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Treatment of Chronic Hepatitis C Infection: Update of the Recommendations from Scientific Leader's Meeting-28th July 2011-Tehran, IR Iran

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ABSTRACT

Hepatitis C remains as an important health problem worldwide. Hepatitis C treatment, especially among patients infected with HCV genotype 1 who are considered difficult to treat, is a high priority for health policy-makers. PegInterferon alfa instead of Interferon and ribavirin combination therapy has been accepted as the standard treatment regimen for hepatitis C patients; however, only 50% of patients infected with HCV genotype 1 achieve a sustained virological response. Published data from various clinical trials of protease inhibitors suggest that new therapeutic regimens may increase the chances of a successful response in patients infected with HCV genotype 1. Triple therapy that includes boceprevir has been shown to result in high rates of sustained virological response in both naive and experienced patients with HCV genotype 1 infection. In this review, we have summarized the results obtained with this new regimen and have attempted to provide a guideline for the treatment of patients in Iran, with emphasis on cost and the occurrence of adverse events.

▸ *Implication for health policy/practice/research/medical education:*
Proper treatment of hepatitis C to control the burden of disease is essential in the society. Nowadays with the new methods of therapy the hope of eradication is more than before. This study is recommended to internal medicine and infectious disease specialists, gastroenterologists, general practitioners, virologists and health policy makers.

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1. Introduction

Hepatitis C is a major cause of liver-related morbidity and mortality worldwide and a major public health problem (1-4). It is estimated that around 170–200 million individuals are living with HCV infection worldwide (5, 6). Hepatitis C is accepted as the most common infection that causes chronic liver disease in European patients (7); the occurrence of end-stage liver disease caused by HCV is estimated to peak around 2020 (8). HCV infection is responsible for 20% of acute hepatitis cases, 70% of all chronic hepatitis cases, 40% of all cases of liver cirrhosis, 60% of hepatocellular carcinomas (HCC), and 30% of liver transplants in Europe (9, 10). In addition, 72% of recently admitted HCC patients in Japanese hospitals were infected with hepatitis C (11). Further, HCV infection is recognized as the leading indication for liver transplantation and is estimated to cause 8,000–10,000 deaths annually (1, 10, 12, 13). It is also considered responsible for post-transfusion hepatitis, and is considered the predominant cause of observed chronic liver disease in treated hemophiliacs (14).

1.1. Epidemiology, Current Epidemiologic Trends, and Future Disease Burden

The prevalence and distribution of HCV shows significant geographical variations, and significant demographical variations within the same geographic region (3). HCV prevalence has changed significantly worldwide, showing a decreasing trend in the developed world due to a decrease in infections among injecting drug users, the effect of harm reduction programs, and a reduced risk of transfusion-associated acute hepatitis C infection. In contrast, HCV prevalence is high in underdeveloped countries and high-risk groups. In the USA, the incidence of acute infection has fallen from 230,000 per year in the 1980s to its current level of about 19,000 cases per year, with a current overall incidence of 0.3 per 100,000. Injecting drug use remains the most significant risk factor of HCV infection in the USA, followed by sexual transmission and health related work (3), whereas in the underdeveloped world, the high incidence of HCV is mainly a consequence of the use of unscreened blood transfusions and unsafe parenteral exposure. The major change in the risk factors for HCV transmission over time is reflected in the dramatic reduction of blood transfusion-related cases and in the increasing proportion of cases due to injecting drug use (15-17). The number of new cases is significantly reduced because of advancement of new technologies for product processing and blood screening before transfusion. The prevalence of HCV infection in the general population is less than 1% in Iran (18, 19). The highest frequency by HCV genotype in Iran is almost 45% for genotype 1a, followed by genotype 3a, which is more prevalent in the northwest, and then by 1b (20). The overall risk factors for HCV infection in Iran are male sex, living in a rural area, unmarried status, drug abuse, history of transfusion, tattooing, and imprisonment (21).

1.2. Natural History

On the basis of available data, different courses of natural history emerge depending on the population studied, the duration of infection in that population, how the disease was transmitted, and the relative prevalence of cofactors such as gender, age at onset of infection, and alcohol consumption. Older age at HCV exposure, male gender (22), non-white race (23), higher body mass index

(24), heavy alcohol intake (> 40–50 gm/day) (25-27), the genotype 1 (28, 29), high genotype quasispecies diversity (29), HBV, HIV co-infection (30-34), and cigarette smoking have been variously identified as factors associated with more rapid disease progression (35-38).

