General review

Treatment of hepatitis C: Perspectives

Traitement des hépatites C : perspectives

S. Pol *, M. Corouge

Université Paris Descartes, AP–HP, Unité d’Hépatologie, Hôpital Cochin, INSERM U-1016, Institut Cochin, Paris, France

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Abstract

The treatment of hepatitis C virus (HCV) infection has significantly improved in the last 2 decades. The association of pegylated interferon alfa and ribavirin (PR) has allowed a sustained virologic response (SVR) for nearly 15 years i.e. a viral cure of the infection for 45% of genotype 1-, 65% of genotype 4-, 70% of genotype 3- and around 85% of genotype 2-infected patients. A better understanding of the HCV life cycle has led to the development of direct-acting antiviral drugs (DAAs) targeted against viral proteins (NS3/4A protease, NS5B polymerase with nucleotide and non-nucleotide inhibitors, NS5A viral replication complex). The combination of first-generation protease inhibitors with PR demonstrated a high antiviral effectiveness (75% of SVR but restricted to genotypes 1) with substantial adverse effects for the first-generation protease inhibitors, which obtained market approval in 2011 (telaprevir and boceprevir), recommendations for use in HCV monoinfected patients in 2012, and in HCV/HIV coinfected in 2013. Then, the combination of second-generation protease inhibitors with PR increased SVR rates from 75 to 90%, while reducing treatment duration, adverse effects, and the number of pills. The next step will be using an interferon and ribavirin-free combination of DAAs; it should become the standard of care in 2015. These excellent results in “easy-to-treat” patients and in small populations in the first studies were confirmed in phase III studies and in “difficult-to-treat” patients (treatment – especially protease inhibitors – previously treated patients, cirrhotic patients, liver and renal transplant patients, HIV coinfected patients, and multi-drug treated patients, at increased risk of drug interaction). The high antiviral potency of these new combinations has changed the definition of “difficult-to-treat patients”. These unique achievements in drug history make any previous publication on hepatitis C treatment obsolete.

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Keywords: Hepatitis C virus; Direct-acting antiviral drugs; Protease inhibitor; Polymerase inhibitor; Replication complex inhibitor

Résumé

Le traitement de l’infection virale par le virus de l’hépatite C (VHC) a singulièrement progressé ces 2 dernières décennies. Depuis 15 ans environ, la combinaison de l’interféron alfa pégylé et de la ribavirine permettait d’obtenir un taux de réponse virologique prolongée, assimilable à une guérison, chez 45 % des patients infectés par un génotype 1, 65 % de ceux infectés par un génotype 4, 70 % des génotypes 3 et environ 85 % des génotypes 2. Une meilleure compréhension du cycle réplicatif du VHC a permis le développement d’antiviraux directs spécifiques du VHC ciblant les protéines virales (la protéase NS3/4A, la polymérase NS5B avec des inhibiteurs nucléosidiques et non nucléosidiques, la protéine multifonctionnelle NS5A du complexe de réplication). La combinaison d’inhibiteurs de première génération en association avec l’interféron pégylé et la ribavirine a montré une efficacité antiviraire élevée (75 % de guérison des génotypes 1) avec une tolérance difficile pour les inhibiteurs de protéases de première génération qui ont fait l’objet d’une autorisation de mise sur le marché en 2011 (telaprevir et boceprevir) et de recommandations d’utilisation chez les patients mono-infestés par le VHC en 2012 et chez les co-infestés VIH/VHC en 2013. Puis des combinaisons d’antiviraux directs de deuxième génération avec l’interféron pégylé et la ribavirine ont permis d’augmenter les taux de guérison de 75 à 90 % et de réduire la durée des traitements, les effets secondaires et le nombre de comprimés. La prochaine étape sera la combinaison d’antiviraux directs qui deviendra le standard de traitement en 2015. Ces excellents résultats obtenus chez des patients « faciles à traiter » et en petit nombre ont été confimés dans les études de phase III et dans les « populations difficiles à traiter » (en échec de traitements antérieurs, notamment des inhibiteurs de protéases,

* Corresponding author at: Unité d’Hépatologie, Hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75679 Paris cedex 14, France.
E-mail address: stanislas.pol@cch.aphp.fr (S. Pol).

