



Paradoxes in Novel Hepatitis C Therapies: Is Combination of Sofosbuvir and Ribavirin Without Interferon Effective in Genotype 1b Chronic HCV Patients?

Yeni Hepatit C Tedavilerindeki Paradokslar: Interferonsuz Sofosbuvir ve Ribavirin Kombinasyonu Genotip 1b Hepatit C Virüsü ile Enfekte Hastalarda Etkili mi?

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Key Words: Hepatitis C, sofosbuvir, interferon

Anahtar Kelimeler: Hepatit C, sofosbuvir, interferon

Dear Editor,

Chronic hepatitis C virus (HCV) infection has become a major and significant public health problem whereas this virus has already infected approximately 170 million people worldwide.

It is assumed that nearly 350.000 patients across the globe have lost their lives due to this infection (1). The prevalence of HCV infections in Turkey was reported to be 0.3-0.7% (2). As in developing countries, in our country, the prevalence of hepatitis B infections is gradually decreasing thanks to widespread hepatitis B vaccination programs (3). However, HCV infection makes a turn to become a major problem due to the absence of an effective vaccine to avoid HCV and the increase in intravenous drug addiction.

Regarding chronic HCV therapy, regimens based on interferon which was a drug administered alone at a certain term at the beginning of the treatment of chronic HCV infection while this drug is still used as a touchstone in combined therapy has increased sustained virologic response rate over 70% when administered as triple regimens together with telepravir and boceprevir, drugs which recently entered the market. However, escalated side effects (anemia, neutropenia, rash, sensation

of anorectal discomfort and etc.), increased tablet intake and difficulty in decreasing dosage due to problems with resistance have negatively affected therapeutic compliance when these drugs were used together with interferon and ribavirin, opened the door for investigators to seek new and different therapies (4). Within this context, antiviral agents that may provide a chance for cure in more patients and with a lesser degree of side effect profile and a direct effect in the treatment of HCV infections were reproduced. Sofosbuvir is a novel drug emerged as the first nucleotide polymerase inhibitor, with a pan-genotypic efficacy and high resistance barrier and has been studied as triple therapy with interferon and ribavirin in chronic hepatitis C patients who have not received any therapy before. This new combination raised our hopes as it provided more than 90% sustained virologic response rate in all type of genotype-induced infections. On the other hand, sofosbuvir played a key role in pioneering interferon-free therapeutic regimens in patients who are capable of tolerating interferon and where this drug cannot be administered.

Studies demonstrated that the dual combination of sofosbuvir and ribavirin provided sustained virologic responses over 80% in entire genotypes and, consequently, these regimens found their place in the therapeutic guidelines of

Europe and USA (5,6). However, in multiple studies carried out in our country related to genotype distribution it has been demonstrated that genotype 1b was the most frequently seen genotype in patients infected with HCV (7). Accordingly, the most major and significant point in our country is the recognition of the activity of sofosbuvir in genotype 1b group patients and this activity is well-known.

In recent studies, it was shown that a triple regimen of interferon, ribavirin and sofosbuvir provided 82% sustained virological response in genotype 1b hepatitis C patients who have not received any therapy before. However, in genotype 1b group of patients where interferon was not tolerated or interferon cannot be administered, combined therapy with sofosbuvir and ribavirin provided only a rate of 53% sustained virological response (8,9). Accordingly, sofosbuvir and ribavirin therapy administered to genotype 1b patients without interferon is not assumed to be a good combination to obtain a sustained virologic response (5). The American Association for the Study of Liver Diseases (AASLD) guideline recommends that the addition of simeprevir to this therapeutic regimen (sofosbuvir and ribavirin) in genotype 1 patients can provide higher sustained virologic response in difficult-to-cure chronic HCV patients (6).

More recently, together with a combination of sofosbuvir 400 mg and ledipasvir 90 mg, the dual regimen of sofosbuvir 400 mg and daclatasvir 60 mg has raised up as a more effective combination and is featured as the best therapies with sustained virologic response rate over 95% among interferon-free regimens (10,11,12,13).

Another study carried out by Manns et al. (14) showed that daclatasvir and asunaprevir dual therapy provided sustained virologic response more than 90% in treatment-naïve genotype 1b patients; and more than 82% sustained virologic response in genotype 1b patients who failed to tolerate interferon and respond to classical therapy previously. A recent study has demonstrated that ritonavir boosted ABT-450 (ABT-450/r), ombitasvir, and dasabuvir therapy achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection (15). In another study, twelve weeks of treatment with ABT-450/r, ombitasvir and dasabuvir without ribavirin was found to be highly effective among previously untreated genotype 1 patients with 98% sustained virologic response (16). All these studies indicate that these therapies seem to become the standard of care for hepatitis C genotype 1 infection.

As a result, interferon-free therapeutical regimens is a reality in today's medical world, but not a dream anymore. As it is in classical therapies, especially considering the genotype of the patient, it is very important to personalize therapy for such patients and initiate an appropriate therapeutic regimen for the most convenient patient after taking notice of prognostic markers which may affect the response to the therapy. However, it should not be forgotten that, if interferon intolerance is present in genotype 1b chronic hepatitis C patients, then it is possible to obtain better and more effective results from therapies such as therapeutic regimens of ledipasvir/sofosbuvir (with or without

ribavirin), sofosbuvir plus simeprevir (with or without ribavirin), sofosbuvir plus daclatasvir or by a dual regimen of daclatasvir and asunaprevir than that from sofosbuvir plus ribavirin.

Concept: Ergenekon Karagöz, Vedat Turhan, Hakan Erdem, **Design:** Ergenekon Karagöz, Alpaslan Tanoğlu, Asım Ülçay, Vedat Turhan, **Data Collection or Processing:** Ergenekon Karagöz, **Analysis or Interpretation:** Ergenekon Karagöz, Hakan Erdem, **Literature Search:** Ergenekon Karagöz, **Writing:** Ergenekon Karagöz, **Peer-review:** External and Internal peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors., **Financial Disclosure:** The authors declared that this study has received no financial support.

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