1.3. Therapy of HCV Infection

Antiviral therapy plays an important role in the treatment of HCV-infected patients because a sustained virological response (SVR) prevents progression of fibrosis, decreases hepatic inflammation and necrosis, reduces the risk of HCC, and improves patient survival (39-43). Treatment regimens for chronic hepatitis C (CHC) have progressed within the last 12 years, leading to improved SVR rates. Combination therapy with pegylated interferon alpha (PEG-IFN) and ribavirin (RBV) is considered standard treatment for CHC. PEG-IFN alpha-2a and alpha-2b are two approved and available forms of pegylated IFN. Clinical trials have been conducted to compare these two approved forms of PEG-IFN; in the largest of these trials, the IDEAL trial, similar SVR rates were reported with both types of PEG-IFN (44). The rates of SVR among patients infected with HCV genotype 1 range from 25% to 42% in different studies (45, 46). Despite these findings, the development of new regimens is required to increase the efficacy and safety of treatment options for HCV- infected patients, especially those infected with genotype 1, which is recognized as an HCV strain against which it is difficult to elicit a sustained response. Boceprevir has recently been approved by FDA, and this appears to have opened up a new treatment option for patients infected with HCV genotype 1. We performed a survey of different aspects of this drug, based on electronic searches and expert opinions.

1.4. Response-Guided Therapy (RGT)

In recognition of the important role of viral kinetics during therapy, several studies have attempted to evaluate individualized anti-HCV therapy regimens based on the patient's virological response rather than on genotype alone. Patients with a rapid virological response (RVR; undetectable HCV-RNA level at week 4 of therapy) have an 80-100% likelihood of achieving SVR, while patients who do not attain an early virological response (EVR; undetectable HCV-RNA level at week 12 of therapy or less than a 2-log-unit decrease relative to pre-treatment RNA levels) have only an 8% chance of achieving SVR (47, 48). Shortening of the therapy regimen in rapid virological responders, compared to standard therapy, has been shown to be similarly effective in cases of infection with genotype 2 and 3; however; this has not been demonstrated in the case of genotype 1 infection (49, 50). Additionally, several studies have evaluated the extension of therapy in slow responders.

Response-guided therapy is a model for treating chronic hepatitis C infection in which treatment decisions are based on how rapidly HCV infection responds to therapy. With response-guided therapy, patients who rapidly clear virus from their bloodstream (RVR; after 4 weeks of therapy) are eligible to receive a shorter duration of therapy, while slower responders or partial responders receive extended durations of therapy. The use of response-guided therapy is already well studied in cases of infection with the easier-to-treat genotypes of HCV, specifically genotypes 2 and 3; over the course of the next year, response-guided therapy for HCV genotype 1 infection will also be a commonly used option with direct-acting antiviral agents. This opportunity would allow some patients to be treated with just 24–28 weeks of therapy instead of the standard 48 weeks of treatment. Although the incorporation of response-guided therapies in practice guidelines requires more evidence, studies in recent years have shown that adding protease inhibitors allows the preservation of SVR rates while reducing treatment duration for patients who respond rapidly.

We have conducted a systematic review to assess the comparative efficacy of anti-HCV therapy with PEG-IFN alpha and weight-based RBV, for treatment durations of 72 weeks *vs*. 48 weeks, in genotype 1 slow virological responders who were seronegative for HIV and HBV co-infections. Our results suggest that, in slow virological responders with HCV genotype 1 infection, treatment for 72 weeks achieves a significantly higher SVR rate than does treatment for 48 weeks. Because of the high mean viral load of the included patients, our finding can easily be extrapolated to genotype 1 HCV–infected slow responders with a high viral load, or in other words, hard-to-treat HCV infections. Although there were no significant differences in any single side effect, treatment discontinuation because of safety reasons or voluntarily was significantly greater in the 72-week study group. This might be due to longer or more severe side effects in the extended therapy group. Encouraging patients to complete the 72-week therapy regimen, along with close follow-ups and management of side effects to decrease the likelihood of treatment discontinuation, can increase the SVR rate (51). Among treatment-naive patients, total therapy duration can be shortened from 48 weeks to 28 weeks for patients who have undetectable HCV RNA at treatment weeks 8 and 24 (52). Further, among patients who had previously failed therapy, assessment of early interferon responsiveness can be used to shorten the total therapy duration from 48 weeks to 36 weeks (53). By restricting HCV treatment duration to a shorter period in patients who respond quickly, and extending it to longer periods in patients who respond more slowly, clinicians can potentially improve the efficacy of treatment.

