The Role of Acyclovir in the Treatment of Herpes zoster Virus Infections in Immunocompromised Children

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Abstract

Objective: Varicella and herpes zoster are infectious diseases caused by varicella-zoster virus (VZV) and are generally not serious diseases in immunocompetent patients. However, patients with impaired cellular immunity because of chemotherapy, immune suppressive agent, HIV infection, and primary immune deficiency syndromes have tendency toward causing infections with VZV; also, VZV infections may be more severe with complications in these patient groups. Acyclovir is the drug of choice for treatment of both illnesses. Herein, we aim to describe the characteristics of VZV infections and the role of acyclovir in the treatment of immunocompromised children for these infections.

Materials and Methods: Thirty-three children with primary or secondary immune deficiency syndromes aged less than 18 years who were admitted to the Pediatrics clinic of Marmara University Medical Faculty Hospital for varicella or herpes zoster infections between January 2012 and June 2015 were enrolled in this study. Data about clinical manifestations, treatment, and prognosis of VZV infections are collected by performing a chart review of these patients.

Results: Thirty-three patients enrolled into the study were aged between 6 months and 16 years with the mean age of 96±52 months. The reasons for causing immune suppression were solid tumor in 15 patients, ALL in 7, primary immune deficiency in 5, immune suppressive drug usage in 3, HIV in 1, organ transplantation in 2 patients. Seven patients were treated for herpes zoster and 16 for varicella. Acyclovir was administered with a dosage of 1500 mg/m^2/day divided in three intravenous doses in the first 72 hours of disease manifestations, and the mean duration of treatment was 7 days (range 3–11). Vesicular rash begun to be crusted at 3. Day of treatment and completely crusted at 5th day in all patients. No complications of infection or drug-related adverse effects were observed.

Conclusion: This study showed that acyclovir is still safe and is an effective agent for VZV infections; particularly, to prevent complications and dissemination of infection in immunocompromised children, acyclovir administration should be initiated immediately. *(J Pediatr Inf 2015; 9: 142-6)*

Keywords: Varicella, herpes zoster, immune deficiency, acyclovir

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Introduction

Varicella herpes zoster (VZV) is a member of herpes virus family and is the agent of an infection causing two different clinical tables. Varicella also known as chicken pox is a primary disease table characterized by the eczematous skin rashes following the first encounter of a patient without varicella immunity with the virus. Herpes zoster or shingles is a table that develops as a result of the reactivation of a virus that has remained latent following a primary infection. Varicella and herpes zoster has a mild course in healthy individuals; however, in those with primary or acquired immune deficiency, especially if their cellular immunity has been affected, they may cause serious morbidity and mortality (1). While secondary skin infection is the most frequent complication in varicella, acute cerebellar ataxia, encephalitis, meningitis cerebellitis, and Reye's syndrome are other rare complications. After the herpes zoster clinic, by spreading to

medulla spinals, the virus can cause myelitis, encephalitis or meningitis complications. Previous controlled studies showed that antiviral treatment that was initiated at an early stage in the treatment decreased mortality and morbidity (2, 3), acyclovir was a preferred agent. In the present study, we discussed the role of acyclovir in the clinical course and treatment of herpes zoster virus infections in immunocompromised children.

Material and Methods

The records of patients hospitalized and followed up with the diagnosis of varicella and herpes zoster admitted to the Pediatrics clinics of the Medical Faculty Hospital of Marmara University between January 2012 and June 2015 were scanned retrospectively; age, gender, the diseases affecting their immunity status, the form and length of the treatment they have received, their responses to the treatment and complications were all investigated. We included in the study patients aged younger than 18 years with primary or secondary immune deficiency syndromes, whose varicella or herpes zoster diagnosis was made by the character of the rashes and the clinical course of the disease (Figure 1).

Statistical analysis

For statistical analysis, all the information of the patients, including age, underlying diseases, duration of treatment, and duration of crusting of the lesions, whether complications have developed and side effects of the drugs were entered into the Microsoft Excel. For age, Statistical package for the Social Sciences 16.0 software (SPSS Inc.; Chicago, IL, USA) was used for the information of mean age-median for statistical analysis.

Results

33 patients were included in the study; of these patients, 17 (51.5%) had varicella diagnosis, 16 herpes zoster (48.5%); 17 were male (51.5%), 16 female (48.5%); their ages ranged between 6 months and 16 years of age with average of 96±52. When the conditions suppressing their immunities are examined, it was found that 15 had solid tumor (45.5%), 7 ALL (21.2%), 5 primer immune deficiency (15.2%), 3 the use of immune suppressive drugs (9%), of two, one kidney and one liver transplant (6%), and one HIV infection (3%) (Table 1). All patients were given 1500 mg/m^2/day 3 doses of intravenous acyclovir seven days on average (3-11 days). Crusting of vesicular lesions started the 3rd day of the treatment; on the 5th day on average, all the lesions had already crusted. During the monitoring of the patients that VZV-related complications such as encephalitis, meningitis, cerebellitis, ataxia or Reye's syndrome were seen. All the patients were given acyclovir infusion at least within an hour and they were monitored clinically with regards to the side effects of acyclovir use. Furthermore, in those patients with underlying kidney disease, use of nephrotoxic drugs, neurological disease, or in liver disease, liver function tests, renal function tests and electrolytes were closely monitored, but no distortion was not observed.

