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CASE REPORTS

ROLE OF VALGANCICLOVIR IN NEONATAL HEPATITIS WITH CYTOMEGALOVIRUS

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ABSTRACT

Cytomegalovirus (CMV) is an important cause of neonatal hepatitis. Untreated, though hepatomegaly may spontaneously regress, these children may develop portal hypertension and chronic liver disease. Also, these children can progress to develop biliary atresia. Long term sequelae may be sensorineural deafness and intellectual impairment. Role of ganciclovir and its prodrug valganciclovir for treatment of congenital CMV infection is not completely established. There have been few case series and case reports that have documented resolution of CMV hepatitis on treatment with ganciclovir. However, there is very little literature on role of valganciclovir in neonatal CMV hepatitis. We report for the first time in India, effectiveness of valganciclovir in 3 infants with neonatal hepatitis and CMV. All 3 infants in age group of 2-4 months with neonatal hepatitis and variable CMV viral load were treated with oral valganciclovir (125-250 mg/m^2/day) for 6 weeks and had clinical improvement and undetectable viral load at the end of therapy. One patient however developed long term sequelae of CMV in form of sensorineural deafness and delayed development.

Thus, valganciclovir appears safe and effective in neonatal hepatitis with CMV. However, randomized controlled trials in larger groups are required to determine its efficacy.

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Cytomegalovirus, hepatitis, valganciclovir.

Introduction

Cytomegalovirus (CMV) is the most common cause of congenital infection in humans.[1,2] Severe jaundice and granulomatous hepatitis have been established due to neonatal CMV infection.[3,4] Isolated neonatal hepatitis with CMV has been reported in literature but response to antivirals has been encouraging.[5,6,7,8,9,10] We present 3 infants with neonatal hepatitis and associated CMV and their response to valganciclovir.

Case 1: A 2½ months old boy presented with jaundice and clay-colored stools since birth. Baby was born at 34 weeks by caesarean section in view of premature labour, had a birth weight of 1.75 kg and was put in neonatal intensive care unit (NICU) for 7 days. On examination, weight was 2.75 kg, length was 47 cms and head circumference was 35 cms. He had hepatosplenomegaly and umbilical hernia. Other systems were normal. Investigations are depicted in Table 1. Liver biopsy showed balloon degeneration of hepatocytes with multinucleated giant cells without inclusion bodies. In view of CMV infection, child was started on oral Valganciclovir (250 mg/m^2/dose BD for 21 days, and then 125 mg/m^2/dose BD for 21 days) following which liver function tests improved at end of 6 weeks (Bilirubin = 1.2 mg/dl, SGPT = 62 IU/L, Total proteins = 6.1 gm/dl, Albumin = 3.8 gm/dl), CMV viral load was undetectable. At 8 months of age, child is asymptomatic.

Case 2: A 3-month-old girl was referred in view of jaundice. There were no clay-colored stools. She was born at 9 months gestation with birth weight of 2.75 kg and had achieved milestones appropriately for age. On examination, weight was 4 kg, length was 60 cms. She had with jaundice with massive hepatosplenomegaly with umbilical hernia. Other systems were normal. Investigations are depicted in Table 1. Liver biopsy showed distorted architecture with moderate inflammation and intracellular cirrhosis. The child was treated with valganciclovir for 6 weeks. At end of 6 weeks, the child had no jaundice.

Case 3: A 3½ months old boy born at full term presented with jaundice and clay-colored stools since 1 month of age. The patient had convulsions on Day 2 of life and required NICU stay for 7 days and was on oral phenobarbitone for the same. Mother had fever at 7 months of gestation. Child was investigated at 1 month of age and was found to have direct hyperbilirubinemia [(Bilirubin = 7.3 gm/dl, direct bilirubin = 2.3 gm/dl)] and CMV IgM was positive. Since jaundice did not resolve, child was referred for further management. On examination, at 3½ months of age, weight was 5 kg, length was 63.5 cm and there was splenohepatomegaly with jaundice. Investigations are depicted in Table 1. His vision appeared impaired and fundus examination was normal though visual evoked potential was suggestive of retinal damage. MRI brain showed delayed cortical maturation. EEG was normal. In view of persistent neonatal hepatitis, child was

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Table 1. Investigations of all patients