2. Materials and Methods

We started from a literature review for new management of HCV infection, and asked the governing board of the Iran Hepatitis Network from different universities

and research centers in Iran to participate in a meeting to obtain expert opinions. This Scientific Leaders' Meeting was held on 28th July 2011 in Tehran, IR. Iran in Hotel Espinas; The manager of meeting was Seyed Moayed Alavian and the list of participants is in the appendix. Following this, we conducted a review of the published literature on the prescription and reporting of new therapies to treat HCV genotype 1infection using boceprevir. Databases, including MEDLINE (PubMed), Google Scholar, and Google, were searched. In addition, we checked reference lists and contacted experts in the field. We used the 11 articles retrieved to generate the conference agenda and characterize the efficacy and safety of, and resistance to, boceprevir. We invited experts in the field of gastroenterology and liver diseases from the fields of clinical practice, trials, statistics, epidemiology, social sciences, and biomedical editing from all parts of Iran.

Plenary talks were given by each invited expert on topics specified in the conference agenda. One of the authors of the present review was a facilitator of this meeting, and a recorder summarized the points of discussion for presentation to all participants. Finally, we circulated a checklist for comment to all conference attendees as well as to representatives of several groups who would find the checklist useful. These opinions and comments form part of our conclusions.

The governing board members debated the following questions:

- How should liver disease be assessed before therapy?
- What are the goals and end-points of therapy?
- What factors have an impact on response rate?
- What are the differences between standard therapy and response-guided therapy?
- What is the role of protease inhibitors such as boceprevir in new era therapy of HCV infection?
- What is the effect of RVR on the final response of patients with HCV genotype 1 infection?
- Does early virologic response (EVR) play any role in treatment outcomes of hepatitis C patients?
- What is the role of IL28 B polymorphism in the management of HCV infection?
- What is the state of new drugs in the management of HCV in IR. Iran?
- How should the duration of treatment (short or extended) be determined for patients with HCV genotype 1 infection?
- What is the lead-in phase, and what is its effect on treatment response and resistance reduction?
- What are the Iranian guidelines for treatment of patients with HCV genotype 1 infection by using protease inhibitors such as boceprevir?

3. Results

Our results include a review of published articles as well as opinions of invited experts.

3.1. Protease Inhibitors

The NS3 protease is necessary for HCV replication; this protease has active sites that allow tight binding of small molecules. The geometry of the binding site allows only a few good contacts with small molecule inhibitors, leading to an increased potential for cross-resistance (8).

3.2. Boceprevir Increases Treatment Efficacy among Patients with HCV Genotype 1 Infection

Boceprevir is a serine protease inhibitor that has a new era for the treatment of hepatitis C patients. Boceprevir is an oral bioavailable peptidomimetic and an α-ketoamide HCV non-structural 3/4A protease inhibitor that forms a covalent but reversible complex with the NS3 protease (54), inhibiting complex formation in genotype 1 HCV. However, there is no evidence in favor of its activity against other genotypes of HCV (55, 56). Boceprevir is a promising regimen for both naïve and previously treated patients. In the first evaluation of protease inhibitors among patients with HCV genotype 1 infection, several methods of treatment were compared with control group who did not receive boceprevir. In this study, patients undergoing a 28-week triple therapy regimen exhibited 54% SVR; patients with a 4-week lead-in phase followed by triple therapy for 24 weeks exhibited 56% SVR; patients undergoing a 48-week triple therapy regimen exhibited 67% SVR; and patients with a 4-week lead-in phase followed by treatment for 44 weeks with boceprevir combination triple therapy had the highest SVR of 75%. On the other hand, patients in the control group who were treated with PEG-IFN and RBV (PR) for 48 weeks achieved a low SVR rate of 38%. All treatment regimens evaluated resulted in significantly higher SVR rates compared to the control group. These findings indicate the efficacy of boceprevir and suggest that the lead-in phase results in positive outcomes for patients with HCV genotype 1 infection (57).

Different treatment regimens for naive treatment patients with HCV genotype 1 infection were evaluated in order to identify the best one. Fixed duration (48 week) triple therapy (RBV, IFN, boceprevir) for 44 weeks was found to be more effective and SVR than peginterferon + ribavirin therapy was achieved in 66% of treated patients. The SVR achieved with response-guided triple therapy (treatment for 24 weeks, during which those patients with undetectable HCV RNA levels between weeks 8 and 24 after the lead-in period are withdrawn from all treatments) was 63%, close to that achieved with fixed-duration therapy. However, a significant difference was seen between response-guided triple therapy and the standard therapy regimen with PR, which yielded an SVR rate of 38% (58). Boceprevir (boceprevir and PegIntron/Rebetol) was used for patients with HCV genotype 1 infection who were previously treated with PR with an outcome of either relapse or no response. An impressive increase of SVR was seen among non-responders;

patients who received response-guided triple therapy exhibited a 40% SVR rate, patients with fixed-duration treatment exhibited a higher SVR rate (52%). Patients receiving standard therapy with PR showed a much lower rate of SVR than those receiving boceprevir, with 7% of patients achieving SVR.

