Acta Paediatrica Hungarica 30 (2) pp 263-270 (1990)

EARLY RELAPSES OF VARICELLA-ZOSTER VIRUS INFECTION IN IMMUNOCOMPROMISED CHILDREN TREATED WITH ACYCLOVIR

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Received 8 November 1988

Authors observed one or more early VZV relapses in 8 out of 98 Acyclovir treated immunocompromised children with varicella. None of the 8 children developed VZV antibodies by the end of the 5-day ACV treatment. All VZV relapses were successfully treated with ACV or Vidarabine, but were stopped only after the appearance of VZV antibodies in the patients' sera. The possible role of ACV treatment in pathogenesis of early VZV relapses could be excluded by comparing the VZV antibody production of patients treated with ACV from the first day of varicella on with the antibody response of those, who received ACV as late as on the 5th day of varicella. By prolonging the ACV treatment till the appearance of VZV antibodies, early relapses could be avoided.

INTRODUCTION

Acyclovir (ACV) has opened up new vistas in the history of antiviral chemotherapy /6, 7, 23/. By blocking herpesvirus replication specifically, the drug can be used for the treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. "Open" and "double blind" studies have proved the efficacy of ACV treatment in the management of herpes-virus infections in the immunocompromised host, either in the suppression of recurrences /20/, or in the treatment of the clinical symptoms /2, 6, 21, 24/. In 1983 and 1987 we published the summary of our experiences of an "open" and a "double blind" study. These were performed in immunocompromised

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children with varicella treated with ACV /16, 17, 18/ and remarked that a small number of patients successfully treated with ACV had early relapses of VZV infection shortly after treatment has been terminated. The aim of the present paper is to analyse the cases and the possible way for avoiding such relapses. Since then we have observed this phenomenon in a larger number of patients. We also investigated the possible role of ACV treatment in the lack or delay of VZV antibody production. Finally we examined, whether or not the prolongation of ACV treatment is able to stop early VZV relapses.

PATIENTS AND METHODS

Ninety-eight immunocompromised children aged 1-16 years were admitted to our department with varicella or herpes zoster between 1981-87. In the majority of the cases (93 %) the underlying disease was acute leukemia or solid tumor, a few patients were under immunosuppressive therapy because of autoimmune disorders or nephrotic syndrome. At the onset of the VZV infection the majority of the children (84 %) was in the remission phase of the underlying disease and received only maintenance therapy, the minority was either in the early, active phase of the malignancy (9 %), or in relapse (7 %).

Intravenous ACV ZOVIRAX^{R}, Wellcome was administered in a daily dose of 1500 mg/m^{2} divided in three one hour infusions for five days; if the therapeutic effect was not sufficient, treatment was prolonged for 7 to 10 days. For prolongation oral ACV (tablets) were given in a dose of 5x400 mg and 5x800 mg below and above two years of age respectively in cases referred to in "Results".

If the WBC count was minimum 1x10^{9}/l ongoing corticosteroid therapy or maintenance therapy for leukemic children was continued unchanged. In cases of haematologic relapse the intensive chemotherapy was withheld till crusting of the vesicles. If the patient was in the initial phase of the malignant disease, the induction therapy was continued according to the actual protocol along with the ACV infusions. In the consolidation phase short brakes of protocol depending on the WBC count were tolerated.

Before starting the ACV therapy, on day 3 and after completion of treatment full blood count, liver and renal function tests were performed. On the same day serum was tested for VZV antibodies by immunfluorescence-technique /16/. If the patient has not developed VZV antibodies by the end of ACV treatment, the tests were repeated twice weekly till the antibodies have appeared.

RESULTS

Early relapses of VZV infection were observed in 8 out of 98 ACV treated children. Five children had one, three had two or more VZV relapses. The relapses occurred in the clinical form of varicella in 9 cases and as herpes zoster in 5 cases. None of these children had detectable VZV antibodies by the end of ACV treatment. The relapses and the VZV antibody production in relation to time elapsed, absolute lymphocyte count and antiviral therapy are shown on Table I. As shown, the relapses stopped only after the appearance of the antibodies. Along with the clinical appearance of vesicles the lymphocyte count decreased below the normal range. The relapses responded well to ACV, or - in two cases - to Vidarabine.

TABLE I

Relation between acyclovir treatment and VZV specific antibody production in immunocompromised children with varicella

Treatment before the 5th day of varicella	No of patients with 1:5 antibody titer to VZV on the 5th day of varicella/total
Acyclovir	40/55 = 0.72
None	30/43 = 0.69

In seven out of eight patients ACV treatment started on the first day of varicella, so the question arose, whether or not the delay in antibody production was due to the ACV treatment itself? Therefore, we examined the difference in antibody production between those, who received ACV in the first five days of varicella and those who did not. As shown on Table II no difference could be found between the two groups.

As soon as we realized the relation between the absence of VZV antibody production and VZV relapses, we prolonged iv. ACV treatment with oral ACV (tablets) in further 7 children till the appearance of antibodies. The oral treatment had to be given for 2 to 7 days, and no early relapse was seen.

TABLE II

Course of VZV infection of patients without specific antibodies on day 5 to 10 after onset of primary varicella

Treatment	No of patients With relapse(s)/total	With progression/total
IV. acyclovir for five days	8/11 (0=0.72)	
Iv. acyclovir for 5 days + oral acyclovir[x]	0/7	
None		10/13 (=0.76)

[x] until the patient developed specific antibodies

In Table III the clinical course of varicella was compared in children who were treated with ACV from the first day of varicella on, with those, who were not treated till the fifth day of varicella. As demonstrated, the frequency of early relapses was just the same in ACV treated children, as the frequency of progression of the infection in the untreated group.

