Clinical Article

The Effect of Valacyclovir and Prednisolone in Reducing Symptoms of EBV Illness In Children: A Double-Blind, Placebo-Controlled Study

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Abstract

The Epstein-Barr virus is a common cause of illness in children. Treatment has been through general supportive measures. Management and treatment of Epstein-Barr virus illness are changing rapidly. This study demonstrates that children with EBV illness treated with valacyclovir and prednisolone have more rapid recovery and a milder course compared to children treated conservatively. *Int Pediatr. 2003;18(3):164-169.*

Key words: Epstein-Barr virus (EBV), prednisolone, treatment, valacyclovir

Introduction

During our lifetime, each individual is at risk to develop EBV infection and its associated illnesses.[1,2] This is a contagious illness primarily of early childhood with nearly 80% of all 5-year-old children and 40-50% of children in privileged areas being seropositive.[3] Primary infection may produce mild or inapparent illness or infectious mononucleosis.[3-6] Complications, when they occur, may affect all organ systems and be fatal.[2,7-9] The most frequent complications are otitis media and sinusitis.[4] Severe complications are fortunately rare.

Traditional therapy consists of supportive measures and rest. The current antivirals do not cure but suppress viral replication.[10-12] It is possible that treatment of EBV disease may lessen the occurrence of relapses or recurrences[13] and chronic EBV infection that may predispose to lymphoproliferative disease.[1,14] Steroids may further promote recovery as well as reduce the severity and duration of fever, sore throat, and hematologic changes.[15-17] The management and treatment of Epstein-Barr virus illness are rapidly changing. This report evaluates the efficacy of valacyclovir and prednisolone in treating children with Epstein-Barr virus illness in a double-blinded, single center, placebo-controlled study.

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Materials and Methods

Forty-five children, age 2-18 years, diagnosed with Epstein-Barr virus illness were randomized into three treatment groups. Group I received valacyclovir 20 mg/kg/dose with three doses per day for 14 days and placebo A once per day for five days. Group II received valacyclovir 20 mg/kg/dose with three doses per day for 14 days plus prednisolone 1 mg/kg/day for five days. Group III received placebo B three times per day for 14 days plus placebo A once per day for five days.

For inclusion into this study, a child had to have the characteristic features of Epstein-Barr virus illness (fever, sore throat, lymphadenopathy, exudative pharyngitis) and EBV illness confirmed by a positive EBV antibody profile showing acute illness. Patients were assessed during the study by their clinical manifestations, complete blood count, and physician's clinical impression of improvement. The clinical manifestations including sore throat, stomachache, fatigue, swollen glands, headache, vomiting, rash, loss of appetite, nausea, sweats, chills, swollen eyes, runny nose, cough, and feeling bad were scored as either absent (0), mild (1), moderate (2), or severe (3) from a standarized scoring system developed by the authors. A total score was calculated by summing all but two clinical manifestations, feeling bad and loss of appetite. A selected score was limited to the sum of sore throat, fatigue, swollen glands, nausea, and chills. The patient's pattern of activities and temperature were also recorded. The family recorded data on a standardized tracking form.

A complete blood count with manual differential, heterophile, and EBV antibody profile were collected at the initiation of the study. Informed consent was

obtained as approved by the IRB at Central Baptist Hospital, Lexington, Kentucky. An independent pharmacy was in charge of random group assignment, medicine dispersement, and dosing. A complete blood count and manual differential were repeated at 4-5 days and 20 days after enrollment. Participants were reexamined 20 days after enrollment.

All 45 patients that were randomized were included in all statistical analyses. Patients that did not complete the study or had a missing result on day 20 had their last observation carried forward to day 20 prior to any analysis. The primary efficacy measure was changed from baseline scores at day 20. This endpoint was analyzed for total score, selected score, feeling bad, and fatigue, separately. The change from baseline was compared between valacyclovir plus prednisone and placebo, valacyclovir and placebo, and valacyclovir plus prednisone and valacyclovir using the van Elteren method of the Wilcoxon rank-sum test stratifying by baseline severity. All three pairwise comparisons were made.

The percent change from baseline at day 20 was also analyzed for total score and selected score and summarized for feeling bad and fatigue. The percent change from baseline was compared between valacyclovir plus prednisone and placebo, valacyclovir and placebo, and valacyclovir plus prednisone and valacyclovir using the van Elteren method of the Wilcoxon rank-sum test stratifying by baseline severity. All three pairwise comparisons were analyzed for both total and selected scores.

Shifts in changes from baseline scores at day 20 were examined and analyzed for total score, selected score, feeling bad, fatigue, and temperature. The shift categorized as an improvement if the score decreased from baseline to day 20. The shift was categorized as no change if the score remained the same. The shift was categorized as a worsening if the score increased from baseline to day 20. The shifts were compared between valacyclovir plus prednisone and placebo, valacyclovir and placebo, and valacyclovir plus prednisone and valacyclovir using a Mantel-Haenszel mean score test stratifying by baseline severity. All three pairwise comparisons were analyzed for all five scores.

All analyses were exploratory and no adjustments were made for multiple comparisons.