Among patients with relapse, when boceprevir was used with a 4-week lead-in period, the rate of SVR was more promising, with SVR achieved in 75% of patients receiving fixed-duration treatment; this rate was 69% for patients treated with response-guided triple therapy. On the other hand, treatment with a PR regimen exhibited a 29% SVR rate, which was nevertheless higher than the SVR rate seen among non-responders (53). Kwo *et al.* showed a moderate advantage of boceprevir treatment in patients with HCV genotype 1 infection who were treated for 24–28 weeks, with an SVR rate of 54%–56%, while fixed-duration treatment was associated with a higher SVR rate of 67%–75%. Further, the rate of viral breakthrough during the treatment period was lower in patients receiving a 48-week treatment regimen versus others (57). Patients with bridging fibrosis or compensated liver cirrhosis might be able to achieve SVR with boceprevir, ribavirin, and PEG-IFN triple therapy, although the data is not sufficient (58).

3.3. Lead-in Phase

The lead-in phase plays some roles that help achieve positive outcomes: it allows for real-time assessment of the patient's response to PR and may thereby help in assessing the likelihood of achieving SVR, allows RBV to reach a steady state concentration, may reduce the potential for resistance in patients responsive to PR by decreasing HCV viral load, and allows for an assessment of patient's adherence and tolerability before adding a protease inhibitor. The lead-in phase leads to an improvement in treatment response among patients with poor responsiveness, with SVR rates of up to 33%–34% *vs.* 0% in control; further, its usefulness in providing prognostic information about responsive patients results in SVR rates of up to 73%–79% of SVR in these patients vs. 26% in control (53).

3.4. Do You Think Patients with a Reduction in the HCV RNA Level of Less than 1 log10 IU/mL at Week 4 Should be Discontinued from Therapy?

Patients with an HCV RNA level of less than 1 log10 IU/mL at week 4 are strongly advised to continue treatment. However, with triple therapy the rate of SVR among non-treated previously patients with this decline was 38%, which is a high rate of response for this group, and development of resistance variants was 40% among these patients. Therefore, genotype 1 HCV–infected patients with undetectable levels at week 4 might be withdrawn from the boceprevir regimen, and their therapy continued with PR only (58). The minimum duration of treatment is suggested as 24 and 36 weeks of triple therapy including boceprevir for genotype 1 naive and previously treated patients, respectively, and patients who are eligible for response-guided therapy should have undetectable level of HCV RNA at 8 weeks and for the entire 24-week duration (53, 58). Optimal treatment duration depends on virus kinetics, and patients with undetectable virus by 4 weeks of treatment are more likely to achieve SVR than patients who have undetectable viral loads by 12 weeks of treatment (82%–94% *vs.* 79%). The lowest SVR rate (21%) is seen in patients who have undetectable virus levels after 24 weeks of treatment (59). Detectable levels of HCV RNA at week 12 among previously treated patients, and at week 24 among naive patients, should be considered as failure and all treatment regimens should be withdrawn (54). In addition, a shorter duration of PR treatment, as well as a lower dose of RBV, is associated with poor response and lower SVR rates (8).

3.5. Who Should be Treated for 48 Weeks (4 Weeks Peg INF and RBV + 44 Weeks Triple Therapy)?

Patients who were previously null responders (<2 log HCV RNA decline by week 12 during prior PR therapy), patients with poor PR response (<0.5 log HCV RNA decline by week 4 of PR treatment with lead in), and patients with compensated liver cirrhosis should be treated for 48 weeks (60).

3.6. Adverse Events

Treatment with boceprevir leads to adverse events in genotype 1 HCV–infected patients such as anemia, dysgeusia rash and dry skin. Anemia occurred in approximately 40% to 49% of patients who received boceprevir, and more than 40% required erythropoietin administration for ~150 days (53, 58). Anemia was more severe among patients who have been previously treated; 8% of them exhibited a reduction in hemoglobin to less than 8.0 g/dL and 9% of these patients needed blood transfusion (53). Without blood transfusion, a reduction in the dose of Peg INF and ribavirin is necessary, which leads to response rate reduction. Treatment discontinuation occurred in 8%–12% of patients (53, 61). Patients with lower baseline hemoglobin were not only more likely to have an intervention, but also to experience that intervention earlier in the time course of their treatment (62).

3.7. Early Response Effect to the SVR Rate

Among patients with chronic HCV genotype 1 infection who failed prior therapy, SVR was achieved in 88% of those with an early response to triple therapy (patients who became HCV negative at week 8 of treatment, which included 4 weeks of PR lead-in and 4 weeks of boceprevir + PR). On the other hand, SVR was achieved in 79% of patients with a late response (patients who remained HCV positive early in the course of therapy at week 8 of treat

ment, which included 4 weeks of PR lead-in and 4 weeks of boceprevir + PR, but became HCV negative by week 12 of treatment) (53). Among genotype 1 HCV–infected naïve patients who received a regimen that included boceprevir, SVR was achieved in 88–90% of early responders who remained HCV negative through treatment week 24, and in 66% of late responders who were able to receive at least 28 weeks of therapy (58).

