BOCEPREVIR AND TELAPREVIR FOR CHRONIC HEPATITIS C

- Two new protease inhibitors, boceprevir and telaprevir, were recently approved by the Israel Ministry of Health for treatment of chronic hepatitis C infection, genotype-1, in combination with peginterferon-alfa and ribavirin (i.e. standard therapy).
- Addition of boceprevir or telaprevir to standard therapy (i.e. triple therapy) has been shown to substantially increase the rate of sustained virological response (SVR), accepted as equivalent to cure of active infection. Similar results are unlikely to be achieved in practice unless patient cohorts reflect those carefully selected patients recruited into trials.
- Adverse events with both new drugs were similar in character to those reported for standard therapy, but more frequent. Adverse events associated with both drugs include anaemia and gastrointestinal effects. Telaprevir is also associated with frequent rash and pruritis. In addition to incremental toxic effects, these protease inhibitors have high costs, increased pill burden and many drug interactions.
- There are no head-to-head studies to provide guidance on where each drug should be positioned in therapy of HCV infection. The second article in the Bulletin tries to address this, covering the following questions and issues:
  - Boceprevir or telaprevir?
  - Which peginterferon to use in triple therapy?
  - When to initiate, switch and extend therapy with protease inhibitors?
  - Special patient groups.
  - Differences in administration of boceprevir and telaprevir.

Among people with hepatitis C virus (HCV) infection, 70-80% develop chronic hepatitis, which can progress to cirrhosis and liver cancer. In some patients, the infection can be eradicated by treatment of finite duration. Treatment with pegylated interferon and ribavirin cures about 45% of patients with hepatitis C genotype-1, the main strain in Europe and the USA and in Israel. Both boceprevir (Victrelis; MSD) and telaprevir (Incivo; Janssen-Cilag) have been approved by the Ministry of Health for oral use in combination with peginterferon-alfa and ribavirin for treatment of HCV genotype-1 infection in adults with compensated liver disease (including cirrhosis), who are previously untreated or who have failed previous therapy.

STANDARD THERAPY AND ITS LIMITATIONS

The standard treatment for chronic active hepatitis C is combination therapy with peginterferon (alfa-2b 1.5µg/kg weekly or alfa-2a 180µg weekly) plus ribavirin 800mg to 1200mg daily depending on body weight. Treatment usually lasts 48 weeks. However, with HCV genotype-1, when viraemia is initially low and becomes undetectable after 4 weeks of treatment, a shorter treatment period of 24 weeks appears to have good virological efficacy.

The primary aim of treatment is to eradicate the hepatitis C virus. This is assessed by the achievement of sustained virologic response (SVR) which is defined as undetectable HCV RNA 24 weeks after treatment cessation. About 25% to 50% of patients experience virological failure: viraemia persists during treatment (non-response) or recurs within 24 weeks after treatment cessation (relapse). Those requiring retreatment are recommended to have 49-72 weeks of peginterferon.

Two types (and brands) of peginterferon alfa are currently available in Israel: peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (Peg-Intron). The IDEAL study demonstrated that both types are equally effective in treating HCV genotype-1. For both types treatment duration depends on viral response at week 4 and 12 and can be 24 or 48 weeks in treatment-naive
patients and 49-72 weeks in treatment-experienced patients. If patients do not achieve a 2 log reduction in their HCV RNA by treatment week 12 then treatment is discontinued. If patients have a greater than 2 log drop by treatment week 12 but still have detectable HCV RNA at week 24 then treatment is discontinued.

PROTEASE INHIBITORS: BOCEPREVIR AND TELAPREVI

The protease inhibitors, boceprevir and telaprevir, are the first directly acting, HCV specific antivirals to be licensed for the treatment of HCV infection. They are peptidomimetic inhibitors of HCV serine protease, which is essential for viral replication through cleavage of the viral polyprotein and is implicated in viral evasion of the host inflammatory response.3

There is insufficient clinical data to support the use of boceprevir and telaprevir in patients with HCV genotypes other than genotype-1.

