Review

Ainhoa Fernández-Yunquera
Diego Rincón
Magdalena Salcedo
Rafael Bañares

Update on the use of direct-acting antiviral agents for the treatment of chronic hepatitis C virus infection

Unidad de Trasplante Hepático. Servicio de Medicina de Aparato Digestivo. Hospital General Universitario Gregorio Marañón. Instituto de Investigación Sanitaria Gregorio Marañón

Hepatitis C virus (HCV) infection is among the principal causes of liver cirrhosis and liver cancer. Furthermore HCV infection is the most frequent indication for liver transplantation in the developed world. The WHO claims that some 3% of the world's inhabitants (130-210 million persons) has chronic HCV infection and estimates its incidence at 3-4 million cases per year, making this disease a major worldwide public health concern[1-3]. Only in Spain, it is calculated that around 800,000 persons have the infection, of whom 20-30% will develop liver cirrhosis. The current situation will lead to an increase in HCV-related comorbidities and mortality over the following years and prompts the search for efficient treatment regimens designed to achieve high cure rates and to modify the natural history of chronic hepatitis C infection[4].

The standard of care (SOC) treatment for chronic HCV has been the combination of a pegylated alpha interferon (pegIFN) with ribavirin until May 2011, when the FDA licensed the first direct-acting antiviral agents, boceprevir and telaprevir. The main objective of HCV treatment is to eliminate the virus, which in clinical practice is referred to as a sustained virological response (SVR), defined as the absence of serum viremia HCV-RNA, confirmed by a sensitive PCR assay, six months following discontinuation of therapy. SVR rates obtained in the registration trials for pegIFN plus ribavirin have been around 40-50% for patients with the virus genotype 1 and around 80% for genotypes 2 and 3[5-7]. Recent advances in the management of HCV infection have been based on both the development of direct-acting antiviral agents (DAAs) and the identification of polymorphisms of the IL-28 gene associated with the response to conventional antiviral treatment. Large clinical trials[8], besides their use to license these new agents, have served to develop individualized treatments guided by the different virus-related predictive factors (genotype, viral load), the extent of liver damage and the time taken to achieve a response to the antiviral therapy[9-11].

Correspondence:
Rafael Bañares
Unidad de Trasplante Hepático. Servicio de Medicina de Aparato Digestivo. Hospital General Universitario Gregorio Marañón. Instituto de Investigación Sanitaria Gregorio Marañón.
C/ Doctor Esquerdo, 46 28007 Madrid
E-mail: rbanares@telefonica.net

SELECTING PATIENTS FOR TREATMENT

Candidates for antiviral treatment are patients with a significant extent of fibrosis (F ≥ 2) regardless of serum transaminase levels, essentially meaning those with compensated cirrhosis. In patients with genotype 1 HCV infection, the use of SOC treatment could be considered when there are factors predictive of a favorable response (IL28 polymorphism CC, no prior treatment and absence of advanced fibrosis F3-F4), otherwise the triple treatment regimen (SOC + telaprevir or boceprevir) is the treatment of choice[7]. However, recent guidelines do not provide a prioritization system describing which patients should be preferentially treated. Ongoing phase II clinical trials are currently assessing the use of the new antivirals against genotypes 2 and 3[12], but until the end of such trials, it is recommended that patients with genotypes 2, 3 and 4 are prescribed conventional antiviral therapy.

NEW THERAPEUTIC STRATEGIES

The new DAAs have been developed to act against different molecular targets of the HCV. The longterm objectives of DAAs are to improve the SVR rate and minimize adverse events, either by shortening treatment duration or through their use in regimens based on antiviral combinations without interferon. Over 30 such agents are presently at different stages of clinical development[3,13].

Protease inhibitors

The two licensed DAAs (boceprevir and telaprevir) belong to the family of NS3/4A serine-protease inhibitors and are given in combination with pegIFN and ribavirin (triple therapy); when administered as monotherapy they induce the rapid appearance of resistance[14]. NS3/4A is a serine protein that cleaves viral polyproteins, which then reassemble into new virus particles. The main drawbacks of the use of these agents are a higher rate of adverse effects, a risk of drug resistance, interactions with other drugs and their elevated cost[3].