3.8. Resistance to Boceprevir

Resistance to NS3 protease inhibitor develops rapidly in vivo and occurs in 3 days. Moreover, almost 1% of viral quasispecies carry drug resistance-related mutations before exposure (63). The risk of drug resistance increases with boceprevir monotherapy, but combination therapy with interferon reduces the rate of resistance (64) because drug-resistant HCV strains are sensitive to IFN-α and RBV therapy; therefore, combination therapy increases the SVR rate from 40% to 75% (8). The risk of mutations causing resistance to protease inhibitors is greater in patients infected with HCV subtype 1a than in patients with subtype 1b, because a single nucleotide change is needed among subtype 1a–infected patients, versus 2 nucleotide changes in patients infected with subtype 1b (54). Reported mutations that lead to boceprevir resistance are higher in patients that are not responsive to IFN than those that are (47% *vs*. 4%) (58). Further studies are required to improve the identification of patients infected with HCV genotype 1 based on host and viral factors, who might receive overtreatment with direct acting antivirals (DAAs), such as young patients without any evidence of fibrosis, low baseline HCV RNA levels, and the 'good' rs12979860 C/C IL28B genotype (54).

3.9. Effect of IL28B in Response to Treatment with Boceprevir

IL28B is recognized as a predictor of treatment response in hepatitis C patients and is associated with improved early viral kinetics and a greater likelihood of RVR; a genetic polymorphism rs12979860 is highly associated with SVR among naive subjects as well (62, 65). Among patients with HCV genotype 1 infection, those with IL28B C/C genotype have a greater chance of SVR than patients with IL28B C/T and T/T genotype do with a standard treatment regimen. However, patients with C/T and T/T genotypes benefit more from a regimen that includes boceprevir, and the rate of SVR is significantly higher than in the case of a regimen without boceprevir. On the other hand, triple therapy with boceprevir is not more effective in patients with C/C genotypes and the SVR rate is similar to that seen with a 48-week standard treatment regimen. However, the majority of patients with the IL28B C/C genotype shows a rapid response and can achieve an undetectable level of HCV-RNA by week 8 of treatment. In patients who failed to respond to treatment, IL28B genotypes were not sufficiently reported, and it appears that treatment effects did not vary significantly with IL28B genotypes among these patients (62). *Figure 1* shows different response rates among IL28B genotypes with different treatment regimens (65).

3.10. Preliminary Report of the Role of IL28B in Iranian Patients with Hepatitis C

The role of IL28B as a treatment predictor was investigated among Iranian patients with chronic hepatitis C. Among all the 934 patients included in this analysis, the most common genotype of rs12979860 was C/T (46.5%), followed by C/C (40.5%). Only 13% of the patients had the T/T genotype. For rs8099917, the genotype T/T was the most common with rate of 61.7%, followed by G/T with 33.9%, and then G/G with 4.4%. According to our findings, the C/C genotype was more common among patients infected with HCV genotype 3a (49%). Additionally, this genotype was also present in 38% and 27% of patients infected with HCV genotypes 1a and 1b, respectively. A similar distribution was seen in the rs8099917 genotypes: 67% of patients with genotype 3a had the T/T genotype, and followed by genotype 1a and 1b with 61% and 40%, respectively.

