New trends in hepatitis C management

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Key points

Approximately 2% of the world population is infected by the hepatitis C virus (HCV).
The incidence of new HCV infections is decreasing today, with new contaminations limited to specific risk groups: intravenous drug users and homosexual men.
On the other hand, morbidity and mortality due to infections that occurred in the late 1970s and early 1980s are rising quite substantially.
Approximately 20% of patients infected by HCV develop cirrhosis in about 20 years and every year 5% of them develop hepatocellular carcinoma (HCC).
Current epidemiologic models suggest that the incidence of HCC and of the mortality associated with chronic HCV infection will continue to increase through 2015, a finding consisting with the perception of liver specialists today.

With an estimated prevalence of 2% worldwide, or approximately 123 million infected individuals, the public health burden of hepatitis C virus (HCV) is heavy. Although the incidence of new infections is declining and is limited mainly to intravenous drug users, the morbidity and mortality (and their costs) associated with HCV infections contracted in the late 1970s and early 1980s are expected to increase over the next decade. Approximately 20% of patients with chronic HCV infection progress to cirrhosis after an average of 20 years

Points essentiels

Nouvelles tendances dans la prise en charge de l’hépatite C

L’infection par le virus de l’hépatite C (VHC) concerne environ 2 % de la population mondiale.
L’incidence des nouvelles infections par le VHC est aujourd’hui en baisse, les nouvelles contaminations se limitant aux groupes à risque : usagers de drogues intraveineuses, homosexuels masculins.
Environ 20 % des patients infectés par le VHC développent une cirrhose en 20 ans et tous les ans, 5 % d’entre eux font un cancerne hépatocellulaire (CHC).
Les modèles épidémiologiques actuels suggèrent que l’incidence du CHC et la mortalité liée à l’infection chronique par le VHC vont augmenter jusqu’en 2015, ce qui correspond bien au ressenti actuel des hépatologues.
and about 5% of those with cirrhosis will develop hepatocellular carcinoma (HCC) every year [1]. The findings of current models that the incidence of HCC and HCV-related mortality will increase until ~2015 is consistent with the daily experience of liver specialists.

**Recommended therapy**

Chronic HCV infection is a curable disease, and eradication of HCV improves outcome, especially in patients with HCV-related fibrosis or cirrhosis [2–4]. The currently recommended therapy for chronic hepatitis C is a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV). Two forms of PEG-IFN, α-2a (40 kDa) (Roche Pharmaceuticals, Basel, Switzerland) and α-2b (12 kDa) (Schering Plough, Kenilworth, New Jersey, USA), have been approved for HCV treatment. Although they differ in their pharmacological properties, their longer serum half-lives result in a sustained duration of activity greater than that of conventional IFNα [5,7]. PEG-IFNα-2b has a larger volume of distribution and faster clearance than PEG-IFNα-2a; plasma levels depend on body weight [5,7]. For this reason, PEG-IFNα-2b is administered at a dose of 1.5 μg/kg subcutaneously once weekly, whereas PEG-IFNα-2a is given at a fixed dose of 180 μg subcutaneously once weekly. In patients infected with genotypes 1 or 4 (the so-called difficult-to-treat patients), RBV is given at high doses (≥ 13.5 mg/kg/day). Patients infected with the easier-to-treat genotypes 2 or 3 receive a low dose of RBV (800 mg/day) [8]. Absolute contraindications to PEG-IFN and RBV include pregnancy, breast-feeding, and allergy to either drug. Relative contraindications include decompensated liver disease, neuropsychiatric disorders, cardiac disease, renal impairment, autoimmune disease, and solid organ transplantation. Patients with ongoing alcohol or drug use should be referred and evaluated by an addiction therapist before starting treatment. Treatment has serious side effects in up to 2% of patients. Patients should be informed of common side effects (occurring more than 5% of patients) before starting a course of treatment. A psychiatrist should assess the need for antidepressant drugs in patients with a history of depression. Common side effects related to IFN-based treatment include malaise, fever, myalgia, headaches, hair loss, alterations in mood (depression, anxiety), and thyroid disorders. The main adverse effect associated with RBV is red cell hemolysis, which can cause anemia and its complications. RBV is teratogenic, and strict birth control should be practiced during treatment and for 6 months afterwards. All of these side effects are reversible when treatment is stopped, except thyroid disorders. Combination therapy produces sustained virologic response (SVR), that is, viral eradication, in approximately 50% of patients, depending on host and viral characteristics, especially virus genotype [9–11]. SVR rates range from 38-48% in patients treated for 48 weeks for genotype 1 infection, which accounts for most cases (~60%) of chronic hepatitis C in industrialized countries. SVR rates for patients with the less common genotypes 2 and 3 are 76-80% when treated for 24 weeks. Treatment response to genotype 4, which affects mostly patients from the Middle East, lies somewhere between that for genotype 1 and those for genotypes 2 and 3. Patients with HCV infection other than genotypes 2 and 3 require > 24 weeks of PEG-IFN and RBV treatment; 36 weeks of treatment may be as effective as 48 weeks for patients infected with genotype 4 [12].

