Genes & Immunity (2019) 20:436–446
https://doi.org/10.1038/s41435-019-0066-z

REVIEW ARTICLE

# The remarkable history of the hepatitis C virus

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Received: 28 February 2019 / Revised: 25 March 2019 / Accepted: 1 April 2019 / Published online: 25 April 2019


## Abstract

The infection with the hepatitis C virus (HCV) is an example of the translational research success. The reciprocal interactions between clinicians and scientists have allowed in 30 years the initiation of empirical treatments by interferon, the discovery of the virus, the development of serological and virological tools for diagnosis but also for prognosis (the non-invasive biochemical or morphological fibrosis tests, the predictors of the specific immune response including genetic IL28B polymorphisms). Finally, well-tolerated and effective treatments with oral antivirals inhibiting HCV non-structural viral proteins involved in viral replication have been marketed this last decade, allowing the cure of all infected subjects. HCV chronic infection, which is a public health issue, is a hepatic disease, which may lead to a cirrhosis and an hepatocellular carcinoma (HCC) but also a systemic disease with extra-hepatic manifestations either associated with a cryoglobulinemic vasculitis or chronic inflammation. The HCV infection is the only chronic viral infection, which may be cured: the so-called sustained virologic response, defined by undetectable HCV RNA 12 weeks after the end of the treatment, significantly reduces the risk of morbidity and mortality associated with hepatic and extra-hepatic manifestations, which are mainly reversible. The history of HCV ends with the pangenotypic efficacy of the multiple combinations, easy to use for 8–12 weeks with one to three pills per day and little problems of tolerance. This explains the short 30 years from the virus discovery to the viral hepatitis elimination policy proposed by the World Health Organization (WHO) in 2016.

The hepatitis C virus (HCV) infection is an example of the translational research success. The reciprocal interactions between clinicians and scientists have allowed in 30 years the initiation of empirical treatments by interferon, the discovery of the virus, the development of serological (ELISA, RIA) and virological (reverse transcriptase polymerase chain reaction or RT-PCR enabling the qualitative and quantitative detection of viral RNA, genotyping, resistance analysis such as basic virology) diagnostic tests with an increasing sensitivity and specificity. In parallel, non-invasive biochemical or morphological fibrosis tests, predictors of the specific immune response including genetic (IL28B) have been developed and finally, radically effective treatments with HCV-specific oral antivirals inhibiting non-structural viral proteins involved in viral replication have been marketed this last decade, allowing the cure of all infected subjects. The elimination agenda of the World Health Organization (WHO) illustrates these major advances but must not hide the global challenges of tomorrow. If the diagnosis, efficacy, and tolerability of treatment are no longer an issue, less than 1% of the 71 million infected individuals worldwide has been treated and the majority of patients are unaware of their infection: the next challenges are therefore mainly to improve the screening and access to treatment for this frequent infection, which represents a public health although that is the only viral chronic infection that can be cured.

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## Epidemiology

Between 1990 and 2013, the viral hepatitis raised from the tenth to seventh place worldwide as a cause of death today, higher than the mortality from infection with human

immunodeficiency virus (HIV), malaria, and tuberculosis [1]: the viral hepatitis appear as the leading cause of infectious mortality in the world despite the HCV prevalence decreased from ~170 million chronic carriers worldwide in 1999 [2] to 71 million in 2017 [3, 4]. This reduction in prevalence is linked to reducing the risk of nosocomial infection, improving access to an efficient antiviral treatment (still a minority), but also to the mortality of infected subjects. We now consider that 1% of the world's population is infected with HCV with over one million seven hundred and fifty thousand new infections in 2015 mainly related to the parenteral risk, intravenous drug use in the northern countries but also the lack of hemovigilance in countries of intermediate or low economy [3, 4]; 2.3 million people are co-infected with HIV and HCV. There are major regional disparities in this prevalence since the most exposed areas are Egypt or Mongolia with 15% of the historically infected population. In these countries, the contamination was mainly nosocomial due to the absence of hemovigilance in Mongolia or due to the systematic treatment of schistosomiasis without single-use equipment in Egypt [5]. Other regions, such as West Africa or Central Africa, are heavily infected with ~5–8% of the contaminated population, not only because of nosocomial transmission but also because of certain "folkloric" practices (scarification, excision, cupping in Japan or barber in Sicily). In northern countries, the prevalence of Hepatitis C is less than 1% with a steady decrease in prevalence and incidence over the past 20 years: as an example, in France, the prevalence among insured persons decreased from 1.2% in 1996 to 0.8% in 2011 and probably 0.47% in 2017 and this decline is related to the high rate of the screening and antiviral treatment and to the pro-active policy of harm reduction especially among intravenous drug users (IVDU).

