

## Successful Sofosbuvir/Velpatasvir retreatment in two pediatric oncology patients with chronic hepatitis C after initial DAA failure: A case report

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### Abstract

Hepatitis C virus (HCV) infection remains a significant concern for pediatric oncology patients who require multiple blood transfusions. Although direct-acting antiviral (DAA) therapies have revolutionized HCV treatment, recurrence after initial treatment can occur. We report two pediatric oncology patients who experienced HCV relapse after standard DAA regimens but responded successfully to retreatment with sofosbuvir/velpatasvir. Patient 1, a 14-year-old with acute leukemia, was diagnosed with HCV genotype 1. Despite initial successful treatment with ledipasvir/sofosbuvir, HCV RNA reappeared within 12 weeks of completing the therapy. The patient was subsequently treated with sofosbuvir/velpatasvir, resulting in sustained virologic response (SVR) at 12 and 24 weeks. Patient 2, a 5-year-old with osteosarcoma, was diagnosed with HCV genotype 3. After experiencing a relapse following treatment with sofosbuvir/daclatasvir, the patient was successfully retreated with sofosbuvir/velpatasvir, achieving undetectable HCV RNA levels at follow-up. These cases underscore the importance of early detection and vigilant follow-up in pediatric oncology patients with HCV, as well as the potential for successful retreatment with pangenotypic DAA regimens like sofosbuvir/velpatasvir. Given the evolving nature of pediatric HCV treatment, further research is crucial to optimizing treatment strategies for this vulnerable population.

**Keywords:** Hepatitis C; Direct-Acting Antivirals; Sofosbuvir/Velpatasvir; Treatment Failure; Retreatment

### 1. Introduction

Currently, there are 3 to 3.5 million children globally are infected by hepatitis C virus (HCV) (1). Iatrogenic transmission particularly via blood transfusion remains the most important risk factor in developing countries among children needing regular transfusions (2). Previously, before the widespread blood donor screening that began in the early 1990s, it was shown that 6 to 50% of children undergoing treatment for leukemia tested positive for HCV RNA (3). Even in the 2000s, pediatric oncology groups continued to be at a higher risk of contracting the infection, particularly in under-resourced areas (3). In such patients, infection with HCV poses challenges to cancer management as immunosuppression can increase viral activity leading to deleterious complications such as cirrhosis and liver failure (3). The prevalence of HCV varies across various demographics in Iraq (4-7). Significant efforts are underway in some regions to achieve the objective of HCV eradication by 2030 (8, 9). The discovery of direct-acting antiviral (DAA) medications facilitates the attainment of this objective. The mainstream of HCV treatment has significantly been changed by the discovery of DAAs. In adolescents, DAA regimens that do not contain interferon or ribavirin are both safe and effective (2). Numerous combinations are currently permissible for pediatric use. Sofosbuvir-based treatments show a sustained virologic response (SVR) rates of 95% in children aged 3 years or older without any major side effects

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(10, 11). A study that involved multi-centers that used sofosbuvir/velpatasvir in 216 children (ages 3–17) demonstrated an SVR at 12 months (SVR12) rate of approximately 92% (11). Besides, a combination of ledipasvir/sofosbuvir cured 98–100% of children with HCV genotype 1 or 4, including those with malignancy (12). However, despite the high cure rates, recurrence of infection is still possible. Previous studies showed different reasons for treatment failure including resistance mutations, inadequate adherence, or reinfection (13, 14). In this study, we discuss two pediatric oncology patients with transfusion-related HCV who experienced a relapse after DAA therapy but had a positive response to retreatment with sofosbuvir/velpatasvir.

## 2. Case Report

### 2.1. Patient 1

A 14-year-old boy in remission with acute leukemia, was found to be HCV-positive incidentally during routine check-up. The diagnosis was confirmed by HCV-RTPCR that showed a viral load of  $1.2 \times 10^6$  IU/mL of genotype 1. Further investigations showed that the patient is not co-infected with hepatitis B or HIV. Additionally, the physical examination of the patient was unremarkable. Investigations showed normal liver function test (ALT levels of 30 U/L, AST levels of 28 U/L, and normal levels of bilirubin and albumin). Besides, an abdominal ultrasound demonstrated a flat liver morphology with minimal enlargement without ascites. Then, the patient was prescribed ledipasvir/sofosbuvir (90 mg/400 mg once daily), for a period of 12 weeks. He reported no adverse effects and tolerated the drug well. After four weeks of treatment, the HCV RNA level demonstrated a substantial decrease. The patient's HCV RNA was undetectable at the end of the treatment course. However, twelve weeks after the completion of medication, a quantitative PCR follow-up revealed the presence of the virus (Table 1), which indicates treatment failure. For retreatment, the patient was given sofosbuvir/velpatasvir (400 mg/100 mg once daily) for twelve weeks. HCV RNA was undetectable after four weeks of treatment with sofosbuvir/velpatasvir and at the end of treatment course. After completion of the treatment at the 12<sup>th</sup> and 24<sup>th</sup> weeks of treatment, cure was confirmed with maintenance of undetectable HCV RNA.