Serum concentration of HCV RNA at initiation of antiviral therapy is another determinant of outcome. Sustained response rates are consistently higher in patients with low baseline HCV RNA levels, usually defined as < 800 000 International Units (IU)/mL.

Host factors also affect the likelihood of SVR, albeit less so than genotype does; these include age, race, gender, obesity, degree of hepatic fibrosis, and immunodepression. Among these factors, racial differences in response rates are the most striking. African-Americans with chronic hepatitis C have a response rate of 33%, compared with 50% in white Americans [13].

**Predicting response to hepatitis C virus therapy**

Response to treatment is characterized by different viral kinetic profiles. Patients who achieve SVR typically have a rapid initial decline in viral level (early virologic response, EVR), which reflects the efficiency of suppression of replication, followed by a second, slower phase of decline in viral load until undetectable levels of circulating virus are achieved. The second phase is believed to be due to clearance of virus-infected cells. EVR is classically defined by a decrease of 99% or more (at least 2 logs) in HCV RNA at 12 weeks of antiviral therapy. EVR has a negative predictive value (NPV) of 100% and a positive predictive value (PPV) of 72% for SVR [11,14]. Patients with a 99% decrease (> 2 logs) in HCV RNA level at 12 weeks but who...
remain positive by polymerase chain reaction (PCR) are less likely to achieve SVR (PPV: 21%) than patients who have undetectable HCV RNA at 12 weeks (PPV: 84%). Treatment can be discontinued in patients who do not achieve a 99% decrease in HCV RNA at 12 weeks, if the aim of therapy is viral eradication. However, a biochemical response (normalization of aminotransferase levels) may lead to stabilization or improvement in fibrosis and inflammation in patients with severe liver disease, even in the absence of virologic response (maintenance therapy) [15]. If the 24-week PCR remains positive, treatment can be discontinued, as the likelihood of achieving SVR is about 1%. Rapid viral response (RVR), defined by a negative qualitative PCR assay at week 4, has a high PPV for SVR, around 90% for patients with a single genotype and 82% in patients coinfected with more than one HCV genotype. RVR occurs in only 10% of difficult-to-treat patients [16].

**Tailoring anti-hepatitis C virus therapy**

**Adapting duration of treatment**

In patients who do not achieve RVR, a treatment duration longer than the recommended 48 weeks (72 weeks) may be helpful [17,18]: for patients who are HCV RNA-positive at week 4 but who achieve a significant antiviral response at week 12 (decrease in HCV RNA > 2 logs) and who are HCV RNA-negative at week 24, the continuation of the combination of PEG-IFN and RBV therapy for more than 48 weeks results in a significant increase in the SVR rate. 