The overall mortality attributable to viral hepatitis in 2015 is ~720,000 deaths from cirrhosis and 470,000 deaths from hepatocellular carcinoma (HCC) with an increase of 22% since 2000 [4]. Although the hepatitis B virus infection mortality is almost twice as high, despite a vaccine that has been available for more than 30 years, about 400,000 people die each year because of their chronic hepatitis C infection, mainly because of cirrhosis (about 2/3) and also because of hepatocellular carcinoma (1/3) [4].

## The history of the hepatitis C virus

The history of HCV is unique in the history of microbiology, because its discovery was late, in 1988 occurring after the first empiric therapeutic trials but later developments were extremely fast since in 30 years from HCV isolation of the virus, the reciprocal interactions between the research and the clinical field have led to the development of reliable serological and virological diagnostic tests, the development of effective treatments allowing to hope for the cure of all the patients and the efficacy of HCV elimination policies elimination programs [4].

This policy, promoted by the WHO and initiated by at least 12 countries in the world, is not strictly speaking a policy of elimination since it is expected a reduction of new infections by 30% in 2020 and 90% in 2030 and a reduction in hepatitis-related mortality of 10 and 65%, respectively [4].

In 1988, Michael Houghton's team isolated complementary DNA from the blood of a person infected with a "non-A non-B" virus, allowing the isolation of viral RNA and the rapid development of serological diagnostic tests [6]. Elisa tests (EIA) and radio-immunoassays (RIA, now abandoned) were developed in parallel [6]; their sensitivity and specificity are now excellent. The presence of anti-HCV antibodies testified to the past exposure to HCV but did not determine the active nature of the infection, suspected by the presence of hypertransaminasemia but absent in a quarter of chronically infected patients. The only limit of the serology is the seroconversion time of about 4–10 weeks after contamination compared to HCV viremia, which is detectable by RT-PCR within 4 days post-infection.

The detection of HCV RNA by RT-PCR (and in particular of the negative strand) allows itself to assert the active nature of the infection. The detection thresholds have been lowered over the past 20 years and are now around 1.2 log, i.e 12 IU/mL. HCV RNA is detectable in the liver [7] or in the peripheral blood mononuclear cells and, of course, in the serum where it is classically sought to affirm the active infection. The isolation of the HCV RNA allowed the sequencing of the virus and the definition of different genotypes (numbered from 1 to 7) and subtypes (a, b, c…) [8]. Quantitative tests of viremia have been developed, allowing, for a given patient, the quantification and genotypic identification, at first, conditioning the therapeutic choices and the duration of treatment in the interferon era and enabling communities to trace contaminations and migrations.

Prior to identification of HCV RNA [6], standard Interferon therapies for non-A non-B hepatitis began in the late 80's (Fig. 1) [9]. It had been shown that 3–5 million Interferon units, 5 days a week or every 2 days for 24, 48 or 72 weeks allowed a viral eradication or sustained virological response (RVS) defined by undetectable HCV-RNA within 24 weeks after the end of treatment and corresponding to virological cure [9]. In parallel to the standard virological tests, a serological identification of the HCV capsid antigen has been developed; this test, which has a comparable sensitivity to HCV-RNA quantification, has not experience the expected