To date, there have not been any long-term clinical trials of protease inhibitors therapy for chronic hepatitis C. Trials have largely reported on differences in SVR rather than important complications such as cirrhosis, liver transplant, or hepatocellular carcinoma. SVR has been accepted as equivalent to cure of active infection and is recognised as an acceptable surrogate for these outcomes. Nevertheless studies using surrogate endpoints do not dispense with the need for long-term trials, particularly as the studies do not take long-term adverse effects into account.

CLINICAL STUDIES

Clinical evaluations of boceprevir and telaprevir in hepatitis C are based on clinical trials which were too short to assess clinical outcomes.

Boceprevir

Evidence comes from two randomised double-blind studies of similar design in previously untreated (treatment-naïve) and experienced (not responded or had relapsed after previous therapy) patients, 18 years or over with chronic HCV genotype-1 disease. Treatment began with 4 weeks of standard combination therapy (peginterferon alfa-2b + ribavirin), followed by addition of boceprevir or placebo. Two preliminary trials had shown that boceprevir did not improve the efficacy of standard therapy in very early responders (<4 weeks). The primary outcome in both studies was the achievement of SVR.

Boceprevir 800mg three times daily orally added to peginterferon-alfa and ribavirin (after a 4-week lead-in period) significantly improved SVR compared to adding placebo in patients with chronic hepatitis C genotype-1 (Table1). Interferon responsiveness predicts a sustained response to boceprevir; this was an inclusion criteria in the trial of previously treated patients.5

In the trial among treatment-naïve patients4 (Sprint 2), among early responders, the rate of SVR did not significantly differ whether boceprevir was withdrawn or continued after 24 weeks (96% vs 97%).

Table 1

<table>
<thead>
<tr>
<th>Treatment for 44 weeks</th>
<th>Previously treated patients</th>
<th>Treatment naïve patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo plus P/R</td>
<td>21%</td>
<td>28%</td>
</tr>
<tr>
<td>Boceprevir plus P/R</td>
<td>66%*</td>
<td>66%*</td>
</tr>
<tr>
<td><strong>similar increase in both patients who had had non-response and patients who had a relapse after prior therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P/R peginterferon+ribavirin</td>
<td></td>
<td></td>
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</tbody>
</table>

Editor: Dr. Philip Sax, saxp@netvision.net.il
The studies show that telaprevir is effective in black patients (SVR ~60%) although the number of black patients in the studies were low.

**Table 2**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Telaprevir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>previously untreated patients</td>
<td>75%</td>
<td>44%</td>
</tr>
<tr>
<td>ILLUMINATE</td>
<td>previously untreated patients</td>
<td>72%</td>
<td>-</td>
</tr>
<tr>
<td>REALIZE</td>
<td>previously treated patients</td>
<td>64-66%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*proportion of patients who had undetectable viral RNA for 6 months after treatment

**Table 3**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Telaprevir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous relapse</td>
<td>83-88%</td>
<td>24%</td>
</tr>
<tr>
<td>Previous partial responders</td>
<td>54-59%</td>
<td>15%</td>
</tr>
<tr>
<td>Previous non (null)-responders</td>
<td>29-33%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*proportion of patients who had undetectable viral RNA for 6 months after treatment

Treatment-naïve or prior treatment relapsers can undergo treatment in a response-guided fashion (24 to 48 weeks). Data does not support the use of response-guided therapy in non-responders or partial responders and total treatment duration of 48 weeks is recommended.

SVR rates of 28% were achieved in advanced liver fibrosis non-responsive patients; although this was statistically significant only a very small number of patients were included in this subgroup analysis.

The studies show that telaprevir is effective in black patients (SVR ~60%) although the number of black patients in the studies were low.
has shown that resistant virus tends to revert to wild type virus over time.  

**DRUG INTERACTIONS**

Boceprevir is partly metabolised via cytochrome P450 isoenzyme CYP 3A4/5. Inhibitors and inducers of this isoenzyme were found to have a moderate effect on boceprevir bioavailability. Boceprevir is a potent CYP 3A4 inhibitor and a moderate P-glycoprotein inhibitor. Clinically relevant interactions can thus be expected with drugs that have a narrow therapeutic margin and are metabolised by CYP 3A4.