In the small subgroup of genotype 1-infected patients with a negative PCR at week 4 (mainly those with a pretreatment baseline viral load less than 250 000 IU/mL), the SVR rate is high (92%), even after a short course of only 24 weeks of therapy [19]. In patients infected with genotype 2 or 3 whose qualitative PCR is negative at week 4, reduction of treatment duration to 12-16 weeks did not affect the SVR rate and reduced the occurrence of side effects [20]. However, the recent ACCEL-ERATE trial, which included a large number of patients, clearly showed that a reduction in treatment duration resulted in almost all situations (regardless of genotype or baseline viral load) in a higher relapse rate in the patients treated for 16 instead of 24 weeks [21]. Nevertheless, in easy-to-treat patients infected by genotypes 2 or 3, high doses of ribavirin (1000–1200 mg instead of 800 mg) allow to reduce the duration of therapy.

The utility of prolonging treatment in patients with cirrhosis or coinfectied with HIV or in reducing its duration in patients with genotypes 4 and 5 and a low baseline viral load has not been established.

**Adapting doses**

A policy of increasing the dose of PEG-IFN or RBV might be effective in non-responders, relapsers, and treatment-naive patients. For example, in the REPEAT (Retreatment with Pegasis in Patients Not Responding to Peg-Intron Treatment) trial, double doses of PEG-IFNα-2a for the first 12 weeks of treatment (followed by simple dose of PEG-IFNα-2a for the next 36-60 weeks) in combination with high doses of RBV resulted in EVR in 60% of patients who previously failed to respond to the PEG-IFNα-2b combined therapy [22]. The high level of EVR achieved in this study contrasted with a low level of SVR in the group of patients treated 48 weeks and suggests that high PEG-IFN doses should be pursued longer. Studies are ongoing to verify this hypothesis. A pilot Swedish study suggested that high doses of RBV allowed SVR in 9 of 10 patients infected by genotype 1. This dose effect by RBV is suggested by pivotal studies of RBV doses > 10.6 mg/kg/d, which found a direct relation between the dose and SVR [8,23] and by another study that compared standard doses to the high doses made possible by combining them with erythropoietin (EPO) therapy [24]. Taken together, these studies suggest that the treatment dose and duration should be modulated according to genotype, baseline viral load, and early viral kinetics, to improve the SVR rate and reduce the rate of side effects.

**The future of hepatitis C virus therapy**

New strategies, including new IFN formulations, protease or polymerase inhibitors, internal ribosomal entry site (IRES) inhibitors, and interfering mRNAs are under development. Preliminary results are encouraging in non-responders and trials are underway in treatment-naive patients.

Albuferon (Human Genome Sciences, Rockville, Maryland, USA), a longer-acting IFN formed by the fusion of IFNα-2b and human serum albumin, has a longer half-life than its predecessors and thus allows injections only once every 15 (or 30) days with an efficacy that seems at least as good as the recommended combination [25]. Although the IRES inhibitors have not proved to be effective in clinical practice, protease inhibitors (PIs) and, to a lesser extent, polymerase inhibitors will completely change the practices for hepatitis C treatment in the future, at least in difficult-to-treat patients.