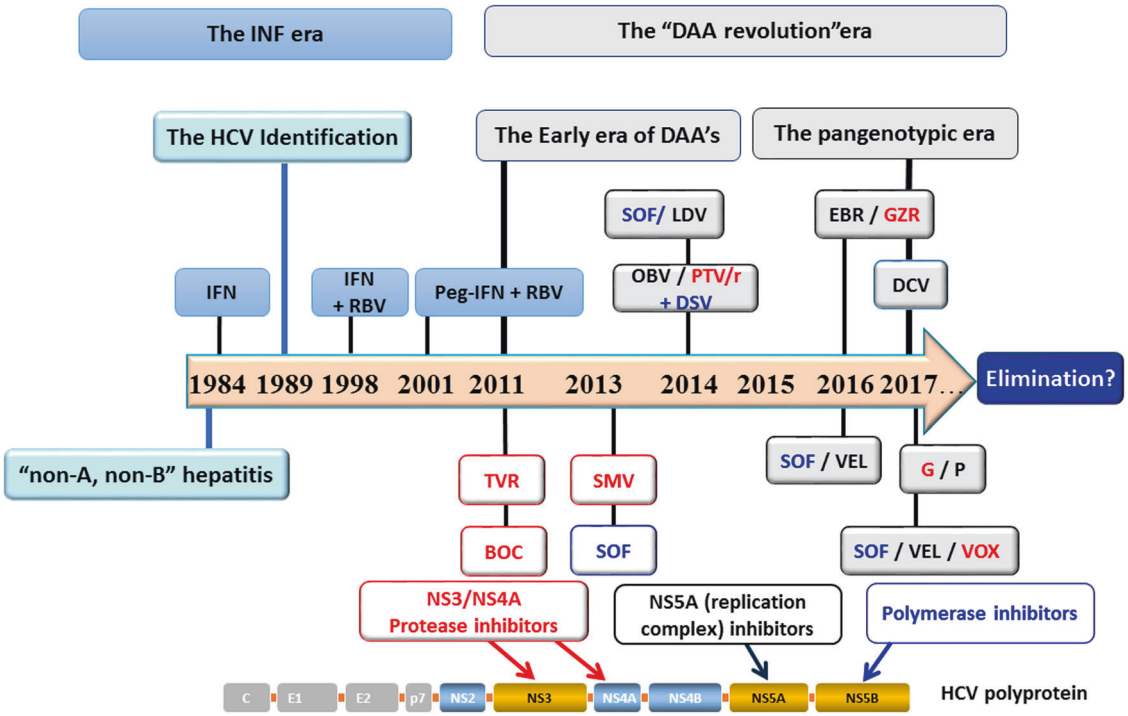


**Fig. 1** Summary of the hepatitis C virus history and the antiviral treatments against the Hepatitis C virus infection. IFN = Interferon; RBV = Ribavirin; the protease inhibitors are in red (TVR = Telaprevir; BOC = Boceprevir; SMV = Simeprevir; PTV/r = Paritaprevir boosted by ritonavir; GZR = Grazoprevir; G = Glecaprevir; VOX = Voxilaprevir); the polymerase inhibitors NS5B are in yellow (SOF = Sofosbuvir; DSV = Dasabuvir) and the replication complex NS5A inhibitors are in white (LDV = Ledipasvir; DCV = Daclatasvir; EBR = Elabsvir; VEL = Velpatasvir; P = Pibentrasvir)

developments but could be a less expensive and as effective test as the viral load quantification.

The development of the serological tests allowed on the one hand the identification of the subjects having met the HCV (presence of anti-HCV antibodies) and the detection of the HCV RNA by RT-PCR in the serum the identification of the subjects having an active infection. Thus a patient with anti-HCV antibodies and undetectable HCV RNA is a patient exposed but cured of his infection. Serological tests allowed for a mass screening including blood donors. After the identification of hepatitis B virus markers (anti-HBc or HBs antigen) leading to the exclusion of blood donation, the identification of anti-HCV antibodies reduced the risk of "transfusion" contamination by HCV related to blood products (blood, immunoglobulins, anti-hemophilic factors, fresh frozen plasma, etc.). Before this screening, the risks were approximately 5 to 10% per transfused blood pellet; they are today about 1 to 700,000 to 1 million, corresponding to occult infections despite the viral genomic diagnosis in blood bank.

The HCV identification thus had a major individual and collective effect, transforming the diagnosis and prevention of nosocomial or community-based risk, particularly among drug-using patients.

## The major scientific steps

### HCV life cycle

HCV is a small, enveloped, positive single-stranded RNA virus belonging to the *Flaviviridae* family, genus *Hepacivirus*. The enveloped particles have an icosahedral diameter of 56–65 nm [10], while the viral core is around 45 nm [11]. It is important to understand the key stages of the HCV viral cycle in order to understand the mode of action of different treatments even if the molecular mechanisms underlying this cycle are not completely understood and remain extremely complex. We have therefore selected important steps in this cycle and their protein actors, in order to introduce therapeutic objectives and the particular relationship of HCV with the liver.