Telaprevir is mainly metabolised by, and inhibits, the cytochrome P450 isoenzyme CYP 3A4. Interactions have been reported with other CYP 3A4 substrates, and with certain drugs transported by P-glycoprotein. This indicates a high risk of pharmacokinetic interactions in patients receiving telaprevir.

**CONTRAINDICATIONS**

Both boceprevir and telaprevir must be used in combination with ribavirin, which is teratogenic, and thus this combination is contraindicated in pregnancy and in men whose female partners are pregnant. Boceprevir is contraindicated in patients with decompensated liver function (Child-Pugh score >6). Telaprevir is metabolised in the liver and is not recommended for patients with moderate to severe liver impairment or decompensated liver disease.

**DOSAGE AND COSTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost (NIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (Victrelis)</td>
<td>800mg tid x 24-44 weeks1,3</td>
<td>133,452 (24 weeks)</td>
</tr>
<tr>
<td>Telaprevir (Incivo)</td>
<td>750mg tid x 12 weeks2,4</td>
<td>194,373 (12 weeks)</td>
</tr>
</tbody>
</table>

1 MoH approved price, which is the basis of patient copayment.
2 Should always be administered as part of a triple-drug regimen with peginterferon-alfa and ribavirin. Total duration of treatment for all 3 drugs varies based on HCV RNA response.
3 Available as a 200mg capsule. Must be taken with food.
4 Available as a 375mg tablet. Must be taken with food(non-low fat).

Erythropoietin use (or blood transfusions) for anaemia will add to the additional cost of the protease inhibitors.

There is response-guided therapy for both treatment-naïve and treatment-experienced patients for boceprevir, but only for treatment-naïve patients for telaprevir (for details see “Differences in the Administration of Boceprevir and Telaprevir” in the next article).

**CONCLUSIONS**

Addition of either of the direct-acting antiviral agents boceprevir and telaprevir to standard therapy with peginterferon-alfa and ribavirin has been shown to substantially increase the SVR rate in patients with HCV genotype-1 infection who have not yet been treated or have experienced treatment failure. In trials among carefully selected patients, for every 3 to 4 patients treated with boceprevir or telaprevir plus standard therapy, one extra patient achieved SVR who would not have done so with standard therapy alone. Similar results are unlikely to be achieved in practice unless cohorts reflect those recruited into trials.

In addition, trials have shown that selected patients who respond early to therapy achieve similar SVR rates with shorter courses of treatment as with full duration treatment. Overall, SVR rates appeared to be somewhat higher in trials among patients treated with telaprevir and more patients with more difficult to treat disease appeared to achieve SVR.

Adverse events with both drugs were similar in character to those reported for standard therapy, but more frequent. Adverse events associated with both drugs include anaemia and gastrointestinal effects. Telaprevir is also associated with frequent rash and pruritis.

There are no "head-to-head" studies to provide guidance on where each drug should be positioned with respect to the other (see next article). The drugs are very costly, far more expensive than protease inhibitors used for other indications.

**References**


**WHAT IS THE PLACE IN THERAPY OF PROTEASE INHIBITORS FOR HCV INFECTION?**

Although the new protease inhibitors (PIs) represent an advance in the treatment of HCV infection, many patients will not benefit. Both drugs have been assessed and are licensed specifically for patients with genotype 1 infection; the many patients infected by other genotypes are unsuitable for treatment with these PIs. Interferon and ribavirin remain important elements of triple therapy protocols, so intolerance of interferon would also prevent
curative therapy with a regimen containing a PI. For other groups of patients – for example, previous null responders with cirrhosis – the new combination therapy affords only a modest benefit.

Ensuring adherence to therapy may be more challenging in clinical practice, due to the burden of adverse effects associated with addition of a PI to standard dual therapy. Triple therapy may be less well tolerated among patients typically encountered in clinical practice than among those enrolled in trials. Preliminary data from an observational study among treatment-experienced patients with cirrhosis suggest that the rates of serious adverse events and resultant treatment discontinuation in this group may be much higher in clinical practice than reported in trials.1

Both drugs have considerable potential for clinically significant interactions with many other drugs, which may complicate therapy. Drugs known to interact with boceprevir and/or telaprevir include several anti-retroviral drugs used in the treatment of HIV infection, anti-rejection agents which might be prescribed after liver transplant and drugs of abuse. Some of the known interactions could have serious and potentially fatal consequences.

