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# A Case of Chronic Hepatitis C with Treatment Failure of Glecaprevir/Pibrentasvir

## Glecaprevir/Pibrentasvir Tedavi Başarısızlığı Gelişen Kronik Hepatit C Olgusu

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### Abstract

Direct-acting antivirals have achieved high sustained virologic response (SVR) rates in the treatment of chronic hepatitis C virus (HCV) infection. However, data on retreatment strategies following failure of glecaprevir/pibrentasvir (G/P) therapy remain limited. We report the case of a 48-year-old man with genotype 3 chronic HCV infection who experienced virologic failure despite full adherence to an 8-week G/P regimen. The patient was subsequently treated with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks, resulting in normalization of liver enzyme levels and undetectable HCV ribonucleic acid at the end of treatment and 12 weeks after treatment, confirming achievement of SVR12. This case demonstrates that SOF/VEL/VOX may represent an effective and safe salvage therapy for patients with genotype 3 HCV infection who fail prior G/P treatment and provides clinical insight to guide retreatment decisions.

**Keywords:** Chronic viral hepatitis C, direct-acting antivirals, hepatitis C

### Öz

Doğrudan etkili antiviraller, kronik hepatit C virüsü (HCV) enfeksiyonunun tedavisinde yüksek kalıcı virolojik yanıt (SVR) oranlarına ulaşılmasını sağlamıştır. Ancak glekaprevir/pibrentasvir (G/P) tedavisinin başarısızlığı sonrasında yeniden tedavi stratejilerine ilişkin veriler sınırlı kalmaktadır. Bu yazıda, genotip 3 kronik HCV enfeksiyonu olan ve 8 haftalık G/P rejimine tam uyum göstermesine rağmen virolojik başarısızlık gelişen 48 yaşındaki bir erkek olgu sunulmaktadır. Hasta daha sonra 12 hafta süreyle sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) ile tedavi edilmiş olup, tedavi sonunda ve tedavi bitiminden 12 hafta sonra karaciğer enzim düzeylerinin normaleştiği ve HCV ribonükleik asidinin saptanamaz olduğu gösterilerek SVR12 elde edildiği doğrulanmıştır. Bu olgu, önceki G/P tedavisinde başarısızlık gelişen genotip 3 HCV enfeksiyonlu hastalarda SOF/VEL/VOX'un etkili ve güvenli bir kurtarma tedavisi seçeneği olabileceğini göstermekte ve yeniden tedavi kararlarına klinik açıdan yol gösterici nitelik taşımaktadır.

**Anahtar Kelimeler:** Kronik viral hepatit C, doğrudan etkili antiviraller, hepatit C

### Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. More than half of infected individuals

progress to chronic infection, which may persist lifelong if left untreated<sup>[1,2]</sup>. The management of hepatitis C has evolved rapidly with the introduction of direct-acting antivirals (DAAs), leading to highly effective and well-tolerated treatment

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regimens. Current guidelines recommend treatment for all patients without contraindications<sup>[3]</sup>.

Despite the high success rates of DAA-based therapies, a small proportion of patients experience virologic failure. Evidence regarding optimal retreatment strategies for patients who fail glecaprevir/pibrentasvir (G/P) therapy remains limited and has not been sufficiently evaluated<sup>[3,4]</sup>. Here, we present a case of chronic HCV infection in which virologic suppression was not achieved following G/P therapy, and successful retreatment was subsequently accomplished using an alternative DAA regimen. Written informed consent was obtained from the patient for publication of this case.

### Case Report

A 48-year-old man presented after testing positive for anti-HCV antibodies during routine laboratory screening. He was asymptomatic at presentation. Although he was aware of his hepatitis C diagnosis, he had not previously sought medical follow-up or treatment. His medical history was notable for intravenous drug use approximately 20 years earlier. He had no known chronic illnesses, was not taking regular medications, and had no family history of hepatitis.