The first step in the HCV replication cycle is its entry into the cell through the interaction of its E1 and E2 surface glycoproteins with the baso-lateral hepatocyte membrane, in contact with the blood stream. HCV can be associated with lipoproteins in the serum, thus escaping neutralizing antibodies [12]. As many other viruses, the initiation of HCV entry seems to utilize for attachment glycosaminoglycans (GAGs) [13, 14]. The HCV particle interacting with

lipoprotein, it is more likely that the apolipoprotein E is responsible for the interaction with GAGs [15]. Many membrane molecules seem to be the target of the pathogen and allow its entry, including ubiquitous CD81 (tetraspanin family protein -TSPAN28) [14, 15], the LDL receptor, claudin-1 (Cldn1) or occludin (OCLN) [16–18]. In vivo, its entry into the cell is done in several steps: the envelope glycoprotein E2 interacts with a co-receptor that is scavenger receptor B1 (SR-B1), and with CD81 [19]. The interaction between CD81 and the E2 glycoprotein appears to be essential for initiating the adsorption [12], then the receptor complex with attached virion is moving to the tight junction, where an interaction with proteins claudin-1 and occluding set up. Finally, other cellular factors such as Epidermal Growth Factor (EGF) receptor [20] and the Niemann-Pick C1-like 1 (NPC1L1) cholesterol uptake receptor [21] are likely involved in HCV entry. Subsequently, the virus is internalized in clathrin vesicles and fused with early endosomes [22–25]. The acidification of the vacuole allows the membrane fusion of the virus, the virus capsid is then released and destroyed while the viral RNA is released in the cytosol. Once in the cystosol, the viral RNA is used for both processes the replication and the polyprotein translation. The RNA translation into polyprotein occurs in endoplasmic reticulum (ER) and is initiated by binding of the 5′UTR IRES to the ribosome [26]. The primary translation product is ~3000 amino acid long polyprotein precursor which contains structural and non-structural proteins of HCV. Then, the polyprotein is cleaved by host and viral proteases into three structural proteins (Core protein, envelop proteins E1 and E2) as well as seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) of the viral replication machinery [12] and in addition a Frameshift protein (F protein) or Alternate reading frame protein (ARFP). The functions of ARFP in the viral life cycle remain to be elucidated [27, 28] and could modulate the dendritic cells function and stimulate the T cell responses [29, 30].

The viral RNA will be replicated by the protein NS5B, the RNA-dependent RNA polymerase (RdRp) containing the GDD motif in its active site [31]. For HCV RNA replication, the polarized positive HCV RNA genome synthesizes a negative strand HCV RNA by the NS5B RNA-dependent RNA polymerase. The newly synthesized negative strand of HCV RNA may act as a template to synthesize the positive strand of viral RNA [32–34].

After an accumulation of structural proteins and the viral RNA in the cytosol, the morphogenesis of virions can start. HCV needs a liver-specific microRNA named miR122 to replicate properly. The latter recruits proteins in 5′ viral RNAs, thus preventing their degradation by intracellular exonucleases [35, 36].

The life cycle of HCV seems to be related to that of lipoproteins: beyond its association with them to escape the immune system in the blood and facilitate its entry into hepatocytes, they are also necessary for its morphogenesis. The Core protein, forming the viral capsid, will bind to intracellular lipid droplets to initiate the virion morphogenesis. The replication of the virus completely changes the distribution of intracellular lipid droplets: they are physiologically distributed equitably throughout the cytosol of the hepatocytes but are found concentrated in the perinuclear domain during the replication of the virus. In addition, apolipoproteins A1, B, C1, C3, and E are found on the surface of the envelope of viruses. Only Apo E seems strictly necessary for the viability of virions. Finally, if one blocks certain proteins necessary for the genesis of VLDL, such as MPT (microsomal triglyceride transfer protein), the virus can no longer replicate. The NS5A protein plays an important role in the assembly of the virus, in the lipid protein C-droplet stage. The lipid-capsid combination will surround the freshly replicated RNA and then bind with the other structural proteins of the glycoprotein envelope (E1 and E2) derived from the endoplasmic reticulum [37–41]. After entering the cell, its replication and translation of its proteins, as well as the assembly of its various components, the virion is ready to be exocyted and to infect new cells [42].

