

## Post transplant complications

# Clinical utility of oral valacyclovir compared with oral acyclovir for the prevention of herpes simplex virus mucositis following autologous bone marrow transplantation or stem cell rescue therapy

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### Summary:

Oral acyclovir has been demonstrated to prevent reactivation of herpes simplex virus (HSV) infections when administered prophylactically to autologous bone marrow transplant (BMT) recipients or patients undergoing stem cell rescue therapy. Oral valacyclovir, which is converted in the body to acyclovir, has greater oral bioavailability than oral acyclovir and compared with oral acyclovir yields similar acyclovir plasma concentrations with less frequent (twice-daily) dosing. This study compared the efficacy of oral valacyclovir with that of oral acyclovir at preventing HSV mucositis in BMT recipients. A total of 60 HSV-1-positive patients scheduled for BMT or stem cell rescue therapy were treated prophylactically with valacyclovir 500 mg twice daily until resolution of neutropenia. Data from these patients were compared with those of a historical control group of 60 patients who had received acyclovir 600 mg every 6 h until resolution of neutropenia or acyclovir 125 mg/m<sup>2</sup> intravenously every 6 h. The results show that none of the patients developed oral or oropharyngeal HSV infection while receiving either treatment. Of the 60 patients receiving valacyclovir, 38 (63%) completed treatment without the need for intravenous acyclovir compared with 12 of 60 (20%) patients in the acyclovir group. Additionally, the total number of doses of drug administered to the valacyclovir group was significantly less than the number received by patients in the acyclovir group. No serious adverse events occurred in either group of patients. This study demonstrates that oral valacyclovir and acyclovir are comparably effective and safe in preventing reactivation of HSV infections in autologous BMT and stem cell recipients. The less frequent dosing schedule with valacyclovir compared with acyclovir offers a potential advantage for patients undergoing BMT who frequently suffer with severe mucositis and have difficulty taking oral medications.

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In patients receiving bone marrow transplants (BMTs) who are seropositive for herpes simplex virus (HSV)-1, the incidence of reactivation of HSV ranges from 65 to 90%.<sup>1–3</sup> Although rarely life-threatening, the oral ulcerations arising from viral reactivation commonly produce significant pain, impair oral function, and may be a portal of entry into the bloodstream for other oral pathogens.<sup>4</sup> Administered orally or intravenously, acyclovir has consistently been shown to be effective against reactivation of HSV among recipients of allogeneic or autologous BMT.<sup>5–9</sup> Orally administered acyclovir, however, has variable and low bioavailability requiring 4-times-daily dosing to achieve adequate efficacy for preventing HSV mucositis infection.<sup>10,11</sup> Patients with severe mucositis who are unable to tolerate oral acyclovir are treated with intravenous acyclovir, a significantly more expensive form of the drug.

Valacyclovir, the L-valine ester prodrug of acyclovir, is rapidly and almost completely hydrolyzed to acyclovir by the liver and gastrointestinal tract and has higher bioavailability than acyclovir.<sup>12</sup> The oral administration of valacyclovir yields plasma concentrations of acyclovir 3–5 times higher than those attainable with similar (200–800 mg) oral doses of acyclovir.<sup>13</sup> Valacyclovir can thus be dosed less frequently than oral acyclovir while maintaining comparable efficacy. For example, in a large, international, multicenter trial, twice-daily valacyclovir proved as effective and safe as 5-times-daily acyclovir in the treatment of genital herpes.<sup>14</sup> The current study was conducted to evaluate the efficacy and safety of oral valacyclovir in reducing the incidence of reactivation of HSV-1 and the occurrence of mucositis in recipients of autologous BMT or stem cells. The results were compared with those from a historic control group of recipients of BMT or stem cell rescue therapy who had received prophylaxis with oral acyclovir.