In patients with genotype 1 HCV infection, NS3/4A serine-protease inhibitors given as triple therapy with pegIFN and ribavirin significantly improve the SVR rate[7]. Their main report-

ed adverse effects have been skin rash, dysgeusia, pruritus ani and hemorrhoids, nausea, diarrhea and hypertransaminasemia.

Treatment-naïve patients (previously untreated)

Telaprevir (TVR). TVR is given as an oral dose of 750 mg/8 h (6 tablets per day taken at meal times). The efficacy of TVR therapy for treatment-naïve patients has been assessed in e two phase III randomized controlled trials: ADVANCE (n=1088) and ILLUMINATE (n=500)[15,16]. These trials have introduced the concept of response-guided therapy (RGT), which establishes treatment duration according to the occurrence or not of an "extended rapid virological response", or eRVR. The definition of an eRVR is undetectable HCV-RNA, using a sensitive test (lower limit of detection 50 IU/mL), at weeks 4 and 12 of treatment. Patients with an HCV-RNA level greater than 1000 IU/mL at these time points were described as non-responders and treatment was discontinued. The ADVANCE study had three treatment arms: two were TVR plus SOC given for 8 or 12 weeks, followed by SOC given for 12 or 36 weeks –depending respectively on whether or not an eRVR was achieved– and a third control arm of patients receiving placebo plus SOC for 48 weeks. The SVR rate was significantly higher among the patients receiving triple therapy with TVR compared to the control group (8-week treatment arm 69%, 12-week treatment arm 75% vs. SOC 44%, p<0.001). The ILLUMINATE trial assessed the success of RGT by comparing the eRVR achieved in each treatment arm (24 vs 48 weeks following 12 weeks of triple therapy). The rate of SVR in the 24-week treatment arm was 92% compared to 88% in the 48-week arm. Moreover, around two thirds of the patients included in the trial could discontinue treatment at 24 weeks. Patients in whom an eRVR was achieved, showed SVR rates of 83-92%. The conclusions of these two randomized trials were, respectively, that the optimal duration of triple therapy with telaprevir is 12 weeks, and that 24 weeks of RGT is as effective as 48 weeks in patients showing an eRVR (at weeks 4 or 12). Among patients showing factors predictive of a worse response to treatment, such as black patients or those with advanced liver fibrosis, a higher SVR rate was observed in those receiving triple therapy. Thus, the subsets of patients with advanced fibrosis undergoing 12 weeks of triple therapy showed an SVR of 62% in the ADVANCE trial compared to 80% in the ILLUMINATE trial. However, given the small proportion of patients with cirrhosis in the treatment arms of both studies (<10%), North American guidelines recommend a treatment duration of 48 weeks (12 weeks of triple therapy followed by 36 weeks of SOC) in these patients. Infection relapse rates were also worse in the telaprevir arm compared to placebo (7% vs. 27%, p<0.001). When adverse effects were considered, it emerged that around 8% of patients receiving triple therapy had to shorten their duration of therapy because of adverse events compared to 4% of patients in the control group. The effects most frequently related to triple therapy were maculopapular rash (56% vs. 32% for SOC), hemolytic anemia, pruritus ani, nausea and diarrhea. Eczematous rashes were considered serious (affecting > 50% of the body surface) in 4% of patients. Fewer than 1% developed Stevens-Johnson syndrome. Rashes were treated with topical or oral corticosteroids and antihistamine agents. Anemia (Hb < 10 g/dl) was detected in 36% of patients versus 14% in patients receiving SOC treatment. It should be noted that the SVR rate remained unchanged in the subset of patients who received triple therapy but had to reduce their ribavirin dose because of anemia.