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Hepatitis C virus (HCV), an ARN virus, was discovered in 1988, and induces acute hepatitis with spontaneous recovery in 1 out of 3 patients: this high rate of chronicity (70%) accounts for 170 billion patients with chronic HCV infection worldwide [1]. HCV infection is one of the main causes of liver transplantation and hepatocellular carcinoma, at least as documented in industrialized countries, and should increase until 2030 [2,3]. The currently observed genuine therapeutic revolution is unique both because of the speed at which new treatments have been developed (with a constant improvement of their effectiveness and safety) and because of the approval of regulatory agencies to put on the market drugs tested without randomized trials and control groups. This is clearly due to 2 facts: on one hand, HCV infection is the only chronic infection which may be cured and on the other hand, liver has a unique ability to regenerate; fibrosis is continuously remodeled by liver enzymes, allowing its regression in case of moderate or non-necrotic-inflammatory activity. This encourages an extensive screening for a broader access to more effective treatments.

1. Chronic HCV infection: a systemic disease

HCV infection results in 3 kinds of damage: hepatic, vascular through cryoglobulinemic vasculitis and systemic. Liver injury, mostly immune-mediated, is responsible for chronic hepatitis [4], possibly resulting (in 1 case out of 3) in extensive fibrosis or cirrhosis which promotes the occurrence of hepatocellular carcinoma (HCC) (the transforming capacity of some viral proteins is discussed) (Fig. 1). Cryoglobulinemia is due to HCV lymphopitostis, most frequently type II mixed (polyclonal IgG and monoclonal kappa IgM components) in 40% of infected patients. In 5 to 10% of the cases, deposits of antigen-HCV antibody complex and rheumatoid factor in medium-sized arteries cause skin (purpura), rheumatologic (polyarthritis), nephologic (membranoproliferative glomerulonephritis), or neurological (peripheral polyneuropathy) manifestations. There is also a risk of clinical selection with the development of lymphoma (particularly splenic lymphoma with villous lymphocytes) [5].

Finally, other extrahepatic manifestations could be related to chronic inflammation as a consequence of chronic viral infection (lymphocytic activation as observed in HIV infection): an increased risk of adult-onset diabetes (from 1.5 to 1.8), cardiovascular diseases (from 2.0 to 2.5), cerebrovascular diseases (from 2.5 to 3.0), and also cancer (hepatic and extrahepatic) (Fig. 1). Hepatic and extrahepatic presentations (among which asthenia and psychophysical impact of chronic infection, often the major complaint) are an indication for treatment.

2. Treatment of hepatitis C virus

2.1. Why treat the infection?

HCV infection is the only chronic viral infection that may be cured: there is no viral reservoir and a sustained virologic response (SVR) corresponds to a viral cure of the infection. Viral RNA becomes and remains undetectable in the liver or in blood mononuclear cells [6]. There is no late relapse without reinfection, even when a strong immunosuppressive therapy is used after chemotherapy or transplantation. The treatment of hepatitis C virus infection has evolved over the last 2 decades, with a 10-fold increase in SVR rates. Beginning in 1997, a weekly subcutaneous injection of pegylated interferon associated with fixed (800mg per day for genotype 2 or 3) or weight-adjusted (13–15mg/kg per day for genotype 1 or 4) dosing of ribavirin (Fig. 2) had increased therapeutic effectiveness and allowed to cure the infection in 45%, 85%, 70%, and 65% of respectively genotypes 1, 2, 3, and 4 infected patients [7]. However, many interferon-related adverse events (flu-like syndrome, neurocognitive disorders, immunostimulation of asymptomatic preexisting issues – tuberculosis, sarcoidosis, thyroid dysfunction, diabetes, bone marrow hypoplasia, etc.) or to ribavirin (rash, pruritus, cough, skin dryness, anemia, etc.), have limited the feasibility and safety of treatments lasting between 24 (genotype 2 or 3) or 48 (genotype 1, 4, or 5) and up to 72 weeks (genotype 1 infected slow responders).
Hepatic and extrahepatic benefits are proven in case of virologic cure: resolution of preexisting asthenia in 2 cases out of 3, normalization of hypertransaminasemia, resolution of hepatic pedicle lymph node involvement and of extrahepatic manifestations (cutaneous, rheumatic, neurological, or renal) related to cryoglobulinemic vasculitis [4]. SVR allows remodeling hepatic fibrosis when there is no hepatic comorbidity (overweight, excessive alcohol consumption). This is best illustrated by the significant decrease of liver related mortality, particularly in case of preexisting cirrhosis (almost total resolution of non-carcinomatous related complications of cirrhosis) and significant decrease of HCC incidence (or its relapse), in case of SVR [8]. Hepatic remodeling and regeneration could lead to cirrhosis reversal (only biopsy-proven), and a complete resolution of hepatic disorders [9]. The results of large cohort studies of monoinfected HCV (viremic or not) patients [10] or coinfected HIV-HCV patients [11] with SVR or not, showed a decrease of global, hepatic and extrahepatic (cardiovascular, cerebrovascular, or extrahepatic cancer related) mortality rates in case of SVR.