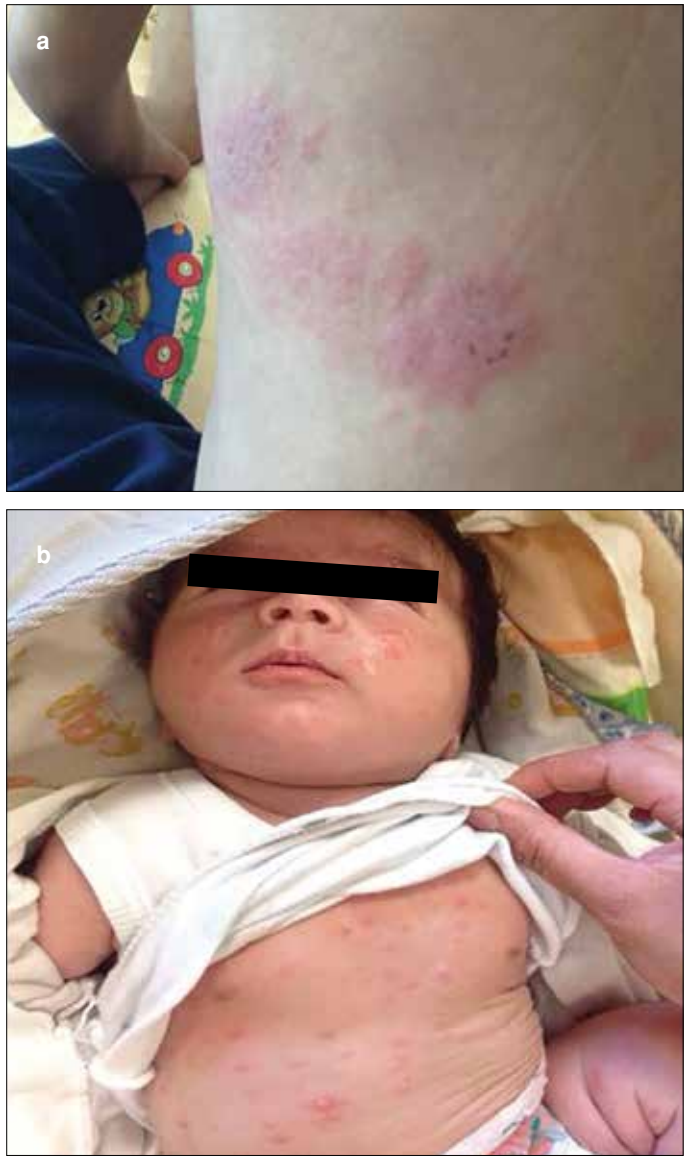

Figure 1. Typical rashes of herpes zoster (a) and varicella (b)

Discussion

Virus-specific cellular immunity is very important in preventing or controlling viral activation or dissemination. Slow course of VZV infections and more frequently seen complications in individuals with primary or acquired immune deficiency has to do with the deficiency of cellular

immunity (1). In different studies, VZY-associated disseminated infection was reported in patients who had organ transplant or received chemotherapy due to hematological malignity, and it was emphasized that this might be accompanied by common visceral involvement which was an emergency and life-threatening condition (4-7). However, in the 33 immunosuppressed patients brought to our clinic, we have not found any symptoms suggestive of common VZV infection or visceral dispersion in the course of three and a half years. Given the fact that mortality related to primary VZV infection (varicella) is between 7-14% (8-10) in patients with immune deficiency, the early onset of antiviral treatment known to reduce mortality and morbidity in patients with immunosuppressed patient becomes crucially important.