Boceprevir (BOC). BOC is given as oral doses of 800 mg/8 h (12 capsules per day). Phase III trials on BOC include a 4-week *lead in* of SOC treatment. The objective of this lead-in period is to reduce the viral load before the introduction of BOC, thus minimizing the risk of drug resistance or infection relapse. In addition, the lead-in period will provide information on the response to 4 weeks of conventional therapy. For example, it may be anticipated that a high proportion of patients showing an eRVR will achieve a SVR with conventional SOC therapy. According to the results of a randomized trial, it appears that patients who do not undergo a log reduction in viral load of at least one (< 1 log10) from the baseline load at 4 weeks, will show a lower SVR rate and are considered to have some resistance to peg-INF[11]. However, when BOC was added to the treatment regimen in these patients showing a poor response to peg-INF, a higher SVR rate was recorded than in patients treated with SOC (28-38% vs. 4%). Accordingly, the clinical guidelines published by the AASLD state that being a poor responder to SOC should not be a contraindication for triple therapy with BOC.

The phase III clinical trial on BOC conducted in treatment-naïve patients (SPRINT-2) included 1,097 patients assigned to two groups undergoing 24 weeks or 44 weeks of triple therapy (BOC + pegIFN + ribavirin) and a control group receiving placebo + pegIFN + ribavirin for 48 weeks[17]. In one of the treatment groups, according to RGT, patients with an undetectable viral load from weeks 8 to 24, were given triple therapy for 24 weeks after the lead-in period (28 weeks of treatment in total), while patients with detectable HCV-RNA continued SOC treatment until week 48. In the second treatment group, patients underwent triple therapy for 44 weeks following the lead in regardless of their response at treatment week 8. SVR rates in the BOC treatment groups were 67% (RGT BOC) and 69% (BOC 48 weeks) compared to 40% in the control group for Caucasian patients (p<0.001); and 42% (RGT BOC) and 53% (BOC 48 weeks) versus 23% (controls) for African-American patients. In 54% of the Caucasian patients, serum HCV-RNA was undetectable at weeks 8 and 24 of treatment and a similar SVR rate was achieved to the rate recorded in the patients receiving 48 weeks of triple therapy with BOC (88% vs. 90%). The relapse rate was 9% in subjects treated with BOC compared to 23% in those given placebo (p<0.001). Patients with HCV-RNA levels >100 IU/mL (at week 8 of triple therapy) were considered non-responders determining a need to suspend treatment.

Despite the design of the SPRINT-2 trial, the FDA recom-

mends that patients with cirrhosis or slow responders with HCV-RNA detectable at treatment week 8 should receive SOC treatment for 4 weeks (*lead in*), at least 32 weeks of triple therapy and 12 weeks of SOC.

Treatment suspension due to side effects was similar in the two BOC arms compared to the control group (12-16% vs. 16%). The secondary effects most often associated with the BOC treatment regimen were anemia and dysgeusia.

Given that the BOC regimen is longer than the treatment regimen with TVR, a greater incidence of anemia was recorded: 49% of patients showed Hb < 10 g/dl vs. 29% for the patients receiving SOC. As with TVR, the SVR remained unchanged in the subgroup of patients receiving triple therapy who had to reduce their ribavirin dose because of this problem.

Previously treated patients

Telaprevir. The phase III randomized control trial REALIZE on TVR treatment in previously-treated patients (n=662), included null responders, partial responders or those relapsing[18]. Around 20% of the patients had cirrhosis and/or a high viral load. The study design comprised three treatment arms of 48 weeks' duration: 1) a control arm consisting of placebo + SOC; 2) triple treatment with TVR for 12 weeks followed by SOC for 36 weeks; and 3) SOC treatment for 4 weeks (lead in) followed by 12 weeks of triple therapy with TVR, and then SOC to complete the 48 weeks. No difference was observed in SVR occurrence among patients assigned to the arm including a lead-in period and those receiving triple therapy from the beginning. SVR rates in the groups receiving TVR were 64% and 66% (83% and 88% in patients relapsing, 59% and 54% in partial responders, and 29% and 33% in null responders) compared to 17% in the placebo group (p<0.001). It therefore appears that the response to triple therapy depends on the previous response in these patients, being greater in those who suffered infection relapse following prior treatment. The decision to retreat non-responding patients, especially if cirrhotic, should be made on an individual basis given that in this subset of patients less than a third achieved a SVR (12/43, or 28%).