Results

Table 1 shows the demographics of the study population at the beginning of the study. The treatment groups were matched by gender, age, and baseline clinical manifestations. They were comparable in their baseline means for clinical manifestations.

Table 2 shows the mean change in the score for the clinical manifestations from the baseline values at day 20 of the study. There was minimal temperature change from the baseline for all three treatment groups. However, those receiving valacyclovir and valacyclovir plus prednisone had a greater decrease from baseline than placebo for total score, selected score, feeling bad, and fatigue. Valacyclovir plus prednisone showed a statistically significant difference in change from baseline fatigue scores over placebo (Table 2). The mean percent change also showed that those receiving valacyclovir and valacyclovir plus prednisone had a greater decrease from baseline than placebo for total score, selected score, feeling bad, and fatigue.

Table 3 shows the shifts (improvement, no change, worsening) from baseline to day 20. Though the mean change in temperature was minimal, the shifts indicated that the two valacyclovir treatments revealed a stronger trend for patients improving rather than worsening as compared to placebo. More patients receiving valacyclovir and valacyclovir plus prednisone showed improvement from baseline than placebo for total score, selected score, feeling bad, and fatigue. The shift was statistically significant for valacyclovir plus prednisone over placebo for selected score, feeling bad, and fatigue (Table 3).

These results were consistent with the clinical impression on day 20 of treatment shown in Figure 1. Eighty-seven percent of those receiving valacyclovir and prednisolone, and 73% of those receiving valacyclovir and prednisolone were significantly improved. None of the children receiving only placebo significantly improved. The rest of the children in either valacyclovir group improved by day 20. No child in these two groups failed treatment or had not improved at reevaluation. Conversely, by day 20 for the placebo group, 60% of the children had improved and 40% had failed treatment or had no improvement.

The mean change in atypical lymphocyte count after treatment compared to the initial value decreased for both valacyclovir treatment groups. These decreases were not clinically substantial. The mean white blood

Table 1 - Results: Demographics

	Val+Pred	Val+PL	PL
Gender (male/female)	9/6	8/7	8/7
Age (range)	9.7 (3-16)	8.7 (3-18)	9.9 (2-16)
Baseline			
- Temperature (°F)	98.6	99.2	99.2
- Fatigue Score	1.9	1.9	1.7
- Feeling Bad Score	1.9	1.7	1.9
- Selected Score*	4.7	5.1	4.5
- Total Score †	9.1	10.7	8.7

* sore throat, swollen glands, fatigue, nausea and chills
† 13 clinical manifestations (not including feeling bad and loss of appetite)

Table 2 - Analysis of Change from Baseline Scores at Day 20

	Valacyclovir + Prednisolone (VPR) (N=15)	Valacyclovir + Placebo (VPP) (N=15)	Placebo (PP) (N=15)	VPR vs PP
Total Score [1]				
n	15	15	15	0.541
Mean	-5.33	-6.93	-2.47	
Standard error	1.379	1.507	1.775	
Selected Score [2]				
n	15	15	15	0.165
Mean	-3.07	-3.00	-1.13	
Standard error	0.613	0.683	0.850	
Feeling Bad Score				
n	14	15	15	0.137
Mean	-1.21	-0.93	-0.47	
Standard error	0.261	0.248	0.336	
Fatigue Score				
N	14	15	15	0.045*
Mean	-1.29	-1.07	-0.40	
Standard error	0.286	0.300	0.321	

P-values were obtained using a van Elteren Test stratified by baseline severity.
*indicates p_value <=0.05. No comparison between VPP vs PP and VPR vs VPP were statistically significant.
[1] Total Score does not include feeling bad and loss of appetite.
[2] Selected Score consists of sore throat, fatigue, swollen glands, nausea, and chills.

cell was slightly higher after treatment compared to the initial value for each treatment group. Overall, no significant change in the total leukocyte count or atypical lymphocyte number occurred between initial and final values in any treatment group. No patient developed thrombocytopenia or anemia during the study period.

Discussion

Recovery from Epstein-Barr virus illness is usually complete but variable and may occur over several weeks to several months from the onset of illness. Children may lose significant time from school and

Table 3 - Analysis of Shifts in Change from Baseline Scores at Day 20

	Valacyclovir + Prednisolone (VPR) (N=15)	Valacyclovir + Placebo (VPP) (N=15)	Placebo (PP) (N=15)	VPR vs PP
Total Score [1]				0.320
Improvement	12 (80%)	14 (93%)	10(67%)	
No Change	2 (13%)	0	0	
Worsening	1 (7%)	1 (7%)	5(33%)	
Selected Score [2]				0.036*
Improvement	14 (93%)	13 (87%)	9 (60%)	
No Change	1 (7%)	0	2 (13%)	
Worsening	0	2 (13%)	4 (27%)	
Feeling Bad Score				0.028*
Improvement	11 (73%)	11 (73%)	6 (40%)	
No Change	4 (27%)	3 (20%)	5 (33%)	
Worsening	0	1 (7%)	4 (27%)	
Fatigue Score				0.019*
Improvement	12 (80%)	11 (73%)	5 (33%)	
No Change	2 (13%)	2 (13%)	8 (53%)	
Worsening	1 (7%)	2 (13%)	2 (13%)	
Temperature				0.108
Improvement	10 (67%)	10 (67%)	6 (40%)	
No Change	2 (13%)	2 (13%)	2 (13%)	
Worsening	3 (20%)	3 (20%)	7 (47%)	