## Methods

### Oral valacyclovir group

In total, 60 consecutive patients were enrolled at The Jewish Hospital/University of Cincinnati Bone Marrow Transplant Program. Patients were at least 18 years of age and were scheduled to undergo either autologous BMT or high-dose chemotherapy with stem cell rescue. Only patients with IgG antibody titers to HSV-1 greater than 0.23 U (SmithKline Beecham Clinical Laboratories) were eligible for the study. Informed consent was obtained from all patients. Patients were excluded from the study if they had a positive herpes simplex culture of the oral cavity or oropharynx at baseline, a documented herpes simplex infection 3 days prior to hospital admission, a history of sensitivity or intolerance to acyclovir or valacyclovir, an estimated creatinine clearance less than 20 ml/min, or if they had received an allogeneic BMT.

After screening, patients received oral valacyclovir 500 mg twice daily beginning at the time when transplant conditioning was initiated and continuing until neutropenia had resolved (ie neutrophil count greater than 1000 cells/ml). This dosage is within the range used for other valacyclovir indications and has been shown to be well tolerated.<sup>12-14</sup> The dosage of valacyclovir was decreased by 50% in patients with a creatinine clearance less than 30 ml/min, and the drug was discontinued in those with a creatinine clearance less than 20 ml/min.

During prophylaxis, patients who were unable to tolerate oral medication received intravenous acyclovir 125 mg/m<sup>2</sup> every 6 h until they were capable of resuming treatment with oral valacyclovir. The number of prophylaxis days treated and the total number of doses of oral valacyclovir and intravenous acyclovir administered were recorded for each patient.

Pretreatment evaluations included a complete medical history and physical examination, culture of the oral cavity and oropharynx, and standard clinical laboratory tests. Laboratory tests were repeated daily during the treatment phase. Weekly during the treatment phase, patients were examined for signs or symptoms of active herpes infection or any unusual clinical manifestations in the oral cavity or oropharynx, and viral cultures for HSV-1 and HSV-2 were taken. The date of onset of any adverse effects, as well as their duration, severity, and possible relation to therapy, was recorded. Once a HSV infection was strongly suspected clinically or proven by culture, the infection was treated with intravenous acyclovir, and the patients were withdrawn from the study.

Thrombotic thrombocytopenic purpura (TTP) has been reported with doses of 8 g/day of valacyclovir for the prevention of cytomegalovirus (CMV) infection in patients with end-stage AIDS or undergoing BMT or renal transplant. Although the low dose of valacyclovir (500 mg twice daily) employed in this study was not expected to result in this syndrome, patients were followed prospectively for evidence of TTP with daily complete blood counts, serum creatinine levels, and clinical evaluations.

### Oral acyclovir group

The historical control group comprised 60 patients who underwent autologous BMT or high-dose chemotherapy with stem cell rescue between January 1996 and June 1999. All patients had IgG antibody titers to HSV-1 greater than 0.23 U. Those with normal renal function were prophylactically treated with oral acyclovir 600 mg every 6 h until neutropenia resolved. Those who did not tolerate the oral medication were given 125 mg/m<sup>2</sup> intravenously every 6 h until neutropenia resolved (ie neutrophil count increased to more than 1000 cells/ml). Patients with an estimated creatinine clearance of 60–80, 30–60 ml/min, and below 30 ml/min were dosed every 8 h, every 12 h, and once daily, respectively. In addition to patient demographics, the results of oral and oropharyngeal viral cultures taken during prophylaxis with acyclovir, and treatment and outcome of patients with reactivation of HSV infection were recorded. The number of days patients tolerated oral medication and did not require intravenous acyclovir was assessed, as were the total doses of acyclovir administered orally and intravenously.

### Data analysis

Data were summarized using descriptive statistics, but no formal statistics were performed.

## Results

All 60 patients enrolled in the valacyclovir group completed the study. There were no significant differences between the valacyclovir group and the acyclovir group in patients' age, sex, or diagnosis (Table 1). Details of patients' conditioning regimens are presented in Table 2. The differing components of the chemotherapeutic regimens between the valacyclovir group and the acyclovir group reflect evolving trends in the selection of conditioning agents.

For patients in the valacyclovir group, a total of 1946 doses of valacyclovir and 682 doses of intravenous acyclovir were administered. For patients in the acyclovir group, a total of 2621 doses of oral acyclovir and 1988 doses of intravenous acyclovir were administered.