On physical examination, vital signs were within normal limits, and no abnormal findings were observed. Laboratory evaluation revealed alanine aminotransferase (ALT) of 155 U/L (reference <45 U/L), aspartate aminotransferase (AST) of 142 U/L (reference <45 U/L), platelet count of 87,000/ $\mu$ L (reference >100,000/ $\mu$ L), and HCV-ribonucleic acid (RNA) level of 16,000,000 IU/mL. Serologic testing showed negative hepatitis B surface antigen, negative antibody to hepatitis B surface antigen, negative antibody to hepatitis B core antigen immunoglobulin G (IgG), positive antibody to hepatitis A virus

IgG, and negative antibody to human immunodeficiency virus antibodies. Other laboratory parameters were within normal limits, including a white blood cell count of 5,000/ $\mu$ L, hemoglobin level of 14.8 g/dL, hematocrit of 44.4%, and serum creatinine of 1.04 mg/dL.

The fibrosis-4 (FIB-4) score was calculated as 6.29, and the AST-to-platelet ratio index (APRI) score was 3.98. Hepatobiliary ultrasonography demonstrated a liver craniocaudal length of 156 mm, which was at the upper limit of normal, with regular contours and no evidence of cirrhosis or splenomegaly.

The patient was initiated on the pangenotypic regimen G/P (100 mg/40 mg). At week 8 of treatment, laboratory testing showed ALT of 136 U/L, AST of 95 U/L, HCV-RNA of 2,000,000 IU/mL, and a platelet count of 81,000/ $\mu$ L, indicating virologic failure. Changes in laboratory parameters during treatment are summarized in Table 1.

Although the HCV-RNA level decreased during the fourth week of G/P therapy, a high viral load was detected at week 8. Repeat testing confirmed persistently elevated HCV-RNA levels. Consequently, the patient's adherence to therapy was carefully evaluated and confirmed to be appropriate, with regular and correct medication intake. The patient denied the use of concomitant medications, alcohol, or other substances.

HCV genotyping revealed genotype 3 infection. An antiviral resistance analysis was requested from the Public Health Microbiology Reference Laboratory; however, the test was not processed. Based on current clinical guidelines, a review of the available literature, and the antiviral agents accessible in our country, retreatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) (400 mg/100 mg/100 mg) was initiated and continued for 12 weeks.

**Table 1. Laboratory results during G/P treatment.**

Parameter	Before treatment	Week 4	Week 8
ALT	155 U/L	59 U/L	136 U/L
AST	142 U/L	50 U/L	95 U/L
HCV-RNA	16,000,000 IU/mL	15,000 IU/mL	2,000,000 IU/mL
Platelet	87,000/ $\mu$ L	82,000/ $\mu$ L	81,000/ $\mu$ L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; G/P, glecaprevir/pibrentasvir; HCV-RNA, hepatitis C virus/ribonucleic acid.

**Table 2. Laboratory results during SOF/VEL/VOX treatment.**

Parameter	Before treatment	Week 4	Week 8	Week 12
ALT	145 U/L	56 U/L	50 U/L	53 U/L
AST	102 U/L	40 U/L	40 U/L	39 U/L
HCV-RNA	3,900,000 IU/mL	62 IU/mL	30 IU/mL	Negative
Platelet	81,000/ $\mu$ L	89,000/ $\mu$ L	91,000/ $\mu$ L	100,000/ $\mu$ L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; G/P, glecaprevir/pibrentasvir; HCV-RNA, hepatitis C virus/ribonucleic acid; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

Throughout the treatment period, ALT and AST levels were closely monitored and demonstrated a gradual decline. At the end of treatment, ALT was 53 U/L, AST was 39 U/L, and the platelet count was 100,000/ $\mu$ L. HCV-RNA testing performed at the end of therapy showed undetectable viral levels (Table 2).

At 12 weeks post-treatment, the patient's ALT was 31 U/L, AST was 37 U/L, platelet count was 104,000/ $\mu$ L, and HCV-RNA was not detected. Liver enzymes had returned to normal, and thrombocytopenia had resolved. Sustained virologic response (SVR) was confirmed at the end of treatment and 12 weeks post-treatment.