2.2. A therapeutic revolution

A better understanding of the mechanisms of HCV entry and release (during the 2000s) and the characterization of viral proteins involved in HCV replication [12,13] has led to the development of HCV specific antiviral drugs [14] (Fig. 3).

2.2.1. First stage: first-generation protease inhibitors

Protease inhibitors, especially telaprevir and boceprevir, first obtained their market approval in 2011. They showed a higher antiviral effectiveness in genotype 1 infected patients in combination with PR (pegylated interferon alfa and ribavirin): SVR rates of 75% in naive patients, 85% in relapers, nearly 50% in partial responders, and only 30% in non-responders to prior PR treatment. These results were also obtained with a reduction of treatment duration from 48 to 24 weeks in half of the patients with a rapid virologic response (RVR), i.e. undetectable viral load at week 4, and still undetectable after 12 weeks of treatment [15–20].

The main limitation of these treatments was additional adverse events besides those related to PR: skin effects for telaprevir with serious rashes in 5 to 10% out of the cases [21] and anemia for telaprevir and boceprevir [22–24]. Cost is a

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Fig. 2. History of the rate of sustained virologic response corresponding to a complete cure over the last 2 decades (the rates correspond to the treatment of genotype 1). IFN corresponds to interferon and riba to ribavirin; PI are first-generation protease inhibitors (telaprevir or boceprevir and direct-acting antiviral drugs).

Histoire des progrès thérapeutiques au cours de l’infection virale C (les chiffres donnés de guérison virologique correspondent au traitement des génotypes 1). IFN correspond à l’interféron, riba à ribavirine et PI aux inhibiteurs de protéases de première génération (telaprevir et boceprevir).

Fig. 3. Specific hepatitis C virus (HCV) viral proteins and cyclophilin (host target) which are involved in HCV replication, and which are the targets of specific inhibitors, including oral antiviral agents in development.

Cibles virales spécifiques du virus de l’hépatite C (protéines virales essentielles à la réplication) dont les antiviraux oraux, inhibiteurs spécifiques de ces cibles, sont en cours de développement et la cyclophiline, cible de l’hôte.
limitation of treatment, at least in less wealthy countries than Northern Europe or the United States (around 35,000 euros for direct costs only) and the number of pills: 6 for telaprevir and 12 for boceprevir, to be taken every 8 or 12 hours during a high-fat meal, in addition to the 4 or 6 pills of ribavirin.

These 2 oral antiviral agents were the first stage of the therapeutic revolution and remained the standard of care for genotype 1 (mainly 1a and 1b) infections in 2013. They were particularly necessary for patients presenting with cirrhosis, extensive fibrosis or intermediate fibrosis, and with hepatic comorbidities (excessive alcohol consumption, overweight) promoting a rapid progression of fibrosis [4]. Progress has been made so rapidly that these triple therapies were no longer recommended as of January 2014, in American or German guidelines; whereas in Italy reimbursement was accepted only in spring 2013, and in Portugal it was accepted only in the first trimester 2014.

2.2.2. French recommendations for the use of first-generation protease inhibitors

An expert meeting was held by the French association for the study of the liver (French acronym AFEF) in spring 2011, at the same time as availability of the early access program (French acronym ATU, temporary authorization for use TAU) of first protease inhibitors, to better define the indication of triple therapy with telaprevir or boceprevir. The objective was to provide recommendations for the prescription of these new agents reserved for genotype 1 infections. These recommendations are available on the AFEF website and published in international journals [22]. Briefly, the combination of pegylated interferon, ribavirin, and a protease inhibitor (telaprevir or boceprevir) allowed obtaining viral eradication in 70% of naive patients, 75 to 85% of relapers, 52 to 57% of partial responders, and 31% of non-responders [16–20,25–27]. The treatment duration could be shortened for some patients, particularly those with RVR and without extensive fibrosis. These “new” treatments were responsible for an increase of adverse effects: anemia, skin effects, and dysgeusia [21–23]. But they should decrease hepatitis C related mortality [8,9,28–31].

One year later, the AFEF and the societies of internal medicine and infectious diseases held an expert meeting similar to the previous one, to define the relevance of recommendations for triple therapy in genotype 1 HCV monoinfected and HCV HIV coinfection patients [32]. The recommendations for coinfection patients were quite similar to those for monoinfected patients, not to mention drug interactions, especially because of interactions between HCV inhibitors and antiretroviral agents [33].