P-values were obtained using a Mantel-Haenszel mean score test stratified by baseline severity.
*indicates p_value <=0.05. No comparisons between VPP vs PP and VPR vs VPP were statistically significant.
[1] Total Score does not include feeling bad and loss of appetite.
[2] Selected Score consists of sore throat, fatigue, swollen glands, nausea, and chills.

daycare and their parents time from work. This could result in financial and emotional turmoil for the family. Further, we are now recognizing EBV illness in younger children. This may be the result of better recognition or increasing symptomatic manifestations of EBV illness in children.[1,18]

Traditionally, rest has been the mainstay for treatment of EBV illness. However, results of our study favor treatment with both valacyclovir and valacyclovir plus prednisone with an improved outcome over placebo. All four scores (total, selected, feeling bad, and fatigue) showed greater improvement in the valacyclovir groups versus placebo. This was further supported by the clinical impression on day 20.

Three double-blind controlled studies and one match-controlled trial have shown significant reductions of both fever and pharyngitis by corticosteroid treatment without unacceptable side effects or risk in young adults with acute infectious mononucleosis.[15-18]

Prednisone at an initial dose of 40 mg/day and decreased to 5 mg/day by day 12 reduced the duration of fever from six to two days.[23] Temperature was not substantially modified in either treatment group versus placebo in our study. This may have been the result of the acute febrile period ending prior to enrollment in the study.

Doses of acyclovir significantly inhibit oropharyngeal EBV replication in patients with

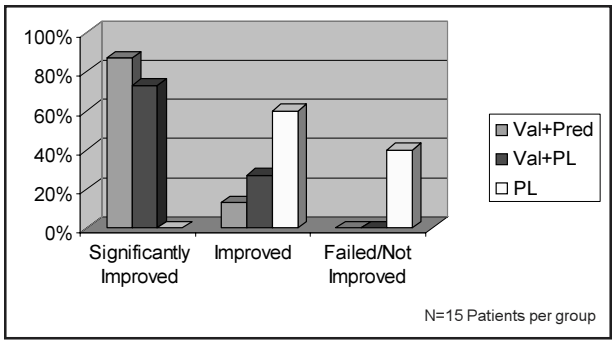

Fig 1 – Results: Clinical Impression at Day 20.

infectious mononucleosis without effecting the clinical symptoms.[13] Acyclovir stops viral replication and the steroid reduces the fever and pharyngitis associated with EBV illness.[18-20] Both intravenous acyclovir 10 mg/kg three times per day and oral acyclovir 800 mg five times per day for seven days causes a complete but transient inhibition of oropharyngeal EBV replication.[1,11,19] After acyclovir and prednisolone administration, virus excretion returned to the pretreatment levels within one week after medications were withdrawn.[18] This is consistent with results of studies using intravenous and oral acyclovir as the sole treatment and early phase of infectious mononucleosis.[11,19] Effective serum concentrations are achievable to suppress EBV in patients with infectious mononucleosis.[25]

Children receiving treatment may have reduced immune response compared to controls. However, treatment favored an improved clinical response. The more that was done to block the immune response, first blocking viral replication with valacyclovir and then blocking both viral replications with valacyclovir and blocking immunomodulation with prednisolone may produce greater interference with the immune response. In a study reported by Simon, use of prednisolone and valacyclovir followed by intravenous acyclovir resulted in no measurable increase in levels of interferon γ and sIL-2 in a patient critically ill with EBV pneumonia and hepatitis.[27] This suppression in immune response was also reflected in the mean atypical lymphocyte count change in this study.

The disease is probably the consequence of the immunologic response induced to control the virus rather than a direct effect of the viral replication.[26] A number of lymphokines have been shown to be elevated in infectious mononucleosis. Soluble interleukin-2 receptors, and soluble CD 8 and serum neopterin levels are significantly elevated in patients with infectious mononucleosis.[26] Additionally, Interferon gamma, interleukin-2, interleukin-6, and tumor necrosis factor-B (TNF-B) producing cells are found in the tonsil tissue of patients with infectious mononucleosis.[24] The increased production of these cytokines by activated cells may be responsible for the clinical symptoms in acute infectious mononucleosis.[22,26]

Optimal treatment would be to suppress viral replication and thereby reduce the immunologic mechanisms activated to control infection and secondarily to block the effects of immunomodulations produced by viral effects before suppression of viral replication occurs.[27] The majority of cases of infectious mononucleosis are probably mild and self-limited. Early therapy with the combination of an antiviral and steroid could significantly reduce the morbidity and duration of symptoms. This study is a small pilot study and no conclusions can be made about efficacy. However, it suggests that treatment lessened the duration of symptoms and severity of illness compared to the placebo group. This study should serve as a beginning for future studies to elucidate more effective measures to treat Epstein-Barr virus disease.

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