More patients in the valacyclovir group compared with the acyclovir group were able to complete therapy on oral treatment without the need for intravenous intervention. Of the 60 patients in the valacyclovir group, 38 (63%)

**Table 1** Demographics and patient characteristics

	Valacyclovir	Acyclovir
Number of patients	60	60
Mean age, years	53	47
Number of females	47	48
Diagnosis, <i>n</i>		
Non-Hodgkin's lymphoma	6	11
Hodgkin's lymphoma	4	2
Leukemia	2	4
Breast carcinoma	35	34
Ovarian carcinoma	4	5
Multiple myeloma	9	2
Mean duration of neutropenia, days	16	18

**Table 2** Conditioning regimens for patients receiving valacyclovir or acyclovir

Conditioning regimens	Valacyclovir (n = 60)	Acyclovir (n = 60)
Cyclophosphamide/thiotepa/carboplatin	30	8
Cyclophosphamide/mitoxantrone/carboplatin	1	
Carboplatin/VP-16	1	
Melphalan/ ± TBI	6	2
VP-16/cyclophosphamide	6	20
VP-16/cyclophosphamide/TBI	6	
VP-16/cyclophosphamide/thiotepa	5	
VP-16/cyclophosphamide/melphalan	1	
Cyclophosphamide/BCNU/VP-16	3	1
Busulfan/cyclophosphamide	1	
Thiotepa/carboplatin	3	3
Cyclophosphamide/thiotepa	3	12
Cyclophosphamide/carmustine/etoposide	1	
Cyclophosphamide/etoposide/TBI	2	
Cyclophosphamide/etoposide	2	1
Cytosine arabinoside/idarubicin	1	
SWOG 9106	1	

completed the study without the need for intravenous acyclovir; 20 of the remaining patients required intravenous acyclovir; two of these patients were able to resume valacyclovir after their nausea and vomiting resolved. In contrast, only 12 (20%) of 60 patients in the oral acyclovir group completed the study with oral dosing only.

No positive HSV-1 or HSV-2 cultures or suspected clinical herpetic infections occurred in either group of patients receiving oral medication. One patient who initially received valacyclovir did have HSV cultured from the oral cavity 12 days after his antiviral medication was changed to intravenous acyclovir. The patient died shortly afterwards of multiple organ failure.

There were no serious clinical adverse reactions or laboratory abnormalities attributed to acyclovir or valacyclovir. Of the 60 patients receiving valacyclovir, six (10%) required dosing adjustments because of a reduction in creatinine clearance compared with 21 (35%) of the 60 patients in the acyclovir group.

## Discussion

The results of this study demonstrate that the prophylactic administration of valacyclovir 500 mg twice daily until resolution of neutropenia prevents reactivation of HSV infection in patients receiving autologous BMT or stem cell rescue therapy. Only one extremely ill patient grew HSV-1 post mortem after a course of valacyclovir followed by 12 days of intravenous acyclovir. The more convenient twice-daily dosing regimen for valacyclovir compared with oral acyclovir allowed more patients to continue oral prophylaxis with significantly fewer days of intravenous acyclovir (35% with oral valacyclovir compared with 20% with oral acyclovir).

HSV is the most common viral pathogen associated with oral lesions in patients receiving myelosuppressive chemotherapy or BMT. Unlike HSV infections in immunocom-

petent patients,<sup>15</sup> oral and pharyngeal lesions in immunocompromised hosts are associated with severe ulcerations that develop on both keratinized and non-keratinized mucosal surfaces.<sup>16</sup> The mucositis that results from the reactivation of latent disease is often severe, painful, and prolonged, and HSV infection may lead to esophagitis and, rarely, disseminated infection.<sup>5</sup> In view of the serious morbidity associated with HSV reactivation, acyclovir and valacyclovir are used routinely in BMT centers for the prevention of HSV infections in HSV-seropositive neutropenic patients. Double-blind studies have demonstrated the safety and efficacy of acyclovir as prophylaxis against reactivation of HSV among severely immunocompromised patients.<sup>1,9,17</sup> The results of the current study are consistent with previous findings in demonstrating prevention of HSV reactivation in the 60 patients in the acyclovir control group. In contrast, a higher incidence of HSV reactivation has been reported with a lower total daily dosage of acyclovir than was employed in the current study.<sup>18</sup>

