Acta Biomed 2025; Vol. 96, N. 6: 17041 DOI: 10.23750/abm.v96i6.17041

Case report

Overcoming HCV treatment failure: From drug resistance to HCC: A case report

Evgeniya Kazakova, Nargiz Ibadullaeva, Umed Ismoilov, Bekzod Umurzakov, Erkin Musabaev

Research Institute of Virology, Tashkent, Uzbekistan

Abstract. Chronic hepatitis C remains one of the leading causes of liver fibrosis progression, cirrhosis, and hepatocellular carcinoma (HCC). The introduction of direct-acting antiviral agents (DAAs) has significantly improved treatment outcomes, achieving a sustained virologic response (SVR) in most patients. However, in some cases, therapy fails due to the development of viral resistance, which is associated with mutations in therapy target regions of the viral genome. This article presents a clinical case of HCV drug resistance to DAAs, analyzes the possible reasons for treatment failure and detection of HCV-induced HCC, and discusses management strategies for such patients in the context of modern molecular diagnostics and personalized therapy approaches. (www.actabiomedica.it)

Key words: HCV, drug resistance, DAA, treatment failure, HCC

Introduction

Chronic hepatitis C remains a significant global health concern, contributing to progressive liver disease, cirrhosis, and hepatocellular carcinoma. While achieving a sustained virologic response with direct-acting antiviral agents significantly reduces the risk of HCV-related HCC, approximately 30% of HCC cases are still attributed to HCV infection (1). In 2021, Uzbekistan launched a national program for the elimination of hepatitis C, aiming to reduce the incidence to zero by 2030. As part of this initiative, approximately one million individuals are tested annually for hepatitis C, while around 50,000 patients receive therapy each year (2). Due to the implementation of this program, patients with hepatitis C in Uzbekistan now have access to treatment either free of charge or at a reduced cost. The introduction of direct-acting antiviral agents has revolutionized HCV treatment, providing high cure rates with fewer side effects (3). However, despite their efficacy, treatment failures still occur, often due to resistance-associated substitutions (RASs), suboptimal patient adherence, variability in drug quality, and restricted access to certain antiviral regimens due to their high cost. Understanding these factors is crucial for optimizing therapeutic strategies and improving patient outcomes. One of the key challenges in achieving sustained virologic response is the emergence of HCV resistance to DAAs. Resistance can arise due to naturally occurring polymorphisms or mutations selected under antiviral pressure, reducing drug susceptibility and limiting treatment success (4,5). The detection of RASs through molecular diagnostics enables a more personalized approach, allowing regimen adjustments to overcome resistance. However, treatment outcomes are also influenced by patient-related factors, including awareness of disease risks, adherence to therapy, and access to high quality and affordable medications (6). This article presents a clinical case of HCV resistance to DAAs, highlighting the multifactorial nature of DAA treatment

failure. By analyzing this case in the context of viral resistance mechanisms, patient adherence, drug quality, financial constraints, and treatment accessibility, we emphasize the urgent need for comprehensive management strategies. Addressing these challenges requires continuous monitoring, advanced molecular diagnostics, patient education, improved access to high quality and cost-effective antiviral therapies, and policy-driven initiatives to reduce financial barriers in HCV treatment.