## Discussion

The efficacy of DAA therapies for HCV infection is well established. G/P therapy achieves SVR at 12 weeks post-treatment (SVR12) in over 95% of patients, including those with prior DAA exposure, with virologic failure rates ranging from 0% to 1%<sup>[5-10]</sup>. However, evidence regarding retreatment strategies for patients who fail G/P therapy remains limited.

In the EXPEDITION-8 trial, 343 treatment-naive cirrhotic patients with genotypes 1–6 received G/P for 8 weeks, with 18% infected with genotype 3. The overall SVR12 rate was 97.7%, while patients with genotype 3 achieved 95.2%<sup>[11]</sup>. This study highlighted the relatively lower success rate in genotype 3 infections, consistent with our case of a patient with genotype 3 who failed G/P therapy.

Treatment options for chronic hepatitis C patients with prior NS5A inhibitor exposure are limited. Pibrentasvir exhibits a higher in vitro resistance barrier than other NS5A inhibitors, making combination therapy with sofosbuvir a promising alternative<sup>[3,12]</sup>. The MAGELLAN-3 study reported a 96% SVR12 rate with 12–16 weeks of G/P plus sofosbuvir and ribavirin in patients with previous G/P treatment failure<sup>[13]</sup>.

According to European Association for the Study of the Liver (EASL) guidelines, genotype 3 patients with prior treatment experience and no cirrhosis may be treated with SOF/VEL or G/P. For patients with cirrhosis, the triple regimen SOF/VEL/VOX is recommended<sup>[3]</sup>. In our patient, these standard regimens could not be implemented because sofosbuvir-containing drugs were unavailable locally. Although cirrhosis was not assessed via biopsy or noninvasive methods, elevated fibrosis scores (APRI and FIB-4) suggested advanced liver disease. Based on available evidence and treatment options, SOF/VEL/VOX therapy was initiated.

The efficacy of SOF/VEL/VOX in patients who fail G/P therapy remains unclear, as most studies predate widespread G/P use<sup>[14]</sup>. While EASL guidelines recommend 12 weeks of SOF/

VEL/VOX for all DAA-experienced patients, data specific to G/P failures are limited. SOF/VEL/VOX serves as a salvage regimen for patients with prior NS5A inhibitor exposure<sup>[3,11]</sup>. In a study of 31 patients who failed G/P therapy and received SOF/VEL/VOX, 94% achieved SVR12, supporting its efficacy<sup>[4]</sup>. Consistent with these findings, our patient achieved SVR12 following SOF/VEL/VOX therapy. A limitation of this case was the absence of resistance testing following G/P failure.

This case demonstrates several distinctive features that add real-world evidence to the management of G/P failure. Despite the high efficacy of G/P across genotypes, including genotype 3, our patient exhibited an unusual virologic pattern: an initial on-treatment response followed by viral rebound at week 8, a rare occurrence in the literature. Although resistance testing and standard retreatment algorithms could not be applied, SOF/VEL/VOX led to complete virologic suppression. The regimen was well tolerated, even in the context of laboratory indicators suggestive of advanced fibrosis, underscoring its therapeutic potential in challenging scenarios.

## Conclusion

In conclusion, a 12-week course of SOF/VEL/VOX can achieve SVR12 in genotype 3 chronic hepatitis C patients with G/P treatment failure. This regimen should be considered a safe and effective salvage option in similar clinical contexts.

## Ethics

**Informed Consent:** Written informed consent was obtained from the patient for publication of this case.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: S.A., Y.Ç., Concept: S.A., Design: S.A., Y.Ç., Data Collection or Processing: S.A., Analysis or Interpretation: S.A., Literature Search: S.A., Y.Ç., Writing: S.A., Y.Ç.

**Conflict of Interest:** Yasemin Çağ, the author of this article, is a member of the editorial board of the Mediterranean Journal of Infection, Microbes and Antimicrobials. However, she was not involved in any stage of the editorial review or decision-making process for this manuscript.

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