In the present study, we reviewed antiviral treatment approach in the patient group with immunosuppression who had severe course of VZV infection; in this patient group, vidarabin is the very first drug whose efficiency has been proved. In a study done by Whitley et al. (11) in 1982, vidarabin (10 mg/kg/day) was compared with placebo and it was found that in the patients, who were given vidarabin, formation of new lesions stopped and fever disappeared earlier in comparison to the placebo group. Similarly, it was seen that the frequency of life threatening complications in the group given decreased seriously; if the treatment started within 72 hours, the clinical course was quite positively affected (11). However, due to short half-life, low activity, low water solubility, vidarabin today is not used in VZV infections. The same year, Prober et al. (12) carried out a similar study with acyclovir, and they concluded that acyclovir was not effective on the course of fever and skin lesion, and failed to prevent the development of pneumonia. On the other hand, in their study, Nyerges et al. (13) demonstrated that the use of acyclovir on the clinical course of varicella infection in children with immune deficiency. It was stated in the literature in addition to acyclovir, the use of interferon-α and vidarabin helped to improve the symptoms of the disease. Interferon-α (IFN-α) was used to treat the varicella infection in cancerous pediatric group and it was shown that with the 0.4-3.5 x 10^5 I U/kg/day dose, intramuscular use of IFN-α for 5 days reduced the duration of lesions and visceral distribution (14, 15). In a study done by Mezser et al. (16), on the other hand, in 25 immune deficiency patients with varicella infection diagnosis, 7 day 5 x 800 mg/dose oral acyclovir was used; oral acyclovir needed to be converted into intravenous form only in two children; and VZV infection was successfully treated in all children. Today, although acyclovir treatment is effective, as the use of five doses is not considered practical, there have also been attempts for alternative ways of treatment; in 2013, Gopal et al. (17) compared acyclovir and famciclovir treatments, found the effectivity the same for the two agents and concluded that the use of famciclovir was more practical and cheaper. Given the effectivity of acyclovir in the VZV disease, today after autologous hematopoietic stem cell transplant, prophylactic use is recommended in the first year (18).

Table 1. Demographic features of patients with VZV infection

	Herpes zoster	Varicella
Number of patients (n)	16	14
Age (month on average)	126±25	69±43
Immunodeficiency status		
ALL (n)	2	5
Solid tumor (n)	11	4
Congenital immune deficiency (n)	1	4
Immunosuppressive drug users (n)	2	1
HIV infection (n)	0	1
Solid organ transplantation (n)	0	2
Duration of treatment (days on average)	7±1	7±3
Crusting duration of lesions (days on average)	5±1	5±2
Complication (n)	0	0
Acyclovir side effect (n)	0	0

ALL: acute lymphoblastic leukemia; VZV: varicella zoster virus; HIV: human immunodeficiency virus

In the present retrospective study, we used acyclovir in the 33 participating patients who had immune deficiency due to solid tumors, ALL, congenital immunodeficiency, immune suppressive drugs, organ transplantation and HIV infection. Since majority of our patients were closely followed up by the relevant hospital departments due to their underlying diseases, they came to the hospital within the first 24 hours as soon as the lesions were seen; acyclovir treatment was initiated within the first 72 hours in all patients by dividing 1500 mg/m^2/day into three doses; intravenous was used 7±0.7 day on average. In both disease groups, vesicular lesions started to crust on the 3rd day on average; the entire lesion in herpes zoster, on the other hand, in 4.6 day on average, in varicella in five day on average. Considering the fact that the new lesions continue in healthy people until the 7th day without antiviral drug use (19, 20), it is possible to say that acyclovir shortened the healing period of lesions. In support of our inference, a multi-center, double-blind, placebo-controlled study that included 815 the healthy child with varicella, acyclovir (20 mg/kg orally 4 doses a day) was initiated within the first 24 hours when the symptoms emerged; treatment continued for 5 days; while in the

group that used acyclovir, new lesions did not appear after the 3rd day and fever continued for 3-4 days, in 20% of the control group, new lesions continued to appear after the 6th day and fever continued longer than 4 days (21). Even though the number of lesions was few in the group that used acyclovir, it was found that antibody level was the same as the placebo group. Another point is that vesicular in previous studies that lasted for weeks in immunosuppressed patients, was reported that it could be seen as the complication of large and hemorrhagic skin lesions, pneumonia, or disseminated intravascular coagulation (DIC) (22), no complications were seen in any of our patients. This particular result was interpreted as that intravenous acyclovir treatment in the early period prevented the visceral spread of the VZV infection and the development of severe complications (12, 13). For this reason, even though acyclovir treatment is recommended within the first 24 hours upon the emergence of symptoms in varicella and herpes zoster, even if the 24-hour limit is exceeded in the patient group with immune deficiency, recommendation of the acyclovir treatment is appropriate. Acyclovir is a well-tolerated antiviral agent, whose side effects include gastrointestinal sensitivity, headaches, reversible renal failure in dehydration patients or in the rapid intravenous infusion (23). No serious acyclovir-related clinic or laboratory side effects were observed in our follow-up patients; however, since the present study was a retrospective one, it should be remembered that mild symptoms might have been missed or not recorded down.

Significant disadvantages of the present study are that it is retrospective study and the number of patents is small. Furthermore, since it is not ethical not to use acyclovir treatment in patients with immune deficiency, the absence of a control group with which we can compare our patient group with immune deficiency, but a group that did not have acyclovir treatment is another factor that has limited our study.

As the present study has demonstrated, when acyclovir is used in the early periods of the disease in VZV infections, it is an effective treatment agent without serious side effects; it significantly prevents the dissemination and complications of the VZV infection; for this reason, it is vitally important to use it in patients with immune deficiency.

Ethics Committee Approval: Ethics committee approval was not received due to the retrospective nature of this study.

Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

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