Case report

In 2010, a 54-year-old male was first diagnosed with anti-HCV using ELISA at a private clinic. Patient reported no significant symptoms. At that time, the standard therapy in Uzbekistan consisted of Pegylated Interferon combined with Ribavirin. However, due to the severe side effects associated with this regimen, which were explained to the patient, he chose to decline treatment. The absence of symptoms, combined with an underestimation of the potential risks associated with disease progression and complications, significantly influenced the patient's decision to refuse therapy. In 2015, the patient still reported no significant symptoms but consulted a hepatologist at the same clinic regarding his HCV diagnosis. He was prescribed a 24-week regimen of direct-acting antivirals, consisting of Sofosbuvir, Daclatasvir, and Ribavirin. Due to significantly lower costs abroad, he independently procured the medication through personal contacts in India and, in his words, adhered to the prescribed treatment. In January 2016, the patient underwent a PCR test for HCV RNA, which returned a positive result. Subsequently, in March 2016, at the clinic where he was being monitored, he was prescribed a 12-week course of Sofosbuvir and Velpatasvir (commercially known as Sofosvel). These medications had been officially imported into the country and were dispensed by prescription. However, according to the patient, he missed one or two doses of the medication, and after completing the treatment course, he did not undergo follow-up testing for HCV viral load. In May 2018, the patient began to experience discomfort in the right upper quadrant and fatigue and sought medical care at the Research Institute of Virology, where HCV RNA was detected via PCR, confirming genotype 1b. The patient reported that over the past three years, he had not engaged in high-risk behaviors, undergoing medical procedures, or experienced other potential exposure factors. Based on these findings, the physician suspected of HCV drug resistance. At that time, the Research Institute of Virology lacked the capability to perform HCV sequencing. Therefore, the patient was referred to the National Scientific and Methodological Center in the field of epidemiology, medical virology, microbiology, immunology and parasitology in Minsk, Belarus, where such testing was available. In June 2018, the patient underwent HCV drug resistance testing in Belarus, which identified RAS 31M (7) and 93H (8). As a result, resistance to NS5A inhibitors including Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, and Velpatasvir, was confirmed. Treatment with NS3 and NS5B inhibitors was recommended, as no RAS were detected for these drug classes. However, due to the high cost of the recommended 12-week treatment regimen-exceeding $30,000, the patient was unable to access therapy and was subsequently lost to follow-up. In 2021, the patient learned from acquaintances about a newly available generic, commercially known as Virvel (manufactured in India). Patient independently purchased and completed a 12-week course of the therapy without consulting a physician. This medication was available over the counter in pharmacies at an affordable price and did not require a prescription. However, the patient was unaware that Virvel contained Sofosbuvir and Velpatasvir, the latter being a drug to which he had previously developed resistance. In October 2023, the patient returned to the Research Institute of Virology. He reported discomfort in the right upper quadrant and fatigue, and denied any harmful habits such as smoking or alcohol consumption, as well the use of hepatotoxic medications. However, he was overweight, with a body mass index (BMI) of 29, which may have contributed to liver strain. PCR testing detected an HCV viral load of 1.9×10^6 IU/mL, genotype 1b. A Fibroscan revealed a liver stiffness measurement of 26.3 kPa. Ultrasound imaging showed diffuse liver changes and a hepatic hemangioma. Laboratory tests indicated elevated ALT (85.6 U/L) and AST (100.0 U/L) levels. No co-infection with other

hepatotropic viruses or HIV was identified. The patient was diagnosed with HCV-induced liver cirrhosis (non-responder to DAA), classified as Child-Pugh class A. Repeat HCV resistance testing was recommended, as the Research Institute of Virology had, by that time, developed an in-house sequencing method for detecting HCV RAS in collaboration with Hiroshima University. The analysis identified RAS 31V (9) and 93H, conferring resistance to Daclatasvir, Elbasvir, Ledipasvir, Ombitasvir, and Velpatasvir. Additionally, the 170I (10) substitution was detected, potentially reducing susceptibility to Boceprevir, Simeprevir, Telaprevir, and Voxilaprevir. The obtained results closely matched those from Belarus in 2018, supporting the hypothesis of drug resistance rather than reinfection. Based on these findings, a 16-week triple therapy regimen consisting of Glecaprevir+Pibrentasvir, and Sofosbuvir was recommended for the patient. A counseling session was conducted to emphasize the importance of treatment and adherence to therapy. The patient independently purchased Maviret (Glecaprevir/Pibrentasvir) and Sofosbuvir and successfully completed the full course of treatment. At that time, the cost of Maviret was $535 per 21-tablet pack, resulting in a total treatment cost of $2,854, which continues to pose a significant financial burden in Uzbekistan. Upon completion of the therapy, PCR testing for HCV RNA returned a negative result, confirming successful viral elimination. However, post-treatment testing revealed ALT and AST levels of 82.3 U/L and 90.5 U/L, respectively. The patient was also advised to undergo additional diagnostic procedures, including contrast-enhanced liver CT to rule out hepatocellular carcinoma and serum alpha-fetoprotein (AFP) testing. However, the results were concerning-AFP levels >100, and contrast-enhanced CT imaging revealed a mass lesion in the right liver lobe classified as LI-RADS 4B (Figure 1). Consequently, the patient was referred to an oncologist for further evaluation and management.