Several prophylactic acyclovir regimens that vary considerably in cost, total daily dosage, and route of administration have been advocated, but no specific protocol is widely adopted for BMT recipients. The current study employed the protocol proposed by Rayani *et al*,<sup>11</sup> who found that the therapeutic benefits of acyclovir prophylaxis were cost effective. Rayani *et al* successfully implemented a standardized HSV prophylaxis protocol in BMT recipients, and demonstrated that 600 mg oral acyclovir administered every 6 h provides systemic concentrations similar to those achieved in prophylaxis studies utilizing intravenous acyclovir 125 mg/m<sup>2</sup>.

Both acyclovir and valacyclovir were well tolerated by the patients in this study despite patients' frequent concomitant acute illnesses and the administration of a number of other medications. The use of acyclovir and valacyclovir was not associated with toxicity. Central nervous system events including hallucinations, agitation, and depression, observed in patients taking valacyclovir or

intravenous acyclovir after renal transplantation were not observed in the current study.<sup>19,20</sup> Furthermore, no cases of TTP were observed in the current study. TTP and/or hemolytic uremic syndrome (TTP/HUS) have been reported with increased frequency with valacyclovir in patients with advanced human immunodeficiency virus (HIV) infection.<sup>21</sup> The thrombotic microangiopathies are a spectrum of clinical syndromes characterized by the presence of microangiopathic hemolytic anemia, microvascular thrombosis, thrombocytopenia, and multiple organ dysfunction.<sup>22</sup> The overall incidence of TTP/HUS in BMT patients has been reported to range from 3 to 7% and is almost twice as frequent in allogeneic BMT recipients as in autologous BMT recipients.

One source of concern regarding the use of any prophylactic antimicrobial agent in immunocompromised patients is the potential for the selection or development of resistant organisms. For this reason, there is controversy regarding the use of acyclovir prophylaxis against reactivation of HSV infection in BMT recipients.<sup>23</sup> Some authors advocate acyclovir use only for documented infections and caution against overuse, which can lead to HSV resistance.<sup>24,25</sup> Indeed, HSV resistance to acyclovir arises relatively frequently in immunocompromised patients as evidenced by the study of Englund *et al*,<sup>26</sup> who reported seven such cases in 148 immunocompromised patients.<sup>26</sup> In the current study, no infections with resistant HSV were observed among acyclovir or valacyclovir recipients. It is possible that the short course of prophylaxis, which averaged less than 20 days, compared with the prolonged courses of prophylaxis utilized in other studies reduced the risk of selecting or inducing resistant virus. Additionally, in the current study, the follow-up period after discontinuation of prophylactic therapy was often less than 20 days – perhaps an insufficient duration of time to recognize infections with resistant viruses. In previous studies, acyclovir-resistant HSV infections have required high-dose intravenous treatment with acyclovir<sup>12,27</sup> or the use of other antiviral medications. In this context, the advantage of achieving enhanced plasma levels of acyclovir following oral dosing with valacyclovir is potentially significant in BMT recipients. Given the favorable safety profile and improved bioavailability of valacyclovir, additional studies treating patients with acyclovir-resistant HSV infections with valacyclovir are warranted.

In summary, this study of 120 patients receiving BMT or stem cells treated with oral antiherpetics demonstrates the value of less-frequent twice-daily dosing of valacyclovir over 4-times-daily oral acyclovir administration. Prophylactic twice-daily 500 mg valacyclovir during chemotherapy-induced or BMT regimen-induced neutropenia was associated with a reduction in the need for intravenous acyclovir (administered when patients could not tolerate oral medication) and provides the advantage of less-frequent administration compared with 4-times-daily oral acyclovir.

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