Because these new antiviral therapies directly inhibit HCV, viral resistance has become an important issue, essentially precluding use of monotherapy with PIs, and potentially restricting future treatment options for patients who consequently do not achieve SVR.

Shortened treatment duration is a potential benefit over standard therapy. Boceprevir treatment duration can be as short as 24 weeks, based on HCV RNA loads at week 4. Response-guided treatment with telaprevir can be as short as 24 weeks in treatment-naive or prior treatment relapers.

**BOCEPREVIR or TELAPREVIR?**

The available evidence does not permit firm conclusions regarding the relative efficacy, safety or tolerability of boceprevir and telaprevir. Head-to-head comparisons are needed to determine whether the differences observed between trials are due to differences between drugs, differences in trial design or differences between the populations treated. Nevertheless, the trial data indicate that the increase in SVR rates achieved with triple therapy may be slightly greater with telaprevir than with boceprevir.

Prior null responders have had minimal to no reduction in viral load on prior therapy and are the most challenging patients to treat. These patients may benefit from triple therapy with telaprevir, although the response rate is expected to be lower than in other patients. There is a lack of RCT data on this population for triple therapy with boceprevir.2

Trial data indicate differences in adverse effects: although similar proportions of patients withdrew from boceprevir and telaprevir trials due to adverse events, the difference in withdrawals due to adverse events between triple therapy and standard treatment arms was greater in the telaprevir trials. Despite shorter duration of exposure, the overall difference in common adverse events between triple therapy and standard therapy arms appeared to be greater with telaprevir than with boceprevir. Rash was reported by more than half of trial participants exposed to telaprevir.

If overall adverse event rates are higher in clinical practice than in trials, any differences between boceprevir and telaprevir may be magnified. Rates of haematological adverse effects may be expected to be higher in clinical practice than in trials, potentially increasing both treatment costs and discontinuation rates. The increased risk of neutropenia associated with boceprevir use in trials may thus be more significant in clinical practice. Serious adverse events and treatment discontinuation were both observed more frequently with telaprevir than boceprevir in a large cohort of treatment-experienced patients with cirrhosis observed in routine clinical practice.1

The recommended four-week lead-in with peginterferon-alfa plus ribavirin before adding boceprevir may have advantages in clinical practice, particularly among treatment-naive patients whose ability to tolerate and adhere to therapy is untested. Lead-in therapy may also identify a group of patients who are likely to achieve SVR with standard therapy and who may not need to be exposed to PIs.

**Adherence:** The likelihood of adherence to therapy is an important factor in management of HCV infection. Although similar proportions of patients completed therapy in clinical trials, in routine clinical practice the shorter period of triple therapy required for telaprevir (fixed 12 weeks vs 24, 32 or 44 weeks for boceprevir) and the lower pill burden (two tablets three times a day compared with four capsules three times a day for boceprevir) may have an impact. The difference in duration of triple therapy may be particularly relevant for prior null responders and patients with cirrhosis, for whom 44 weeks of boceprevir treatment is recommended.

Boceprevir can be withdrawn without impairing efficacy in early responders to standard therapy. The same is probably true for telaprevir, but there is a lack of available evidence.

Telaprevir tablets can be stored at room temperature, while boceprevir capsules must be stored in a fridge or out of the fridge for up to 3 months; a fridge is in any case necessary for storing peginterferon-alfa.