Discussion

Treating HCV is a race against time. The longer the virus persists in the patient's body, the higher the risk of liver fibrosis progression and the development of HCC. Physicians must act promptly to detect antiviral resistance, optimize treatment strategies, and ensure patient adherence before irreversible liver damage occurs. Timely intervention, combined with effective antiviral regimens, is essential to prevent severe complications, including HCC, and to improve long-term clinical outcomes (11). This case underscores the multifaceted challenges in managing chronic HCV infection, particularly in resource-limited settings. The patient's initial refusal of standard interferon-based therapy, primarily due to fear of side effects and the absence of symptoms, illustrates a common clinical dilemma. Asymptomatic presentation frequently results in underestimation of the long-term risks associated with HCV infection, including progression to liver cirrhosis and HCC (12). The patient's subsequent self-directed approach to treatment, involving the unsupervised procurement of medications abroad, underscores the critical importance of medical supervision in antiviral therapy. Inadequate adherence to prescribed regimens, absence of follow-up testing, and repeated use of medications against which resistance had already developed significantly compromised treatment outcomes. These factors ultimately led to persistent viremia, selection of resistant viral variants, and progression of liver disease. The development of RASs to NS5A inhibitors, as identified in two separate resistance tests, illustrates the consequences of incomplete or inappropriate therapy. Although effective antiviral combinations were available, economic barriers significantly limited access to optimal regimens (13), thereby delaying appropriate intervention. The affordability of newly available generics prompted unsupervised retreatment; however, the presence of pre-existing resistance rendered the selected therapy ineffective. Ultimately, despite achieving SVR following triple therapy the patient developed HCC, emphasizing that viral eradication does not eliminate the need for ongoing surveillance in patients with advanced liver fibrosis or cirrhosis. The importance of early diagnosis, regular monitoring, patient education, and affordable access to high-quality antiviral drugs cannot be overstated in improving long-term outcomes for patients with chronic HCV infection.

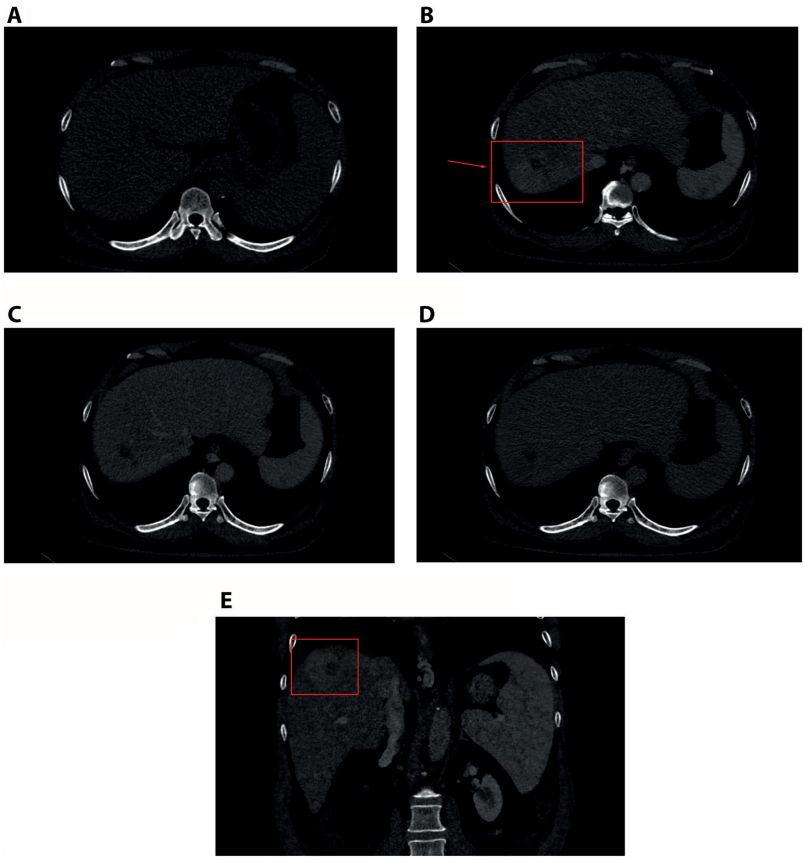

Figure 1. Dynamic Contrast Enhancement Phases of HCC. (A) Native examination (without contrast). (B) Arterial phase. The formation is visible. (C) Venous phase - the formation is no longer visualized. (D) Delayed phase. The formation is already identical to the liver parenchyma. (E) Frontal section of the arterial phase.

Limitations

This case report has several limitations that must be acknowledged. First, the clinical history and treatment adherence are primarily based on the patient's self-report, particularly regarding medications obtained and used outside formal healthcare supervision. This introduces a risk of recall bias and limits the ability to verify the accuracy of treatment and adherence. Second, the absence of serial HCV RNA testing following each treatment course prevents a definitive assessment of the patient's virologic response and the precise timing of treatment failures. Third, no histological confirmation (e.g., liver biopsy) was obtained to support the diagnosis of liver cirrhosis, and liver stiffness measurements were only performed at a single time point. Fourth, RAS were evaluated at only two time points (2018 and 2023), which may not fully capture the dynamics of viral evolution or potential reinfection. Lastly, the absence of follow-up laboratory testing during and after the final course of therapy limits the evaluation of liver function improvement and treatment durability.