**Protease inhibitors**

The NS3-4A region of the HCV polyprotein contains a serine protease that cleaves the viral polyprotein into functional proteins essential for replication. The first HCV protease inhibitor to undergo clinical trials was BILN-2061 (Boeringer-Ingeheim, Ingelheim, Germany), and these showed a 1-log decline in HCV RNA after 2 days of treatment. This treatment was more effective in patients with genotype 1 than with other genotypes [26–28]. Further studies of BILN-2061 were not performed, however, because of the cardiotoxicity observed in the animal model. Telaprevir or VX-950 (Vertex Pharmaceuticals, Cambridge, Massachusetts, USA) is a peptidomimetic inhibitor of the NS3-4A
protease that includes an α-ketoamide moiety that anchors at the active site. In a phase 1b study, all patients receiving telaprevir had at least a 2-log(10) decrease in HCV RNA by 72 hours; in patients receiving a dose of 750 mg every 8 hours, a median 4-log(10) reduction in HCV RNA concentration was observed. In combination with PEG-IFN, there was a median 5.5-log(10) decline in HCV RNA concentration, with HCV RNA becoming undetectable after 14 days of treatment in 4 of 8 subjects [29]. In a 24-week combined regimen of Telaprevir, PEG-IFN, and RBV, treatment-naive HCV genotype 1 patients achieved SVR rates 20% higher than controls receiving the standard of care (ie, PEG-IFN and RBV) in the phase 2b PROVE 1 and PROVE 2 studies [30,31]. Similar results have been obtained for another protease inhibitor, boceprevir, or SCH 503034 (Schering Plough, Costa Mesa, California, USA), which was the first available nucleoside analog for treating chronic HCV infection. Although valopicitabine’s antiviral profile was interesting (albeit less powerful than PIs), the US Food and Drug Administration suspended its use because of an unacceptable high incidence of gastrointestinal side effects. Similar polymerase inhibitors in development include R1626 (Roche Pharmaceuticals, Basel, Switzerland) and HCV-796 (Virapharma, Exton, Pennsylvania, USA). In 14-day studies, drugs produced modest reductions in HCV RNA: R1626 was associated with a slight reduction in hemoglobin and lymphocytes, and both drugs caused an increased number of headaches [35,36]. Non-nucleoside inhibitors of HCV RNA-dependent RNA polymerase are also in development. These drugs may be less potent than the NS3-4A protease inhibitors. As with the protease inhibitors, the development of resistance may be a problem, but, to date, has not been reported. Two of these compounds, JTK-003 and JTK-109 (Japan Tobacco, Tokyo, Japan), are entering phase 2 trials.

### Immune modulation and other drugs

Modulation of the immune response is a further area of interest. CPG-10101 (Actilon®, Coley Pharmaceutical Group, Wellesley, Massachusetts, USA), is a Toll-like receptor 9 agonist that activates plasmacytoid dendritic cells. This compound exerts its effect through T-helper type 1 cytokines; the results include increased IFN concentrations and stimulation of natural killer cells. In a phase 1b trial, patients receiving CPG-10101 at 1 mg twice a day for 4 weeks had increased concentrations of endogenous IFN and a reduction in HCV RNA by 1-log10 [37]. The phase 2 study failed to show significant improvement in SVR rates compared to the standard of care and the company decided in 2007 to suspend further investment and development in Actilon®. ANA245 (isatoribine; Anadys Pharmaceuticals, San Diego, California, USA) is a Toll-like receptor 7 agonist. After 1 week of treatment with 800 mg a day intravenously, there was a median reduction in HCV RNA concentration of 88% [38]. Second generation Toll-like receptor 7 agonists are currently under development by the company.

Given the problems of anemia caused by ribavirin, a drug with the efficacy of ribavirin but without its hematologic side effects would be very useful. Viramidine (Valeant Pharmaceuticals, Costa Mesa, California, USA) is the inactive prodrug of ribavirin. In a phase 2 study of PEG-IFN with viramidine versus the standard combination treatment, the antiviral efficacy of viramidine was similar but the anemia rates were far lower (4% versus 27%) [39]. Finally, RNA-based treatments and vaccines may also be available in the future, but all require further evaluation and development.

### Conclusion

Great progress has been made since the discovery of HCV 20 years ago, in molecular diagnosis (genotype, subtype, quasispecies, quantification) as well as in treatment. Chronic HCV infection may be now cured in more than 50% of infected patients with short-term (24 weeks) or long-term (72 weeks) treatments. In combination with PEG-IFN and RBV, new oral anti-HCV compounds (protease and polymerase inhibitors)
make it possible to increase the rate of viral eradication to about 70% in genotype-1-infected patients. Viral eradication leads to recovery from most HCV-related liver diseases (including "early" cirrhosis, which is reversible) and extrahepatic disease (vasculitis and remission of HCV-associated lymphoma). These very encouraging results demonstrate the need for early diagnosis of HCV infection, early treatment, and control of any comorbid diseases, to reduce the morbidity and mortality associated with chronic HCV infection.

Conflicts of interests: Honoraria: V. Mallet (Schering-Plough, Bristol-Myers Squibb), S. Pol (Bristol-Myers Squibb, Schering-Plough, Wyeth, Roche, Novartis, Gilead, Tibotec, Boehringer Ingelheim).

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