

## CASE REPORTS

# ROLE OF VALGANCICLOVIR IN NEONATAL HEPATITIS WITH CYTOMEGALOVIRUS

Ramya Uppuluri, Ira Shah.

Pediatric Liver Clinic, Department of Pediatrics, B J Wadia Hospital for Children, Mumbai, India.

### 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<sup>2</sup>/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.

### Introduction

Cytomegalovirus (CMV) is the most common cause of congenital infection in humans.<sup>1,2</sup> Severe jaundice and granulomatous hepatitis have been established due to neonatal CMV infection.<sup>3,4</sup> Isolated neonatal hepatitis with CMV has been reported in literature but response to antivirals has been encouraging.<sup>5,6,7,8,9,10</sup> 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<sup>2</sup>/dose BD for 21 days, and then 125 mg/m<sup>2</sup>/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

### ARTICLE HISTORY

Received 9 January 2020  
Accepted 29 July 2021

### KEYWORDS

**Address for Correspondance:** Dr Ramya Uppuluri, Department of Pediatric Hematology, Oncology and BMT, Apollo Specialty Hospital, 320, Padma Complex, Anna Salai, Chennai, 600035 India.  
**Email:** ramya.december@gmail.com

©2021 Pediatric Oncall

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.<sup>2,3</sup> 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.<sup>3</sup> In 2 of our patients, liver biopsy did not show inclusion bodies suggestive of direct cytopathic damage to the liver. In 3<sup>rd</sup> 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.<sup>2,3</sup>

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.<sup>5,6,7,8,9,10</sup>

Ganciclovir is recommended as first step antiviral agent for management of congenital CMV infection.<sup>1</sup> Oral valganciclovir could be an alternative because of its excellent bioavailability, reaching plasma concentrations similar to those achieved by intravenous ganciclovir and feasibility of available as oral preparation.<sup>1</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>9</sup> 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<sup>1</sup>, however none of our patients developed any adverse effects.

Recent recommendations for treatment of congenital CMV have now increased duration to 6 months.<sup>1</sup> 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

Funding: None

Conflict of Interest: None

### References:

1. Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med*. 2015 Mar 5;372(10):933-43.
2. Ozkan TB, Mistik R, Dikici B, Nazlioglu HO. Antiviral therapy in neonatal cholestatic cytomegalovirus hepatitis. *BMC Gastroenterol*. 2007; 7: 9.
3. Varani S, Landini MP. Cytomegalovirus as a hepatotropic virus. *Clin Lab* 2002; 48: 39-44.
4. Hasosah MY, Kutbi SY, Al-Amri AW, Alshafi AF, Sukkar GA, Alghamdi KJ, Jacobson K. Perinatal cytomegalovirus hepatitis in Saudi infants: a case series. *Saudi J Gastroenterol*. 2012 May-Jun;18(3):208-13.
5. Muller A, Eis-Hiibinger Am, Brandhorst G, Heep A, Bartmann P, Franz AR. Oral valganciclovir for symptomatic congenital cytomegalovirus infection in an extremely low birth weight infant. *J Perinatol*. 2008; 28: 74-76.
6. Vancikova Z, Kucerova T, Pelikan I, Zikmundova L, Priglova M. Perinatal cytomegalovirus hepatitis: to treat or not to treat with ganciclovir. *J Paediatr Child Health*. 2004; 40: 444-448.
7. Fischler B, Casswall TH, Malmbong P, Nemeth A. Ganciclovir treatment in infants with cytomegalovirus infection and cholestasis. *J Pediatr Gastroenterol Nutr*. 2002; 34: 154-157.
8. Tezer H, Secmeer G, Kara A, Ceyhan M, Cengiz AB, Devrim I et al. Cytomegalovirus hepatitis and ganciclovir treatment in immuno competent children. *Turk J Pediatr*. 2008; 50: 228-234.
9. Shah I, Bhatnagar S. Biliary atresia with cytomegalovirus infection and its response to ganciclovir. *Trop Gastroenterol*. 2014 Jan-Mar;35(1):56-8.
10. Shah I, Bhatnagar S. Biliary Atresia and Cytomegalovirus and Response to Valganciclovir. *Indian Pediatr*. 2012;49: 484-486