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Treatment of pediatric patients with Down syndrome, acute lymphoblastic leukemia, and hepatitis C infection by direct-acting antivirals

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ABSTRACT

Millions of people worldwide suffer from hepatitis C, which can lead to hepatitis, cirrhosis, and hepatocellular carcinoma. The risk of hepatitis C virus (HCV) infection is increased in patients with leukemia due to the frequent need for blood transfusion. Owing to their proven effectiveness in treating HCV infection, direct-acting antivirals (DAAs) have become a new treatment approach in children older than 12 years. The patient present in this article is a 9-year-old boy who had acute lymphoblastic leukemia and Down syndrome, who was diagnosed with hepatitis C infection and was successfully treated with a combination of DAA glecaprevir (250 mg/day) and pibrentasvir (100 mg/day) over 8 weeks.

Introduction

Hepatitis C virus (HCV), a small, enveloped, single-stranded positive-sense RNA virus from the Flaviviridae family, is one of the chronic viral hepatitis agents in humans (1). Severe complications, such as portal hypertension, cirrhosis, and hepatocellular cancer, may occur over time in patients with chronic hepatitis C infection (2).

Down syndrome is the most common chromosomal disease characterized by three copies of chromosome 21 and the frequency of leukemia in patients with Down syndrome is higher compared to the general population (3). The risk of HCV infection is increased in patients with leukemia due to the frequent need for blood transfusion and immunosuppressive treatments (3).

According to the classical guidelines, the first-line treatment of hepatitis C in children is the combination of pegylated

interferon and ribavirin (4). Since these drugs have dreadful side effects, such as aggravated cytopenia causing deep immune dysfunction, bone marrow suppression, hepatotoxicity, and the treatment response rates are relatively low, nowadays direct-acting antivirals (DAAs) have started to be administered for treating adult patients with hepatitis C infection. Recently, the possible side effects of DAAs have been minimized and cure rates have reached 90-97% (5). The Food and Drug Administration approved the use of the combination of ledipasvir/sofosbuvir and the combination of sofosbuvir and ribavirin for the treatment of adolescents with chronic HCV infections (12-17 years). Although trials with DAAs are ongoing for younger children, the only available treatment in the US and Europe for those <12 years is still the dual therapy of pegylated interferon and ribavirin. The next generation, ribavirin-free, DAA combinations (i.e. sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) demonstrate high efficacy with a shorter duration of treatment (6).

In this article, we present a 9-year-old boy who had Down syndrome, leukemia, and HCV infection and whose HCV infection was successfully treated with DAAs including a combination of glecaprevir and pibrentasvir.

Case Presentation

A 9-year-old boy with had Down syndrome and ALL was on maintenance therapy with methotrexate and 6-mercaptopurine and his treatment was interrupted for 2 weeks due to the detection of high transaminase levels at a routine examination. However, despite the interruptions of treatment, transaminase elevations continued in the examinations. There was no known history of heart, liver disease, and hypothyroidism. There was a history of multiple blood product transfusions because of leukemia-related problems.

The patient was referred to the pediatric gastroenterology department for the evaluation and treatment of hypertransaminasemia. After detailed investigations, he was diagnosed with hepatitis C infection. Anti-HCV antibody was positive and HCV RNA was 20.790.000 IU/mL. Abdominal ultrasound revealed enlarged liver and grade 2 hepatosteatosis. Liver biopsy was performed for assessing the stage and degree of activity in hepatitis C. Liver biopsy showed prominent secondary hemochromatosis, moderate lymphocyte infiltrates scattered to sinusoids, and reactive changes in hepatocytes, apart from partial degeneration and diffuse apoptosis. Genotype analysis showed genotype 3a. Other tests used for detecting causes of transaminase elevation yielded negative results.

The patient received glecaprevir (250 mg/day) and pibrentasvir (100 mg/day) combination for 8 weeks in October-November 2019 to treat HCV infection. Serum transaminase levels decreased to normal values two weeks after the onset of treatment, and the virus became undetectable in the blood after 8 weeks.

