and sulfamethoxazole/trimethoprim were discontinued. She continues to be in remission without any transplant or infection-related complications.

Discussion

Acyclovir and valacyclovir allergies are rarely reported in the literature, leaving clinicians without evidence-based solutions.¹⁷ As previously mentioned, the 2-aminopurine nucleus is present in many anti-viral medications and may be responsible for provoking both contact allergies and systemic reactions.¹⁶ The present case series provides evidence that, although structurally similar, famciclovir may be a safe and practical alternative in the setting of an acyclovir or valacyclovir hypersensitivity reaction. Famciclovir has a 77% bioavailability following the administration of a 500 mg oral dose.¹³ It has an intracellular half-life of 10–20 h for HSV 1 and 2 and up to 11 h for herpes zoster. As an added benefit, it has minimal drug interactions as it is not metabolized through the CYP 450 enzymatic system.¹² Foscarnet and cidofovir are still viable alternatives to acyclovir, but multiple limitations restrict their use in HSCT recipients.

The American Society for Blood and Marrow Transplantation has not provided any formal recommendations on famciclovir use due to the insufficient amount of safety and efficacy data in the stem cell transplant patient population. However, there has been one randomized, double-blind trial in immunocompromised patients that compares famciclovir to acyclovir at treatment doses for localized dermatomal herpes zoster. The investigators included 148 patients who were immunosuppressed due to bone marrow transplantation, solid organ transplantation, or chemotherapy/radiotherapy for cancer or leukemia. The authors demonstrated similar efficacy and safety among both study drugs.¹⁹

Table 1. Case reports of famciclovir use post acyclovir or valacyclovir hypersensitivity reactions.

Patient no./ reference no.	Age (year)/ sex	Indication for anti-viral therapy	Anti-viral eliciting initial reaction	Anti-viral administered as re-challenge	Onset of reaction after oral anti-viral	Initiation of famciclovir	Presence of reaction to famciclovir
1/19	44/F	Genital herpes	Oral valacyclovir	Topical acyclovir	After 2 tablets	Yes	Yes
2/18	30/F	Labial and ophthalmic herpes	Topical acyclovir	Oral Acyclovir	24 h	Yes	No
3/18	28/F	Labial herpes	Oral acyclovir	None	6 h	Yes	Yes
4/17	23/F	Oral herpes	Topical acyclovir	Oral acyclovir	6 h	Yes	Yes
5	57/F	Antiviral prophylaxis post alloHSCT	Oral acyclovir	2 nd – oral acyclovir 3 rd – oral valacyclovir	Unknown	Yes	No
6	60/F	Antiviral prophylaxis post autoHSCT	Oral valacyclovir	Oral valacyclovir	Unknown	Yes	No

autoHSCT: autologous hematopoietic stem cell transplant; alloHSCT: allogeneic hematopoietic stem cell transplant.

To our knowledge, there have been only four previously published reports of famciclovir use post acyclovir or valacyclovir hypersensitivity reactions. All reports involved young female adults with HSV infections of the ophthalmic, labial, or oral regions (Table 1). Half of the patients initially experienced a local reaction to topical acyclovir cream or ophthalmic ointment and were then re-challenged with oral acyclovir or valacyclovir several months later and experienced a systemic reaction. The other two reported cases were initiated on oral acyclovir or valacyclovir and only one patient was subsequently re-challenged with topical acyclovir, which resulted in a local hypersensitivity reaction. In all patients, the administration of oral acyclovir or valacyclovir led to the development of a systemic hypersensitivity reaction consisting anywhere from an erythematous maculopapular rash to edematous lesions on the face, trunk, extremities, or inner thighs. All four cases included the use of a patch test based on their current standards that included a series evaluating acyclovir, valacyclovir, famciclovir, and one test included evaluation of ganciclovir. All four tests displayed a positive reaction to acyclovir or valacyclovir and a negative result for famciclovir. As a result, all four patients received a trial of oral famciclovir.

Of the four cases, there was only one reported successful famciclovir initiation after a hypersensitivity reaction developed to oral and topical acyclovir. The patient initially presented with labial and upper eyelid eczema after applying topical acyclovir cream and ophthalmic ointment to her HSV lesions. A few months later, after administration of oral acyclovir she developed a widespread maculopapular rash and secondary eczematization within 24 h. Afterward she successfully received an oral trial of famciclovir 250 mg, given four times in one day without any concerns. The other three patients subsequently developed a reaction after being

challenged with famciclovir. Reactions were described as itchy, erythematous patches or dermatitis on the face and trunk of the body with a reported onset between 12 h and 2 days after famciclovir administration. The single report of successful famciclovir use did not refer to the duration of famciclovir use. None of the publications reported any outcomes or long term follow up.

Specifically in our two cases, patients were initiated on oral antivirals (valacyclovir or acyclovir tablets) only. Although patch tests were not conducted in either of these patients, skin biopsies were performed for one case, and both cases were re-challenged at some point in their medical history with oral acyclovir or valacyclovir and were found to encounter a similar hypersensitivity reaction to the initial occurrence. Both reported cases successfully used oral famciclovir (1 year and 6 months, respectively) without any reported HSV reactivations or complications.

This is the first case series of successful famciclovir use in the setting of an acyclovir or valacyclovir hypersensitivity reaction as antiviral prophylaxis in HSCT patients. Famciclovir may represent a therapeutic alternative in this setting. We did not observe any hypersensitivity reactions or breakthrough viral infections after famciclovir initiation in our experience but this observation is limited by a small patient population. Data with famciclovir in HSCT patients is limited to in vitro studies and one trial involving a mixed population of immunosuppressed patients with localized dermatomal herpes zoster. However, there is an approved indication for use in HIV-infected patients with herpes zoster, herpes labialis and genital herpes, which may be extrapolated to HSCT patients. Post HSCT it is essential to have a safe and practical alternative in the setting of a hypersensitivity reaction to acyclovir or valacyclovir. In summary, to further solidify our confidence in using famciclovir to prevent HSV or VZV infectious

complications a larger sample of SCT recipients should be evaluated. However, due to the limited data available famciclovir appears to be a reasonable option in immunocompromised patients with a mild valacyclovir or acyclovir hypersensitivity reaction.

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Conflict of interest

None declared.

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