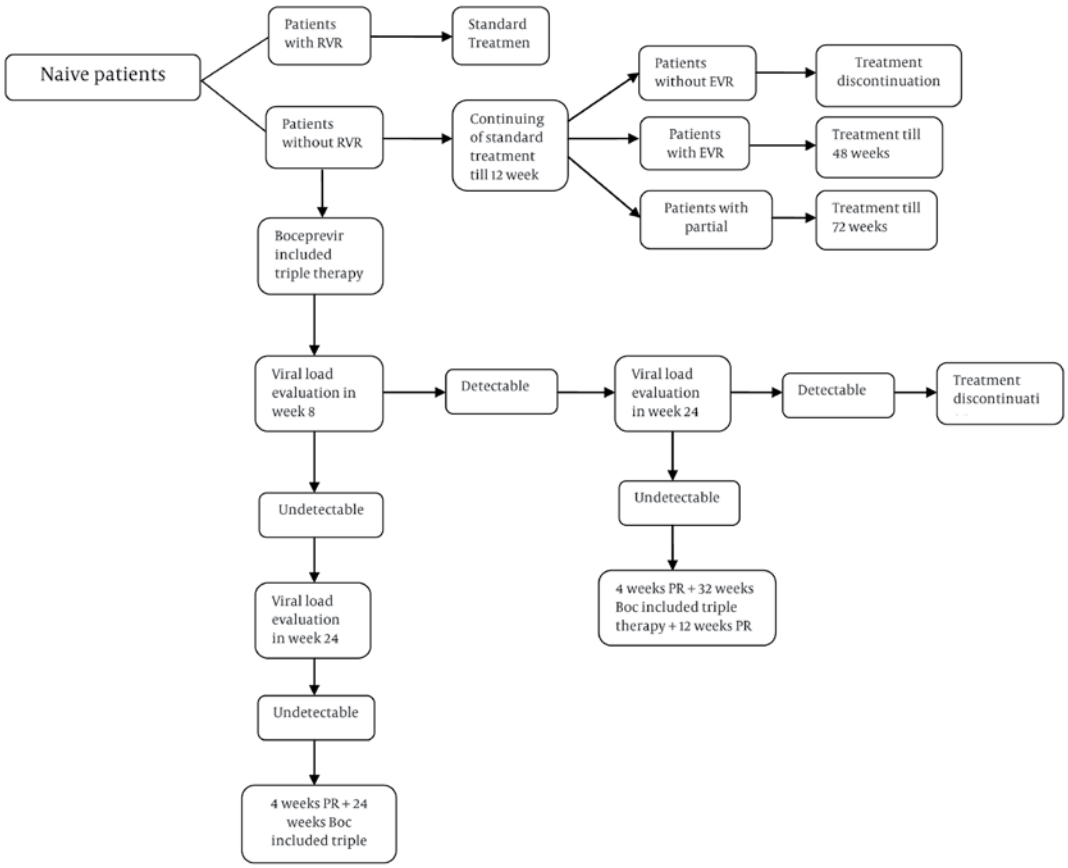
Out of the 934 patients, 110 patients infected with HCV genotype 1 had finished their treatment completely. We evaluated the impact of different genotypes of rs12979860 and rs8099917 in response outcome. Patients with the C/C genotype infection had a significantly greater probability ($P < 0.001$) of achieving SVR, with an odds ratio (OR) of 4.696 (CI: 1.7–10.4), than did patients who were not C/C. For rs8099917 genotypes, a greater probability of SVR ($P < 0.03$) was seen in patients with the T/T genotype infection than in those who did not have infection with this HCV genotype, and the OR was

Table 1. American, European and, Iranian Guideline for Boceprevir Included Treatment Regimen

Patient Profile	FDA [a] – USA [a]	EU [a]	Iran
Treatment naive – early responders	4+24 (PR [a] + PR/BOC [a])	4+24 (PR + PR/BOC)	4+44 (PR)
Treatment naive – late responders	4+32+12 (PR + PR/BOC + PR)	4+32+12 (PR + PR/BOC + PR)	4+32+12 (PR + PR/BOC + PR)
Treatment experienced early responder	4+32 (PR + PR/BOC)	4+32+12 (PR + PR/BOC + PR)	4+32+12 (PR + PR/BOC + PR)
Treatment experienced late responder	4+32+12 (PR + PR/BOC + PR)	4+32+12 (PR + PR/BOC + PR)	4+32+12 (PR + PR/BOC + PR)
Peg 2a or Peg 2b	Both	Both	Both
Management of anemia	EPO [a] not mandated	EPO not mandated	EPO mandated

[a] Abbreviations: BOC, boceprevir; FDA, food and drug administration; EPO, erythropoietin; EU, European; PR, peg-INf and ribavirin; USA, United State of America

Algorithm 1. Iranian Treatment Guideline for Naive Genotype 1 HCV Patients with Boceprevir



PR: Peg-INF and ribavirin, Boc: boceprevir

2.6 (CI: 1.3–6.7). In addition, 59 patients with genotype 3 infection were also investigated. According to our study, rs12979860 seems to be a stronger predictor of SVR than rs8099917. Also, the current study does not provide any evidence to support a role for IL28B in SVR in genotype 3–infected patients(In press data).