2.2.3. Data from the ANRS CO20-Cupid cohort (National agency for the research on AIDS and hepatitis) concerning the TAU of first-generation protease inhibitors in previously treated cirrhotic patients

The TAU data in cirrhotic patients having failed pegylated bitherapy, and treated by 48 weeks of triple therapy with telaprevir (n = 299) or boceprevir (n = 212) was compiled [34,35]. Viral cure (SVR 12) was obtained with telaprevir in 74.2% of relapers or patients having experienced a virological breakthrough, 40.0% of partial responders, and 19.4% of null responders; the rates with boceprevir were respectively 53.9%, 38.3%, and 0% (2-fold higher in genotype 1b than in genotype 1a infected patients). Serious adverse effects were observed in 49.9% of patients: hepatic decompensation or severe infections in 10.4%, and deaths in 2.2% of patients (in multivariate analysis, baseline albuminemia and platelet count were 2 risk factors of death). Briefly, a high rate of viral cure in previously treated patients was obtained in half of cirrhotic patients with triple therapy [35] but common adverse effects, already reported in cirrhotic patients treated with interferon [36]. This real-life observational study changed the indications of triple therapy and it is now clear that cirrhotic patients with predictors of severe adverse effect (albuminemia < 35 g/L and platelet count < 100,000/mm³) must not be treated by interferon but should wait for new treatments.

2.3. Second-stage and second-generation specific inhibitors

Many other antiviral agents have been developed: nucleotide [37,38] and non-nucleotide [39] NS5B polymerase inhibitors, NS5A viral replication complex inhibitors [40], or second-generation protease inhibitors [41,42]. These new antiviral agents were initially used in combination with PR, allowing viral cure in 75 to 95% of patients (Fig. 4). This second-stage in treatment progress was not only characterized by a wide range of new therapeutic alternatives but also by the decrease of treatment duration (12 to 24 weeks) and in pill burden.

The real revolution has come from the development of therapeutic strategies combining direct antiviral agents without interferon (and without its adverse effects), or even without PR [43–52]. These oral multiple therapies are better tolerated, have a lower pill burden, and shorter treatment duration from 24 to 12 weeks. Above all, these oral combinations should cure more than 90% of naive patients but also previously treated patients, and even those who did not respond to triple therapy with a first-generation protease inhibitor, pegylated interferon, and ribavirin.

Fig. 4. Recent and planned history of hepatitis C virus treatments.

Histoire récente et prévue des progrès thérapeutiques dans le traitement du virus de l’hépatite C.
It is currently impossible to summarize all the on-going trials and their effectiveness, but these oral 12–24-week multiple therapies should allow curing all patients in the mid term because:

- they have a pan-genotypic activity;
- there is no cross-resistance among the various classes of direct antiviral agents;
- new agents (third generation) and even new targets (entry inhibitors, release inhibitors) are being studied.

Other antiviral agents (such as cyclophilin inhibitors, antisense RNA) or vaccine therapy should provide answers to unresolved issues such as overcoming an initial non-response to a first-line treatment. The development of these antiviral agents, specific of HCV or of the host, will decrease the role of interferon, including lambda interferon (which has a better hematologic safety than alpha interferon) that will no longer be used. Nevertheless, interferon could still be used as rescue therapy in case of treatment failure after 1 or 2 lines of antiviral agents.

Thus, 25 years after its discovery, HCV history seems to end with the promise of a cure for almost all identified patients. However, many challenges remain. The first is HCV testing: France is world champion of HCV management (including for screening since an estimated 60% of infected patients have been diagnosed), but a lot of work must be done worldwide and especially in Southern hemisphere countries, both for testing and access to specific care. The second is improving health care access, limited by many issues that need to be solved. The most vulnerable people, major targets of HCV infection (drug users, people in difficult socio-economic situations, migrants, prisoners) still do not have an easy access to diagnosis or treatment, because of patients themselves, physicians, or health policy. Nevertheless, the development of rapid diagnostic tests and of new treatments with better safety, effectiveness, and an easier formulation will hopefully improve HCV care. The third challenge is economic, treatment is expensive, and we will have to demonstrate that HCV cure is cost-effective by reducing hepatic and extrahepatic morbidity and mortality. The last challenge is prevention: the development of a prophylactic vaccine is crucial but remains difficult due to the high variability of HCV. Thus, if theoretically a complete eradication of HCV infection should be achieved in rich countries [less than 10% of infected patients were treated and cured in the United Kingdom or in the United States, where HCV systematic screening was recommended for baby boomers in 2012 by the Centers for Disease Control and Prevention (CDC)], a lot remains to be done concerning the screening, management, and cure of patients. There are great differences in screening, access to care, or even to treatment worldwide but also within Europe.

Disclosure of interest

Dr S Pol has received consulting and lecturing fees from Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Vertex, Gilead, Roche and MSD. Dr M Corouge has no conflict to disclose.

References