Conclusion

This case report underscores the critical importance of timely, supervised, and appropriately selected antiviral therapy in the management of chronic HCV infection. Patient-related factors, such as underestimation of disease severity, unsupervised treatment attempts, and poor adherence to follow-up protocols, can significantly compromise therapeutic outcomes and accelerate disease progression. Additionally, financial constraints and

limited access to resistance testing remain major challenges in low- and middle-income countries, often contributing to suboptimal treatment results. Importantly, even after successful viral eradication, patients with advanced liver disease remain at risk for serious complications such as HCC, underscoring the need for ongoing surveillance and multidisciplinary care. A comprehensive, patient-centered approach that addresses medical, economic, and educational barriers is essential for optimizing treatment outcomes and preventing adverse long-term consequences of chronic HCV infection.

Ethics Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: EK: conceived and designed the study, drafted the first version of the manuscript. EK, NI: editing, drafted the final version of the manuscript. UI: collected the data. BU: analyzed the KT data. EM: review, supervision. All authors have read and agreed to the published version of the manuscript.

Declaration on the Use of AI: During the preparation of this article, the authors used ChatGPT in order to improve language and readability. The authors reviewed and edited the content as needed after using this tool and take full responsibility for the content of the publication.

Acknowledgements: We thank Professor Junko Tanaka and stuff of Hiroshima University for their support in designing of the laboratory protocol.

References

1. Shen C, Jiang X, Li M, Luo Y. Hepatitis Virus and Hepatocellular Carcinoma: Recent Advances. Cancers (Basel). 2023 Jan 15;15(2):533. doi: 10.3390/cancers15020533.
2. Musabaev E, Estes C, Sadirova S, et al. Viral hepatitis elimination challenges in low- and middle-income countries-Uzbekistan Hepatitis Elimination Program (UHEP). Liver Int. 2023 Apr;43(4):773-84. doi: 10.1111/liv.15514. Erratum in: Liver Int. 2024 Jan;44(1):266. doi: 10.1111/liv.15652.
3. Lynch EN, Russo FP. Outcomes and Follow-Up after Hepatitis C Eradication with Direct-Acting Antivirals. J Clin Med. 2023 Mar 12;12(6):2195. doi: 10.3390/jcm12062195.
4. Esposito I, Trinks J, Soriano V. Hepatitis C virus resistance to the new direct-acting antivirals. Expert Opin Drug Metab Toxicol. 2016 Oct;12(10):1197-209. doi: 10.1080/17425255.2016.1209484.
5. Kishida Y. Mechanisms of virologic failure in hepatitis C and strategies for treatment failure. MOJ Immunol. 2016; 4(1):00114. doi: 10.15406/moji.2016.04.00114.
6. Chauke GD, Nakwafila O, Chibi B, Sartorius B, Mashamba-Thompson T. Factors influencing poor medication adherence amongst patients with chronic disease in low-and-middle-income countries: A systematic scoping review. Heliyon. 2022 Jun 15;8(6):e09716. doi: 10.1016/j.heliyon.2022.e09716.
7. Sorbo MC, Cento V, Di Maio VC, et al. Hepatitis C virus drug resistance associated substitutions and their clinical relevance: Update 2018. Drug Resist Updat. 2018 Mar:37: 17-39. doi: 10.1016/j.drup.2018.01.004.
8. Li G, De Clercq E. Current therapy for chronic hepatitis C: The role of direct-acting antivirals. Antiviral Res. 2017 Jun;142:83-122. doi: 10.1016/j.antiviral.2017.02.014.
9. Yu W, Ling T, Bin H, et al. Discovery of Chromane Containing Hepatitis C Virus (HCV) NS5A Inhibitors with Improved Potency against Resistance-Associated Variants. J Med Chem. 2016 Nov 23;59(22):10228-43. doi: 10.1021/acs.jmedchem.6b01234.
10. Liu Z, Mao X, Wu J, et al. World-wide Prevalence of Substitutions in HCV Genome Associated With Resistance to Direct-Acting Antiviral Agents. Clin Gastroenterol Hepatol. 2021 Sep;19(9):1906-14.e25. doi: 10.1016/j.cgh.2019.10.046.
11. Ioannou GN. HCC surveillance after SVR in patients with F3/F4 fibrosis. J Hepatol. 2021 Feb;74(2):458–65. doi: 10.1016/j.jhep.2020.10.016.
12. McGowan CE, Fried MW. Barriers to hepatitis C treatment. Liver Int. 2012 Feb;32 Suppl 1(01):151-6. doi: 10.1111/j.1478-3231.2011.02706.x.
13. Bartenschlager R, Baumert TF, Bukh J, et al. Critical challenges and emerging opportunities in hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies. Virus Res. 2018 Mar 15:248:53-62. doi: 10.1016/j.virusres.2018.02.016.

Correspondence:
Received: 5 April 2025
Accepted: 5 May 2025
Evgeniya Kazakova, PhD
Research Institute of Virology, Yangi shahar str. 7A, 100194 Tashkent, Uzbekistan
E-mail: dr.kazakova.evg@gmail.com
ORCID: 0000-0003-1265-7299