DISCUSSION

Reactivation of the VZV infection in immunocompromised children has already been reported by other authors /8, 9, 10, 12, 13/, but there are no reports on early VZV relapses in ACV treated patients.

Relapses were seen only in those cases, where no VZV antibodies appeared by the end of ACV treatment. Although it is well known, that the recovery from VZV infection, i.e. the elimination of the virus infected cells is mainly due to cellular factors of immunity, the appearance of VZV antibodies seems to be a good indicator of the complex immune response

/11/. This supposition corresponds with our observation, i.e. that patients who were not treated with ACV till the fifth day of varicella and did not produce antibodies by this time showed signs of progressive VZV infection.

The early relapses of ACV treated patients suggest, that ACV treatment alone is not sufficient for the elimination of VZV infection, but a certain degree of host's immune responsiveness is mandatory, too. The fact, that even early ACV treatment might fail to save the patient's life in cases of severe lymphocyte depletion or bone marrow aplasia supports this opinion /3, 21/.

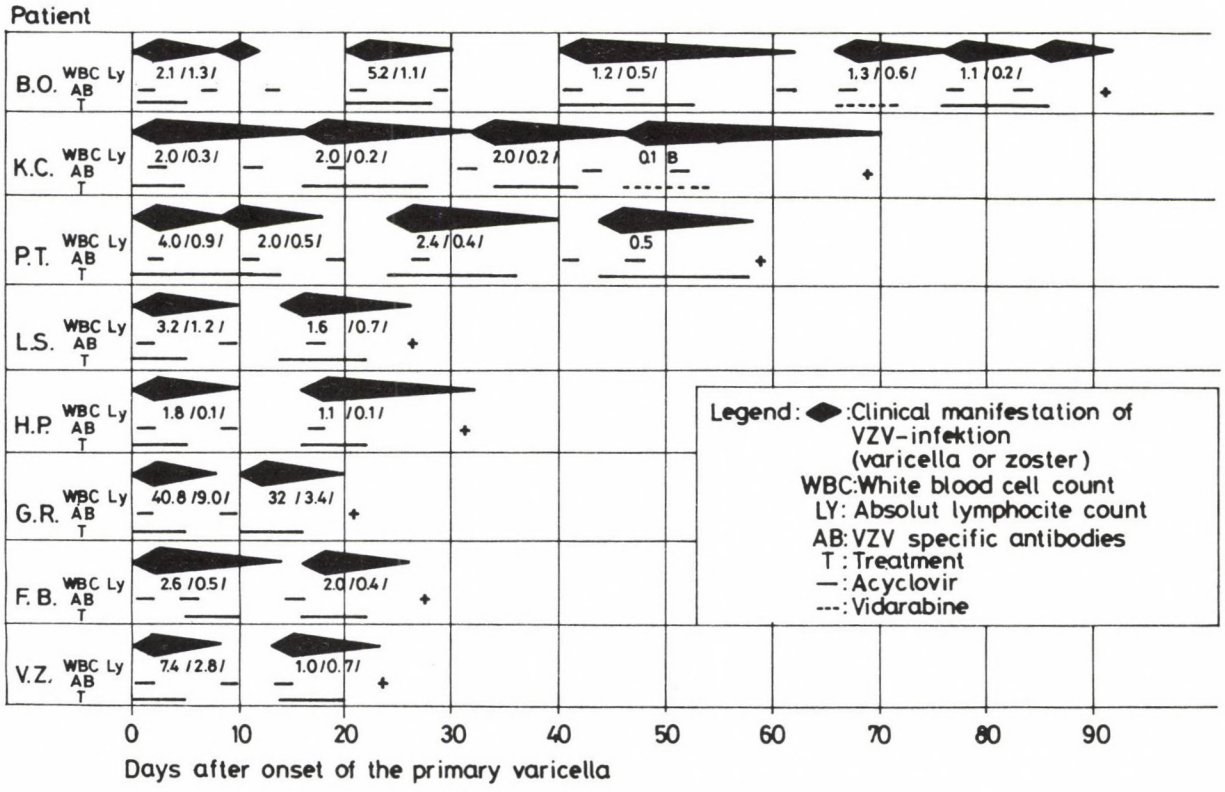
The role of ACV in fighting VZV infection in the immunocompromised host is to decrease the number of virus infected cells by blocking VZV replication and lessening the possible immunosuppression caused by the virus itself /24/, that way helping the host's more or less injured immune response to eliminate the virus infected cells and to stop the propagation of the infection. In severely immunocompromised patients who develop weak or no immune response at all, ACV treatment might seem effective, but suspending the administration of ACV might be followed by clinical relapse of VZV infection.

Naturally it is possible that ACV treatment itself may delay the adequate immune response by reducing the number of VZV infected cells, this way reducing the antigen stimulus for developing specific antibodies, or simply by directly causing further marrow suppression, suggested by other authors /1, 5, 19/. However no difference was seen in the VZV antibody production of patients untreated or treated with ACV in the first five days of VZV infection, so ACV treatment cannot be blamed for the delayed immune response. Therefore, in accordance with others /4/, we do not change our present opinion and practice of treating all immunocompromised children with ACV at the first signs of varicella /18/.

From our observation we conclude that early relapses of VZV infection can be avoided by prolongation of ACV treatment till the appearance of VZV antibodies in immunocompromised children. Several studies showed no side effects of long term - even lasting for months - ACV treatment /14, 15, 22/.

TABLE III

Acyclovir treated patients with early relapses of VZV-infection



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