## Cloning and sequencing of HCV, pseudo-particles: the understanding of HCV replication cycle

The HCV genome was identified in 1989 by cloning it from infected chimpanzee, while in humans the amounts were too low for detection [6]. The first complete full-length HCV cDNA clone was constructed from the HCV strain H77 (genotype 1a). The HCV RNA transcribed from this clone, then followed by several full-length HCV RNAs was found to be infectious after intrahepatic injection in a chimpanzee. The HCV viremia was detected at week 1 and increased from $1 \times 10^2$ genomes/mL to $1 \times 10^6$ genomes/mL at week 8 [43, 44]. Since these HCV clones were found to replicate inefficiently in vitro, this limitation was resolved by R. Bartenschlager et al. when subgenomic HCV replicon, cloned from the HCV genome was constructed after transfection into the Huh7 cells [45]. Several studies demonstrated that the virus and host factors were important for the HCV replication in cells; some mutations in the wide-type (wt) consensus sequence efficiently contributed to the replication and the adaptation to the host cells but if these replicons with adaptive mutations could replicate with a high efficiency, they were not able to produce infectious particles in vitro. Finally, a selectable HCV replicon was constructed containing the full-length HCV cDNA of the genotype 2a infectious clone JFH-1 (the only HCV strain

reported to induce fulminant HCV-related hepatitis) and was shown to produced infectious particles in vitro and in vivo [46]. The most efficient construct is the genotype 2a/2a clone which consists of J6CF and JFH-1 derived sequence [47]. The HCV replicon is remarkably valuable for studying HCV replication and for testing new antiviral drugs. The HCV subgenomic replicons containing reporter genes (luciferase, secreted alkaline phosphatase and chloramphenicol transferase) facilitated the study of the HCV infection. This high-throughput screening assay allowed the visualization and tracking of the HCV replication complex in living host cells without affecting HCV replication [48, 49].

HCV pseudotyped particles were constructed with chimeric genes expressing HCV (genotype 1a) envelope E1 and E2 proteins (HCVpp) and the transmembrane and cytoplasmic tail of vesicular stomatitis virus G protein. These pseudotyped particles allowed a detailed study of the role of HCV receptors in the early steps of HCV infection (adsorption and viral entry) [50, 51] and for testing new antiviral drugs [52]. All these major discoveries have been previously detailed [26, 53].

## Non-invasive tests of fibrosis improving screening and individualizing therapies

Given their limited efficacy and their poor tolerance, interferon-based therapies were restricted to patients with significant fibrosis. The evaluation of hepatic lesions was only performed by liver biopsy. This has been revolutionized by the development of non-invasive fibrosis tests evaluating both the necro-inflammation activity (A) and the fibrosis stage according to different scoring system [54]. At the same time blood tests (Fibrotest, Fibrometer, Hepascore, FIB-4 or APRI) [55, 56] or morphological tests including pulse elastometry [57, 58], which measures a shearing force corresponding to the liver stiffness makes it possible. These tools make it possible to evaluate F fibrosis on a conventional Metavir scale of 0–4, where F0 and F1 correspond to a null or minimal fibrosis as opposed to medium F2 fibrosis, extensive F3 or cirrhotic F4 which justify not only a therapeutic treatment but also a follow-up of the patients because of the risks of hepatocellular carcinoma.

## The polymorphism of IL28B

Well-established on-treatment and baseline predictors of sustained virological response (SVR) to pegylated interferon and ribavirin (PEG-IFN/RBV) in patients with chronic hepatitis C virus (HCV) genotype 1 infection include rapid virological response (RVR; undetectable HCV RNA at week 4), low baseline viral load (<600,000 IU/mL), non-black race, and absence of severe fibrosis or insulin resistance [59, 60]. For some years, low serum levels of the 10 kDa interferon gamma-induced protein (IP-10) have also been associated with a better PEG-IFN/RBV response [61].

Candidate genes have long been targeted to explain the differences in host antiviral response, and it is now well established that host genetics plays a role in the response to IFN-based therapy in HCV infection [62]. Five GWAS investigations described several single nucleotide polymorphisms (SNPs) in the *IL28B* gene region on chromosome 19 as being highly predictive of spontaneous clearance of acute hepatitis C infection [62], response to PEG-IFN α/RBV therapy in the general population as well as in human immunodeficiency virus (HIV) co-infected individuals and liver transplant recipients in whom both donor and recipient *IL28B* haplotypes contribute to the probability of treatment response [63, 64].