### 2.2. Patient 2

Following tumor excision and treatment, a 5-year-old child with a history of osteosarcoma was diagnosed with chronic hepatitis C during follow-up tests. The viral load was measured at  $4.8 \times 10^5$  IU/mL by HCV RNA PCR with HCV genotype 3 and no co-infection with hepatitis B or HIV. Upon examination, the child was a well-appearing with some distress in the right upper quadrant. In addition, other investigations showed liver enzymes were slightly elevated (ALT 45 U/L, AST 48 U/L). Besides, abdominal ultrasonography showed hepatomegaly. The patient was given a daily regimen of sofosbuvir 200 mg and daclatasvir 30 mg for 12 weeks. HCV RNA was undetectable at 4 weeks after treatment and at the conclusion of treatment course. However, the virus had resurfaced 12 weeks after the conclusion of treatment (Table 1). Then the patient was retreated with sofosbuvir/velpatasvir (sofosbuvir 200 mg + velpatasvir 50 mg once daily) for twelve weeks. Furthermore, HCV RNA testing was negative after the fourth week of retreatment and remained undetectable until the 12-week period concluded. Following up the patient showed undetectable HCV RNA at 12 and 24 weeks after treatment completion.

**Table 1** The characteristics of recruited patients

No	1	2
Age in years	14	5
Sex	male	male
Weight in kg	45	20
Genotype	1	3
Treatment	ledipasvir 90 mg / sofosbuvir 400 mg	Daclatasvir 30 mg / sofosbuvir 200 mg
Post-treatment RTPCR IU/mL	1 month	negative
	12 weeks	negative
	12 weeks after of completion treatment	833
		3691

### 3. Discussion

Our cases show the importance of considering essential elements when managing HCV infections in pediatric oncology patients. Firstly, it is important to consider that children receiving cancer treatment continue to be at higher risk for HCV infection. There is a great possibility that our cases in this study were likely to contract the infection because of the multiple blood transfusions administered during their leukemia and osteosarcoma treatments. Although the incidence of HCV transmitted through transfusions has lessened since the 1990s, isolated cases still occur, especially in areas with limited screening or within the acute infection phase of donors. Such cases emphasize the need for strict screening in children undergoing extensive transfusion therapy to enable early intervention and minimize liver damage during chemotherapy (3).

Secondly, while treatment with DAA medications carries high success rates, treatment failure is still possible. Although both patients had an undetectable virus initially, they both experienced a relapse within 12 weeks of starting treatment. Additionally, failure of initial treatment might be explained by poor adherence or the presence of baseline resistance. NS5A inhibitors like ledipasvir and daclatasvir can lead to resistance-associated substitutions (RAS) in genotypes that are tougher to treat, such as genotype 3 (15). Besides, patient 2, who belonged to genotype 3 HCV infection, may have harbored the Y93H RAS linked to daclatasvir treatment failure. In our country, resistance testing is not often available, leading to limited validation of these cases. Patient 2 was prescribed off-label sofosbuvir/daclatasvir due to the unavailability of other options at the time. His initial response to the adjusted dose indicates that he has received an adequate amount of medication. Consequently, resistance is more likely than underdosing. Both cases were retreated with sofosbuvir/velpatasvir. Such a pangenotypic combination offers a superior resistance barrier and broad efficacy by targeting NS5B and NS5A (10). Reportedly, such a combination carries a very high cure rates both in adults and children (11, 12). Our experience further supported that such a combination serves as a feasible salvage treatment in pediatric settings following DAA failure. Additionally, it was previously shown that DAA combinations are associated with minimal side effects (10, 11). In support of this, both participants did not exhibit any adverse symptoms. Furthermore, our cases in this study showed the importance of subsequent PCR testing following therapy. Due to the high success rates of DAA combinations, some physicians may abandon proper follow up may be tempted to believe in a cure due to the high success rates of DAA.

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### 4. Conclusions

It is imperative that children with cancer are at high risk of contracting blood-borne infections particularly HCV. Such a risk mandates prompt diagnosis and treatment, as the treatment of HCV can alleviate the suffering of this at-risk population. Therefore; this research suggests that physicians should be vigilant for the infection and the treatment failures. Besides, this study showed that retreatment with a pangenotypic DAA regimen, such as sofosbuvir/velpatasvir, can effectively eliminate the virus. It is important to mention that continuous research and the exchange of experiences in pediatric HCV retreatment will contribute to the further development of optimal practices, thereby enabling all children—including those who do not respond to first-line therapy to be treated with effective regimens.

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### Compliance with ethical standards

#### *Disclosure of conflict of interest*

The authors declare no conflicts of interest.

#### *Statement of ethical approval*

The ethics committee of the College of Medicine, University of Zakho approved the presentation of these two cases.

#### *Statement of informed consent*

Informed consent was obtained from the parents or legal guardians of the pediatric patients to permit the release of their anonymized clinical information and their participation. To protect patient confidentiality, all personal information was removed. The Nature of this study is retrospective analysis of clinical data, with no experimental interventions exceeding standard medical care.

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