	Patient 1	Patient 2	Patient 3
Hemoglobin (gm/dl)	9.9	11.0	9.4
WBC (cells/cumm)	22,000	23,000	13,600
Platelets (cells/cumm)	5,85,000	5,66,000	Adequate
Bilirubin (mg/dl)	11.9	4.8	6.2
Direct Bilirubin (mg/dl)	6.0	2.3	3.1
SGOT (IU/L)	785	106	128
SGPT (IU/L)	195	49	135
Total proteins (gm/dl)	5.5	6.8	5.8
Albumin (gm/dl)	3.8	3.5	3.8
Prothrombin time (sec)	14.2	106	-
Partial thromboplastin time (sec)	26.6	20.9	-
Alkaline phosphatase (IU/L)	2360	1284	656
GGTP (IU/L)	46	489	-
Ophthalmology	Normal	Normal	Visual impairment
Ultrasound abdomen	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly
HIDA scan	No excretion of tracer in intestines after 24 hours	Excretion of dye in the intestines	Excretion of dye in the intestines
Intra-operative cholangiogram	Excretion of dye in the intestines	Not done	Not done
Echocardiography	Normal	Normal	Normal
Urine reducing substance	Negative	Negative	Negative
Thyroid profile	Normal	Normal	Normal
Hearing screening	Normal	Normal	Profound hearing loss
CMV IgM	1.29 IU/ml	Positive	Positive
CMV IgG	8.54 IU/ml	140 AU/L	-
CMV viral load (copies/ml)	4540	Undetectable	3000

started on oral valganciclovir for 6 weeks. At end of 3 weeks, bilirubin had decreased to 0.8 mg/dl and CMV viral load was undetectable. At 6 months of age, liver function tests were normal, however child appeared to have impaired hearing and BERA showed profound hearing loss. His milestones are also delayed.

Discussion

CMV replicates both in the hepatocytes and cholangiocytes during infection. However, controversy exists about the pathogenesis of hepatic disease, whether related to the direct cytopathic effect of the virus or the immune response of the host.[2,3] In the histopathologic examination of liver, the presence of cytomegalic cells and inclusion bodies refers to the intensive immune activation against viral attack. Cytopathic damage is seen in patients with immature or immune deficient system.[3] In 2 of our patients, liver biopsy did not show inclusion bodies suggestive of direct cytopathic damage to the liver. In 3rd patient, liver biopsy was not done as biliary atresia had been ruled out and child had other features of CMV such as convulsions, retinopathy, and hearing loss. Neonates tend to have an immature immune system and thus may not show immune mediated damage. Thus, hepatic inclusion bodies are rarely found in the histologic examination of pediatric livers.[2,3]

Increasing number of studies indicate the necessity of treatment, especially in cases with symptoms of acute or chronic cholestatic hepatitis and especially in those with high CMV-DNA titer.[5,6,7,8,9,10]

Ganciclovir is recommended as first step antiviral agent for management of congenital CMV infection.[1] Oral valganciclovir could be an alternative because of its excellent bioavailability, reaching plasma concentrations similar to those achieve by intravenous ganciclovir and feasibility of available as oral preparation.[1] In our patients too, valganciclovir led to undetectable viral loads and improvement in hepatitis.

Vancikova et al treated 3 infants with neonatal CMV hepatitis with IV ganciclovir. They had clinical improvement and undetectable viral load but relapsed on stopping treatment. However, they had received IV ganciclovir only for 15 days suggesting that a longer duration of treatment may be needed.[6] In study by Fischler et al, 6 patients with cholestasis and ongoing CMV infection were treated with IV ganciclovir for

3-7 weeks, it was found that 4 patients responded to therapy.[7] In study by Tezer et al, 8 patients with CMV hepatitis were given ganciclovir for a median of 21 days of which 7 patients recovered whereas one patient relapsed and progressed to chronic liver disease.[9] Ozkan et al treated 7 patients with neonatal CMV hepatitis with ganciclovir for 21 days and found that cholestatic parameters significantly improved as compared to non-treatment group ($p < 0.05$). Thus, it appears that ganciclovir for 21 days or more is effective in treating CMV neonatal hepatitis. Similarly in our patients, valganciclovir was given for 6 weeks and all had a response without subsequent relapse. Adverse effects reported with ganciclovir and valganciclovir are neutropenia, thrombocytopenia[1], however none of our patients developed any adverse effects.

Recent recommendations for treatment of congenital CMV have now increased duration to 6 months.[1] Whether the same amount of duration of treatment in patients with neonatal cholestasis and CMV is needed will require further studies.

Conclusion

Valganciclovir appears safe and effective in neonatal hepatitis with CMV. However, randomized controlled trials in larger groups are required to determine its efficacy and duration of treatment.

Compliance with Ethical Standards

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Conflict of Interest: None

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