Boceprevir. The RESPOND-2 trial[19] of similar design to the SPRINT-2 study was conducted in 403 patients partially responding or relapsing following earlier treatment (null responders were excluded) assigned to one of the three arms: SOC and BOC-placebo for 48 weeks (control); BOC plus pegIFN and ribavirin for 44 weeks after 4 weeks of lead in; and BOC as triple therapy using a RGT scheme similar to that of SPRINT-2. According to this scheme, patients with HCV-RNA undetectable at 8 weeks completed 32 weeks of triple therapy (36 weeks total), while those with HCV-RNA detectable at week 8 but undetectable at week 12, completed 32 weeks of triple therapy followed by 12 weeks of SOC (48 weeks total). Patients showing undetectable HCV-RNA before week 8 provided a SVR rate of 86% (after 36 weeks of treatment). The main conclusion of the RESPOND-2 trial was that a lead in with SOC is needed followed by at least 32 weeks of BOC triple therapy in patients showing a partial or relapse response to prior treatment with SOC. SVR rates were 59% and 66% in the BOC groups vs. 21% in the control group (p<0.001). In patients undergoing a less than 1 log10 reduction in viral load at week 4, SVR rates were 33% and 34% in the BOC arms vs 0% in the control arm. Relapsing patients attained SVR rates of 75% and 69% and prior responders rates of 59% and 54% for the two BOC triple therapy regimens compared to patients treated with SOC (29% for prior relapsers and 7% for prior partial responders). Although the drug's registration trials excluded prior null responders from their design, the FDA has approved the use of BOC in these patients with caution given the lack of available evidence.

Treatment monitoring

Interactions with other drugs. Protease inhibitors block several cytochromes, such as cytochrome 450 2C, CYP3A4, CYP1A, determining their interaction with many drugs including statins, immunosuppressors, antiretroviral drugs, or psychiatric drugs. Accordingly, information on possible interactions should be consulted before adding new drugs to the treatment regimen.

Monitoring possible drug resistance. The development of resistance to the antiviral prescribed conditions the response to treatment. In their registration trials, resistance to TVR or BOC in early treatment stages was recorded in a low proportion of patients (TVR 5%, BOC 7%). This has precluded recommendations to determine the resistance profiles of these agents at the start of treatment.

Cross resistances exist with drugs of the same class or different classes. For example, HCV mutations A156T, V36A and R155K confer resistance to almost all protease inhibitors. Resistance rates are especially high in patients showing a null response to interferon and in those with high viral loads and those with genotype 1a infection[20]. The clinical impacts of resistance to DAAs have not been well established, but it is expected that this problem will be approached in the future by combining antivirals of different families not showing cross-resistance.

Drugs under development

- *Nucleoside/nucleotide analogue polymerase inhibitors*: this drug class includes synthetic nucleosides that act upon the active site of HCV NS5B polymerase preventing viral replication. These agents show a high genetic barrier to resistance and are active against all HCV genotypes. Many of the drugs in this class have the side effect of gastrointestinal toxicity.

-*Non-nucleoside analogue polymerase inhibitors*: these drugs bind to less conserved allosteric sites on the viral en-

zyme and block conformational changes to prevent the virus' actions. Their genetic barrier is low such that they are only active against HCV genotype 1.

- *NS5A inhibitors:* these agents (the most representative is BMS 790052) strongly inhibit HCV replication. They are active against all genotypes of the virus, have a high genetic barrier and may be combined with other antiviral drugs.

- *Cyclophilin inhibitors*: these inhibitors bind to host cell proteins that facilitate viral replication. Since they do not belong to the DAA class, these drugs are less prone to induce resistance.

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