The GWAS data demonstrated an association between variations at the *IL28B* gene locus and outcomes in HCV infection, but did not identify a causal variant responsible for these effects: the specific immunologic mechanisms involved in HCV clearance associated with *IL28B* genotype remain elusive and a functional link between *IL28B* genotype and liver cytokine expression has not been established [65]. *IL28B* encodes for IFN- λ3 which belongs to the family of type III IFNs; type III INFs effect their antiviral activity by activating the JAK-STAT pathway, which leads to the induction of IFN stimulated genes (ISGs) from interferon stimulated response elements (ISREs) in the nucleus [65]. Thus, it is involved in the T-cell adaptive immune response [66] and *IL28B* has been associated with increased $CD8^+$ cytotoxic T cell responses. Interestingly, it has been demonstrated that in non-responders, some interferon-stimulated genes were upregulated before treatment. In addition, minor alleles of *IL28B* polymorphisms (i.e. *rs8099917* G and *rs12979860* T) have been associated with reduced *IL28B* expression in peripheral blood mononuclear cells [66]. Thus, *IL28B* genotypes may play a role in viral containment, and it is suggested that *IL28B* polymorphisms associated with poor HCV clearance may actually be protective against hepatic necro-inflammation and fibrosis progression, particularly in patients with HCV genotypes other than 1 [67].

## A chronic infection with liver and extra-hepatic consequences

The natural history of viral infection C is characterized by hepatotropism and lymphotropism of the virus (Fig. 2). Hepatotropism accounts for the risks of chronic hepatitis (there is no risk of fulminant hepatitis outside the only strain of genotype 2 at the origin of the first replicon) and of cirrhosis and hepatocellular carcinoma like all chronic hepatitis [68]. Lymphotropism is characterized by HCV

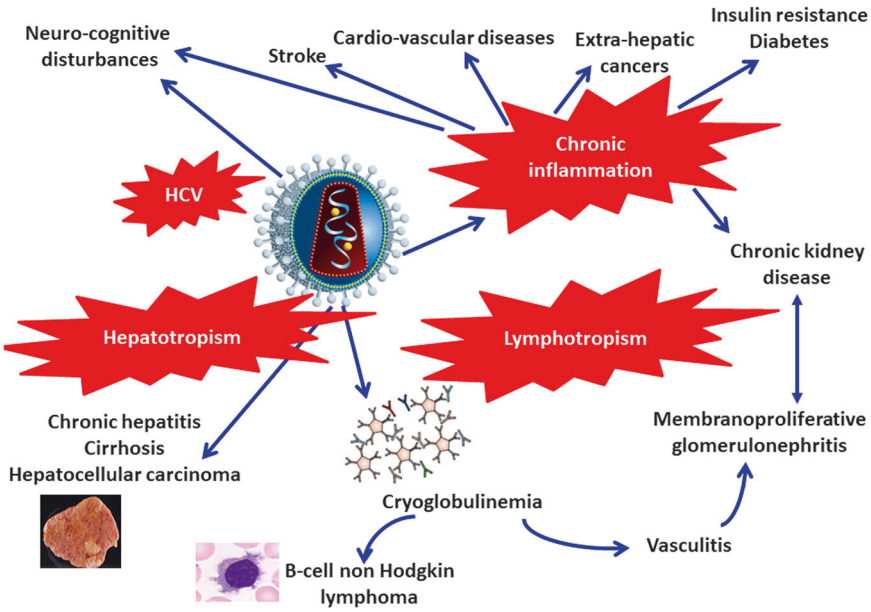


**Fig. 2** The natural history of HCV infection combining hepatic and extra-hepatic manifestations (which may combine manifestations of cryoglobulinemic vasculitis and of chronic inflammation)

replication within B cells and explains the detection of cryoglobulinemia in about half of infected patients. This cryoglobulin is predominantly of type II associating a monoclonal IgM contingent and a polyclonal IgG contingent, and more rarely a type III cryoglobulinemia. It is a protein complex associating the virus with antiviral antibodies and rheumatoid factor that will be deposited in the walls of small and medium-caliber vessels causing cryoglobulinemic vasculitis responsible for cutaneous involvement (purpura, necrotizing vasculitis), rheumatologic (polyarthritis of the small joints), renal (membranoproliferative glomerulonephritis), and neurological manifestations with frequent peripheral neuropathies and rarely central attacks [69–71]. At most, the B lymphocyte infection can lead to a clonal selection responsible for lymphoma predominantly Non-Hodgkin B-cell lymphoma (splenic villous lymphoma, but sometimes more diffuse lymphomas) [72, 73].