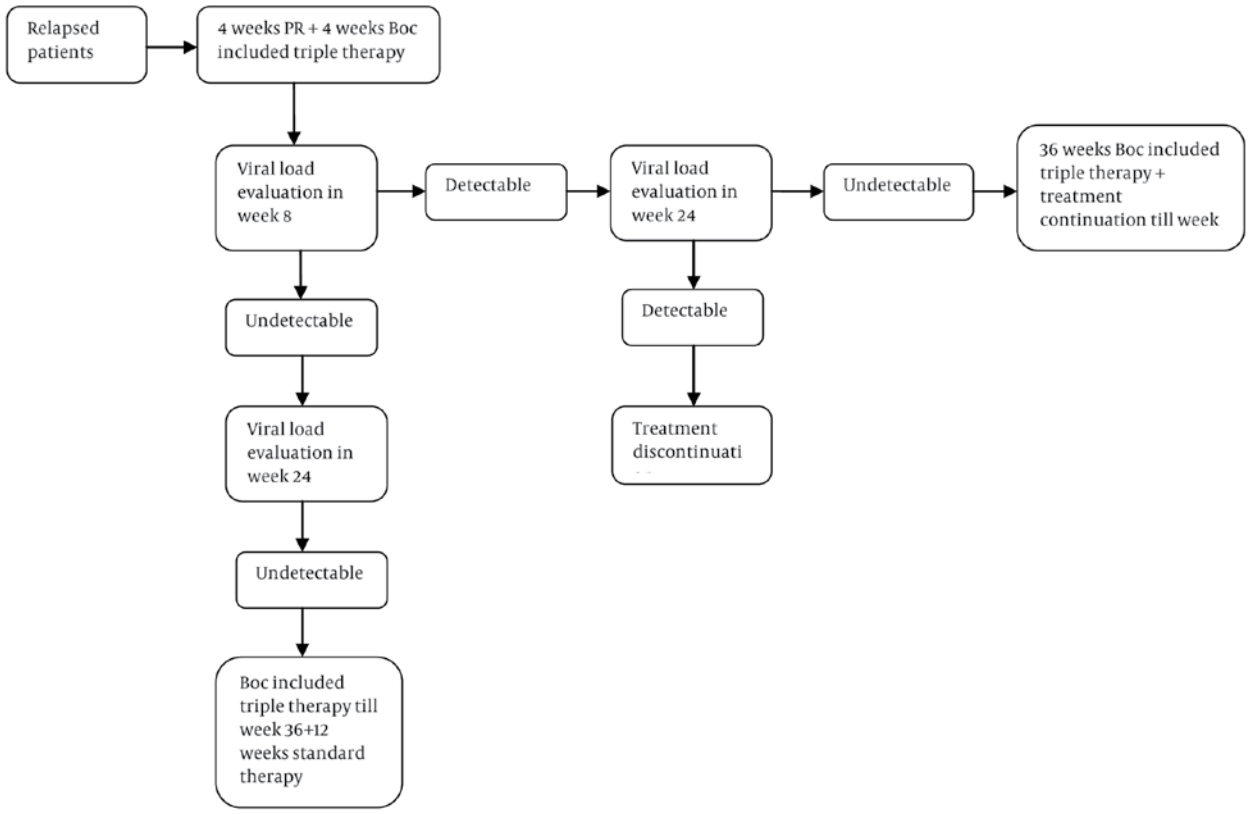
3.11. Recommendations for the Use of Boceprevir

Boceprevir is available as a capsule containing 200 mg, and the recommended dosage is 800 mg, 3 times daily. It is better to consume boceprevir with a meal. It must be used in combination with PEG-IFN/RBV (62, 66). Boceprevir should not be discontinued if patients feel well and a single dose was missed with more than 2 hours to the next dose time; rather, patients should use it immediately and return to their regular dosing schedule. If there is less than 2 hours to the next dose, patients should skip the missed dose rather than taking 2 doses together. Boceprevir interacts with other substances and may be contraindicated in some medical conditions, and clinicians should consider the following before prescribing boceprevir: pregnancy, breast-feeding, herbal preparation, or dietary supplement, HIV infection, anemia, neutropenia, thrombocytopenia, organ transplant, and impending surgery. Furthermore, some drugs are contraindicated with boceprevir, including alfuzosin, anticonvulsants (namely, carbamazepine, phenobarbital, and phenytoin), benzodiazepines (namely, midazolam and triazolam), cisapride, drospirenone, ergot derivatives (namely, dihydroergotamine, ergonovine, ergotamine, and methylergonovine), HMG-CoA reductase inhibitors (namely, lovastatin and simvastatin), lurasidone, pimozide, rifampin, and tadalafil; these medications need to be stopped or adjusted before commencing a boceprevir regimen, and may affect the efficacy and manifestation of side effects of boceprevir (66).

