Does Treatment of Hepatitis C Reduce Inhibitor Titers in Hemophilia A?

Hepatit C Tedavisi Hemofili A'da İnhibitör Titrelerini Azaltır mı?

Memiş Hilmi Atay[1], Emine Türkoğlu[2], Engin Kelkitli[1]

[1]Ondokuz Mayıs University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Samsun, Turkey

[2]Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Infectious Diseases, Tokat, Turkey

To the Editor,

Hemophilia A is an X-linked recessive disorder characterized by a deficiency of factor VIII in plasma [1]. It has been reported that approximately 30% of patients who receive recombinant or plasma-derived factor VIII prophylaxis may develop neutralizing antibodies or inhibitors [2]. Bleeding episodes in patients with low-responding inhibitors are treated with factor VIII, whereas bleeding episodes in those with high-responding inhibitors are treated with bypassing agents, such as recombinant activated factor VIIa (rFVIIa) [3]. Here we discuss the case of a patient with factor VIII inhibitors whose need for factor replacement decreased with the treatment of chronic hepatitis C.

A 47-year-old male patient underwent surgery due to a fracture of the right elbow. He had factor VIII deficiency and was first diagnosed at the age of 10 with a factor VIII level of 4 IU. He was treated with factor replacement due to bleeding episodes. He did not have major bleeding episodes or major surgery. The preoperative factor FVIII level was reported as 1.2 IU/mL. Inhibitors could not be studied. Before the surgery, he was given factor VIII concentrate loading of 3000 units and 2x1500 units (50 U/kg) for one week. On the seventh postoperative day, the levels of factor VIII and inhibitor were assessed due to ongoing bleeding from the operation site. Factor VIII was found to be 2 IU/mL and the inhibitor to be 19.2 BU/mL. No factor VIII inhibitor had been detected in the patient previously. The treatment was switched to a bypassing agent, rFVIIa, at 5400 µg (90 µg/kg/dose) with 3 doses to be administered every 3 hours. Once the bleeding was under control, the rFVIIa treatment was administered with decreasing frequency. The patient was HCV-positive with HCV RNA of 550,000 units of copies. He tested negative for hepatitis B surface antigens and HIV antibodies. The patient, who had HCV genotype 2, was started on direct-acting antiviral (DAA) drug treatment with glecaprevir/pibrentasvir at 1x3 tablets daily. After starting DAA treatment, the patient's need for factor rFVIIa decreased (Figure 1). As a result, the dose frequency was decreased and treatment with rFVIIa continued twice a week. After 8 weeks, HCV RNA was not detected. The level of factor VIII inhibitor was detected as 1.2 BU/mL.

It has been found that patients who are HCV-positive with factor VIII inhibitors have a complex immune profile characterized by higher levels of pro-inflammatory and anti-inflammatory cytokines compared to those who are not [4,5]. The cure rate of chronic hepatitis C has reached 90% with DAA therapy [6]. Triple treatment with interferon, telaprevir, and ribavirin has been reported to result in a decrease in the level of inhibitors and the need for recombinant factors in patients with hemophilia A [7]. We believe that DAA treatment reduces the need for rFVIIa by lowering inhibitor levels through both suppression of hepatitis C and modulation of cytokines.

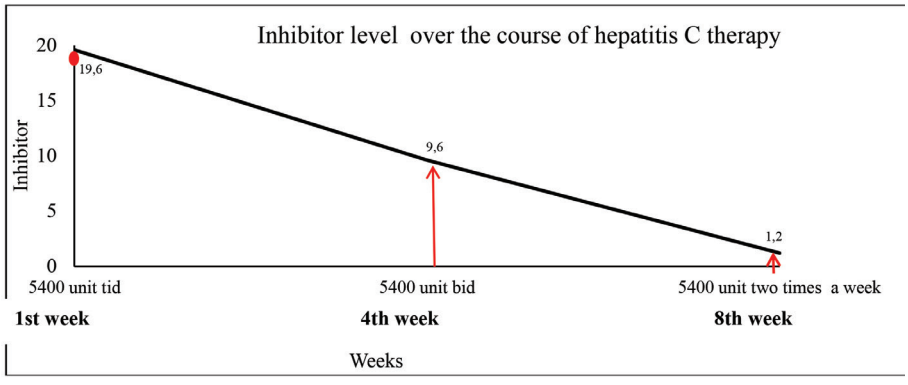

Figure 1. Graph demonstrating inhibitor levels and factor VIIa dosage during direct-acting antiviral drug treatment.

To the best of our knowledge, this case study is the first to report reduced inhibitor levels and a decreased need for rFVIIa after DAA treatment. This treatment may reduce inhibitor titers. The treatment of hepatitis C may also play a role. We hope that our findings will facilitate further studies involving larger numbers of patients.

Keywords: FVIII deficiency, Hepatitis C, Inhibitor

Anahtar Sözcükler: FVIII eksikliği, Hepatit C, İnhibitör

Ethics

Informed Consent: Received.

Authorship Contributions

Surgical and Medical Practices: M.H.A., E.T., E.K.; Concept: M.H.A.; Design: M.H.A.; Data Collection or Processing: M.H.A.; Analysis or Interpretation: M.H.A., E.T., E.K.; Literature Search: M.H.A., E.T., E.K.; Writing: M.H.A., E.T., E.K.

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ljung RCR. How I manage patients with inherited haemophilia A and B and factor inhibitors. Br J Haematol 2018;180:501-510.
2. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003;9:418-435.
3. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, Carcao M, Mahlangu J, Ragni MV, Windyga J, Llinás A, Goddard NJ, Mohan R, Poonnoose PM, Feldman BM, Lewis SZ, van den Berg HM, Pierce GF; WFH Guidelines for the Management of Hemophilia Panelists and Co-Authors. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia 2020;26:1-158.
4. Martins ML, Chaves DG, da Silva-Malta MCF, Bolina-Santos E, Barbosa-Stancioli EF, Carmo RA. Hepatitis C and history of FVIII inhibitor development in a long-term cohort of Brazilian patients with haemophilia A. Haemophilia 2020;26:130-133.
5. Bolina-Santos E, Chaves DG, da Silva-Malta MCF, Carmo RA, Barbosa-Stancioli EF, Lobato Martins M. HCV infection in hemophilia A patients is associated with altered cytokines and chemokines profile and might modulate the levels of FVIII inhibitor. J Med Virol 2022;94:683-691.
6. Holmes JA, Thompson AJ. Interferon-free combination therapies for the treatment of hepatitis C: current insights. Hepat Med 2015;7:51-70.
7. Singh G, Sass R, Alamiry R, Zein N, Alkhouri N. Hepatitis C treatment with triple therapy in a patient with hemophilia A. World J Clin Cases 2013;16:106-107.

Address for Correspondence/Yazışma Adresi: Memiş Hilmi Atay, M.D., Ondokuz Mayıs University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Samsun, Turkey
Phone : +90 530 468 15 59
E-mail : draatay@gmail.com ORCID: orcid.org/0000-0001-9666-6955

Received/Geliş tarihi: March 2, 2022
Accepted/Kabul tarihi: April 8, 2022
DOI: 10.4274/tjh.galenos.2022.2022.0085