The chronic infection that occurs in three quarters of infected subjects is also responsible for chronic inflammation that will lead to extra-hepatic manifestations associating neurocognitive disorders, insulin resistance with a risk 1.5 times higher of diabetes, a risk two to three times higher of cardio-, cerebro- or reno-vascular diseases and an increased risk of extra-hepatic cancers [69–75]. These liver and extra-hepatic events account for a ten-fold higher mortality in patients with antibodies to HCV with detectable viral C RNA compared to those without detectable HCV RNA or in patients who have never met HCV [74, 75]. Extra-hepatic mortality is twice as frequent in patients with active infection as in patients without active viral infection C or without prior HCV exposure. When HCV infection is confirmed, it is important to evaluate the clinical consequences of hepatic and extra-hepatic infections. The evaluation of hepatic lesions was previously performed only on the basis of a liver biopsy and has been revolutionized by the development of non-invasive fibrosis tests (see above). Patients with "significant" fibrosis (extensive F3 or cirrhotic F4) or even intermediate (F2) but with hepatic co-morbidities justify not only a priority therapeutic management and therefore a virological cure, a hygiene and dietary education to reduce chronic alcohol consumption, overweight or metabolic syndrome (liver co-morbidities) but also a follow-up because of the risk of occurrence of hepatocellular carcinoma, admittedly reduced but not zero [68].

Thus, HCV infection is not only a hepatic infection but a systemic disease [69–75] whose consequences are less related to a direct toxicity of the virus than to immuno-mediated mechanisms: chronic hepatitis is mainly related to a destruction of hepatocytes by specific cytotoxic T lymphocytes recognizing the viral antigens expressed on the surface of the cells.

In immunocompetent and immunocompromised patients with little, or no intrahepatic damage, including inflammation, high levels of the HCV replication have been reported [76]. In about 30% of HCV liver transplanted patients, despite the high levels of HCV replication, a recurrent hepatitis is developed one year after transplantation. However, high levels of an intrahepatic HCV replication are usually tolerated by the host immune system. A lymphomononuclear infiltrate represented mainly by $CD8^+$ T cells is expected to play a major role in the viral containment, though other subsets, such as $CD4^+$ T and natural killer (NK) cells, and regulatory T cells (Treg) are considered [77]. The intrahepatic $CD4^+$ and $CD8^+$ T cells can recognize HCV structural and nonstructural antigens [78].

However, why in most patients the immune response cannot resolve the infection, remains obscure. In fact, cytotoxic $CD8^+$ T cell-mediated killing could be blunt by a predominant Treg response [79].

## The only chronic viral infection that is virologically cured

The biology of HCV is simple with a positive-polarity HCV-RNA that will be translated into a polyprotein that will be split by a protease into different structural and non-structural proteins. The NS3/4 protease, the NS5B polymerase are like the key enzymes in viral replication as well as the NS5A protein or replication complex which participates not only in the replication of the viral RNA but also in the assembly of the viral particles. The specific inhibition of these proteins from the years 2005 allowed a control of the viral multiplication [80]. Viral replication and viral organogenesis are exclusively cytoplasmic, which facilitates the targeting of antiviral drugs. In contrast to HIV or hepatitis B virus (HBV), there is no reservoir, no pro-viral DNA, no microchromosome (HBV cccDNA) and no genomic integration.

This explains that one can obtain with the treatments a virologic cure, the so-called SVR, defined by undetectable HCV-RNA at 12 weeks after the infection or after the end of the treatment which corresponds to a true virological cure. HCV RNA undetectability in the serum is accompanied by undetectability in peripheral blood mononuclear cells and in hepatocytes testifying to the complete and lasting nature of virologic cure [81]. This cure is confirmed by organ transplantation of infected subjects who have benefited from effective treatment, unlike HBV for example, transplantation (derogatory) of these organs, and despite deep immunosuppression, does not lead to any infection [82].

## Clinico-biological benefits of virological cure and reversibility of manifestations

Virologic cure is usually accompanied by clinical improvement or even clinical cure of liver and extra-hepatic manifestations [71, 75, 83–89]. This explains the expected reduction in mortality from hepatic and extra-hepatic impacts of chronic infection. As an example in the prospective CIRVIR cirrhotic compensated cohort of ANRS-INSERM, we observed a reduction in the risk of the HCC occurrence at 3 and 5 years (13.6 20.6% versus 3.3% and 8.8% in cured patients, respectively) [90]; in cured patients, HCC is observed only in cases of hepatic comorbidity (metabolic syndrome, overweight, diabetes, alcohol abuse). In addition to the reduced risk of HCC observed in cirrhotic and non-cirrhotic patients, a virological healing also reduces liver and overall mortality in patients [75, 91]. The reduction in hepatic mortality is at least in part, related to the ability to remodel fibrosis at all stages of the disease, including the possibility of cirrhosis reversibility that contributes to this reduction in mortality [85, 86]. Alongside the significant reduction in liver risk (HCC and decompensation) in cirrhotic patients, there is a similar reduction in the risk of bacterial infections and a reduction in vascular risks (myocardial infarction, stroke or peripheral arterial disease) with a reduction from 9.1 to 2.3% at 3 years and 12.3 versus 3.5% at 5 years in cirrhotic patients cured compared with non-cured patients [92]. An extensive fibrosis or cirrhosis is associated with an increased risk of carotid arteriosclerosis, and oral antiviral therapies allow rapid reduction of carotid intimal thickness [93].