At the last follow-up visit, 10 months after completion of DAA treatment, the patient continued to show negative HCV RNA. An off-label prescription was approved for the use of DAAs and an informed consent form was obtained from the patient's family.

Discussion

There are currently approximately 11 million children under the age of 15 with HCV infection worldwide (7). Approximately 20% of infected people have self-limited acute hepatitis, but in the remaining 80%, the virus is not cleared, which leads to a chronic HCV infection (8).

Until recently, the treatment of pediatric patients with HCV infections was controversial because pegylated interferon and ribavirin used in the treatment of HCV cause major side effects such as severe neutropenia, immune system dysfunction, growth impairment, hepatotoxicity, and poor tolerability (7,9). Both the side effects and the low success rates of the treatment have led to the development of new-generation drugs. Currently, DAAs show a success rate of over 95% in the treatment of hepatitis C. DAAs target specific nonstructural proteins of the virus, resulting in the disruption of viral replication and thereby infection (8).

Although DAAs have been routinely used in adult patients, data on the use of these drugs is very limited in children, especially among those younger than 12 years of age. The investigation of the efficacy of DAAs for treating pediatric patients older than 12 years with HCV infection yielded similar results with adult patients (6). DAA therapy has several advantages over pegylated interferon therapy and it is used orally for up to 8 weeks (8).

There are no definitive guidelines for treating children 3-11 years of age with HCV infections. In children younger than 12 years of age, the decision to start treatment should be individualized to patients based on the HCV genotype, the severity of liver disease, the potential for side effects, the possibility of response, and the presence of co-morbidities. The possible off-label use of DAAs may be considered for treating children younger than 12 years with chronic HCV infection (6). We treated our patient successfully with a DDA over 8 weeks, which is a fixed-dose combination of an HCV NS3/4A protease inhibitor (glecaprevir) and an HCV NS5A inhibitor (pibrentasvir).

Conclusion

Our experience shows that treatment with DAAs may be used off-label in HCV-infected children under the age of 12 years. The advantages of treatment with DAAs over pegylated interferon and ribavirin therapy include shorter duration of treatment, higher effectiveness, and a lower rate of side effects.

Ethics

Informed Consent: A consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.G., N.B., Concept: A.S., O.G., N.B., Design: M.A., O.G., N.B., Data Collection or Processing: A.S., Analysis or Interpretation: A.S., M.A., Literature Search: A.S., M.A., Writing: A.S., M.A.

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References

1. Lindenbach BD, Thiel HJ, Rice CM. Flaviviridae: The viruses and their replication. In Fields Virology. 5th ed. Philadelphia, Lippincott-Raven; 2007.
2. Zaltron S, Spinetti A, Biasi L, Baiguera C, Castelli F. Chronic HCV infection: epidemiological and clinical relevance. BMC Infect Dis. 2012;12(Suppl 2):S2.
3. Massey GV, Zipursky A, Chang MN, et al. A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481. Blood. 2006;107:4606-4613.
4. Wang X, Gao F, Yuan G, et al. Ten-year follow-up analysis of chronic hepatitis C patients after getting sustained virological response to pegylated interferon-α and ribavirin therapy. J Viral Hepat. 2016;23:971-976.
5. Deming P. Viral hepatitis. In: Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, NY; 2019.
6. Indolfi G, Hierro L, Dezsofi A, et al. Treatment of Chronic Hepatitis C Virus Infection in Children: A Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018;66:505-515.
7. Schwarz KB, Molleston JP, Jonas MM, et al. Durability of Response in Children Treated With Pegylated Interferon alfa [corrected] 2a ± Ribavirin for Chronic Hepatitis C. J Pediatr Gastroenterol Nutr. 2016;62:93-96.
8. Jakobsen JC, Nielsen EE, Feinberg J, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017;9:CD012143.
9. Tsunoda T, Inui A, Kawamoto M, Sogo T, Komatsu H, Fujisawa T. Effects of pegylated interferon-α-2a monoterapy on growth in Japanese children with chronic hepatitis C. Hepatol Res. 2014;44:251-258.