**WHICH PEGINTERFERON TO USE IN TRIPLE THERAPY?**

In the pivotal trials, boceprevir was studied in combination with peginterferon-2b and ribavirin capsules, and telaprevir was studied in combination with peginterferon-2a and ribavirin tablets. An additional phase III study in treatment-experienced patients has been conducted to examine use of boceprevir with peginterferon-2a and ribavirin tablets. The European
Medicines Agency (EMA) considered that the data from this additional study were adequate to substantiate a claim that boceprevir can be used with either peginterferon regimen. Use of telaprevir with peginterferon-2b has been compared to use with peginterferon-2a in one underpowered phase II trial in treatment of naïve patients. The EMA noted that the available data does not provide direct support for the equivalence of the two peginterferons in combination with telaprevir.

WHEN TO INITIATE, SWITCH OR EXTEND THERAPY WITH PROTEASE INHIBITORS?

The two new PIs were studied in different clinical trial programmes, and it is not entirely clear what differences exist between the two agents. Clinicians will need to establish where each should be positioned with respect to the other. The question of when to initiate therapy for chronic hepatitis C (CHC) infection is a key issue associated with this condition. There is a dilemma with respect to existing standard PR therapy, particularly in treatment-naïve patients. Should treatment-naïve patients be initiated on triple therapy or, for economic and tolerability reasons, should triple therapy be reserved for patients who fail or are responding poorly to PR regimen.

It may be important to know also whether patients who fail on one PI can still be considered candidates for a trial of the other. Similarly, if a patient has a poor response to or is not tolerating one PI, is there evidence that they can safely and effectively be switched to the other? Evidence relating to prolongation of PI therapy beyond the duration approved in the product license may also be of interest for patients experiencing inadequate response to therapy.

SPECIAL PATIENT GROUPS

CHC infection is a major co-morbidity seen in HIV patients. The safety and efficacy of these agents has not been established in patients with HIV co-infection. Nonetheless, interim results are available from a study of patients with HCV genotype-1 infection with HIV who were treated with triple therapy, including telaprevir. 12 weeks after treatment was completed, 74% of previously untreated patients with co-infection had undetectable HCV RNA when treated with a telaprevir-based regimen, compared with 45% of patients treated with peginterferon plus ribavirin and placebo. Tolerability was comparable to that of telaprevir treatment in patients with hepatitis C mono-infection. CHC infection adds to the burden of disease for the patient, and its treatment adds to the pill burden and adverse effects already experienced by the HIV patient, as well as additional cost. Additionally, there is the potential for drug interactions with a number of antiretrovirals demonstrating pharmacokinetic interactions with other agents.

With standard therapy, SVR rates were typically higher in patients with minimal or no fibrosis, and decreased as patients progressed to cirrhosis. Not all patients will progress to serious complications such as cirrhosis or hepatocellular carcinoma; whether response rates to triple therapy are impacted by baseline fibrosis status remains to be determined.

DIFFERENCES IN ADMINISTRATION OF BOCEPREVIR AND TELAPRE VIR

Response-guided therapy: Dosage regimens vary according to patients’ previous treatment experience and current response (Table below).

<table>
<thead>
<tr>
<th>Boceprevir</th>
<th>HCV-RNA results</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated</td>
<td>Undetectable</td>
<td>PR to 4 weeks, then PI-PR to 28 weeks</td>
</tr>
<tr>
<td>Previously treated</td>
<td>Undetectable</td>
<td>PR to 4 weeks, then PI-PR to 36 weeks</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>HCV-RNA results</td>
<td>Dosage</td>
</tr>
<tr>
<td>Previously untreated or prior relapse</td>
<td>Undetectable</td>
<td>PI-PR to 12 weeks, then PR to 24 weeks</td>
</tr>
<tr>
<td>Prior partial response or prior null response</td>
<td>All patients</td>
<td>PI-PR to 12 weeks, then PR to 48 weeks</td>
</tr>
</tbody>
</table>

HCV = hepatitis C virus; PI = protease inhibitor; PR = peginterferon-alfa and ribavirin.
**Futility rules:** Product monographs give guidance by manufacturers on when to stop therapy due to lack of effect. Patients should stop all therapy (both PI and PR) if hepatitis C virus levels are:

- With boceprevir, >100IU/mL at 12 weeks or detectable at 24 weeks;
- With telaprevir, >1,000IU/mL at 4 weeks or 12 weeks, or detectable at 24 weeks.

**References**


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