3.12. Experts' Comments

Different treatment regimens were reported from the European and American liver disease societies. The recommendations of Iranian experts for a regimen including boceprevir (*Table 1*). According to experts' opinions, a lead-in phase is necessary for treatment with boceprevir, since it may reduce viral load and improve virological response. Additionally, boceprevir should be used in combination with PEG-IFN and RBV, to minimize the

Algorithm 2. Iranian Treatment Guideline for Relapsed Genotype 1 HCV Patients with Boceprevir

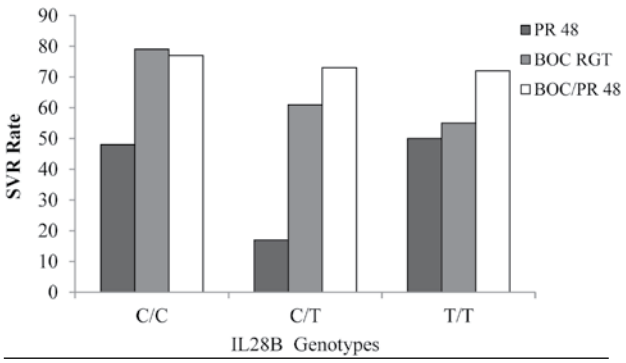


PR: Peg-INF and ribavirin, Boc: boceprevir

probability of developing drug resistance, an important consideration for clinicians. The most effective treatment plan appears to involve 4 weeks of a standard treatment regimen, followed by 44 weeks of a treatment regimen that includes boceprevir.

Expert opinion was divided with regard to treatment of naive patients with boceprevir. The consensus that emerged was to begin with a standard treatment regimen in naïve patients and subsequently make a decision on including boceprevir on the basis of RVR, which is accepted as a determinant of SVR. Patients who have achieved RVR should continue the standard treatment regimen for the duration of the treatment period, as SVR is thought to be possible with standard treatment among these patients. However, for patients who do not exhibit RVR, two options are recommended. The first option involves treatment with the standard regimen up to week 12, followed by a check of the viral load. Patient with detectable viral load after week 12 should be discontinued, patients with undetectable viral load at this point should be treated with standard therapy for 48 weeks. Patients with the partial response will benefit more from an extended duration of treatment for 72 weeks. Alternatively, patients could be treated with triple therapy including boceprevir, with the viral load evaluated in week 8. Patients with undetectable viral load will be treated for 24 weeks with triple therapy. For patients who exhibit a positive viral load in week 8, viral load evaluation in week 24 will determine the treatment plan: patients with undetectable virus levels at week 24 will benefit from a 32-week triple therapy regimen followed by 12 weeks of standard therapy, while patients with detectable viral load in week 24 should be withdrawn from treatment plan (*Algorithm 1*). Experts agreed that patients who exhibited RVR and undetectable viral

Figure 1. SVR rates by IL28B genotypes



PR: Peg-INF + ribavirin
BOC RGT: boceprevir included response guided therapy
BOC / PR: boceprevir included 48 week therapyt

load in week 8 with a regimen including boceprevir could be treated for a shorter duration (24 weeks), while versus patients who did not exhibit RVR should be considered for 48 weeks of treatment.

For patients with relapse, viral load should be evaluated after 8 weeks, which includes the 4-week lead-in phase with the standard treatment regimen and 4 weeks of triple therapy with boceprevir. If patients were negative for HCV-RNA in week 8, an undetectable viral load in week 24 indicates triple therapy for 36 weeks with boceprevir. On the other hand, if they were viral load positive in week 8 and exhibit undetectable viral loads in week 24, they should be treated for 12 weeks with a standard treatment regimen following their 36-week treatment *(Algorithm 2)*. The experts were all in agreement that boceprevir treatment is the best regimen for patients with breakthrough, and that other regimens are not capable of eliciting improved responses or outcomes. There is insufficient evidence regarding non-responders and patients who are resistant to treatment. However, it appears that only a regimen that includes boceprevir can increases the probability of a favorable outcome.

In addition, evaluation of IL28B polymorphisms was suggested for selection of patients for boceprevir treatment. Patients with the C/C genotype infection benefit less from a regimen including boceprevir. More evidence is required to confirm the role of IL28B in boceprevir treatment, but it is conservatively accepted that patients having infection with the C/T and T/T genotypes benefit more from triple therapy that includes boceprevir. While many studies have investigated the effects of protease inhibitors in patients infected with HCV genotype 1, there is not enough evidence about the role of these drugs in patients with HCV genotype 3 infection, although there are significant numbers of non-responders and relapses among these patients (67). We therefore believe that health policy makers should consider new treatment plans for these patients, and further studies are required to determine the effects of new drugs on these patients.

4. Conclusions

The overall conclusions from the meeting were that evidence-based decisions must be made for any new drug to be used in HCV therapy in Iran. A cost-benefit analysis should be carefully considered before a decision is made. The main recommendation of the experts to clinicians and scientists in Iran was to produce and publish evidence that will guide health policy makers in future decisions. Other recommendations included participation in international and local multicenter clinical trials, and establishment of a web-based program for gathering data in Iran.

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Appendix

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