## Antiviral treatments

For more than 20 years Interferon for its antiviral and immune-stimulatory properties has been used as the main treatment for chronic infection with HCV [9, 59, 60].

Pegylation after 1997 resulted in weekly subcutaneous rather than tri-weekly injections, and the addition of Ribavirin, a nucleoside analogue, in the early 1990s significantly increased the treatment efficacy [94]. Their limitations were mainly poor clinical tolerance (flu-like syndrome, acuity of dysimmunitary conditions, neurocognitive disorders aggravated by Ribavirin) and biological (myelosuppression with neutropenia and thrombocytopenia for Interferon, haemolytic anemia for ribavirin). The SVR rate increased from about 6% to at most 50% with 48-week treatments for the most common genotypes 1 and 4 (24 weeks for genotypes 2 and 3 with a SVR rate of about 75%) [59]. A large number of factors limited therapeutic efficacy, extensive fibrosis, overweight, genotype 1, HIV-associated infection or insulin resistance (see above). This limited efficiency and this difficult tolerance of interferon-based treatments explain that availability of direct oral antivirals, specific inhibitors of viral proteins, has been a real therapeutic revolution. The first protease inhibitors, Telaprevir and Boceprevir, used from 2011 to 2014, were combined with standard treatment with pegylated interferon and ribavirin: they allowed a halving of the treatment duration of genotypes 1 and 4 (24 weeks) and cured about three quarter of the patients [95] but the safe issues remained. Since 2014, the combination of 2–3 antivirals has been used to cure almost all patients [80, 83, 84, 96–100]; the duration of the pangenotypic treatments available since 2017 are 8–12 weeks with one to three capsules per day (Fig. 1). The efficacy of these pangenotypic treatments (RVP > 97%) completely removed the factors of poor response to treatment that can be given in all clinical situations [96–100].

Therapeutic recommendations are today to treat all patients infected with HCV by prioritizing those with

advanced liver diseases (fibrosis) or extra-hepatic (vasculitis), risks of rapid progression of fibrosis (liver comorbidities or transplants) or risks of community diffusion [83, 84]. The benefit of these treatments is not only individual but also collective by reducing the risk of infection and infection/re-infection in risk communities such as men who have sex with men (MSM) [101] or drug addicts [102, 103].

The only limits that can be avoided today are the drug interactions, the therapeutic observance and the rare side effects associated with these treatments [104].

In summary, the history of HCV ends with this great pangenotypic efficacy of multiple combinations, easy to use 8–12 weeks with one to three pill(s) per day and little problem of tolerance. The virological cure allows a clinical benefit with at worst a stabilization and at best a reversibility of the clinico-biological manifestations. This explains the short 30 years from the discovery of the virus to a policy of elimination proposed by the WHO in 2016 [4].

## HCV elimination

With the antiviral efficacy and good tolerance of pangenotypic drugs, the elimination (and not eradication in the absence of an effective vaccine) is feasible provided that the screening and access to care policies are improved. It is considered that only 1% of the infected population worldwide has been treated and cured [105]; this is, of course, linked to the policy lack of screening and access to care but also the drugs price. Of the approximately 5 million subjects treated worldwide, probably 3 million have been treated with low-cost generic treatments.

The provision of universal treatment and the simplification of therapeutic strategies should make it possible to hope for the effectiveness of elimination policies [106] subject to: (1) improving screening policies through rapid diagnostic orientation and "Point of Care" tests allowing, in the different structures of care, to identify the infected subjects with active infection and to initiate the treatments ("test and treat" policy); (2) to open beyond the hospital and specialized hepato-gastro-enterology, infectiologist or internist structures an access to the prescription; (3) "decentralize" patient care by relocating diagnostic and treatment policies to sexual health structures, care facilities in different communities, prisons, addiction centers, maternity wards, migrant care centers, psychiatric services. The provision of easy-to-use and low-cost treatment should make this elimination possible.

The elimination as defined by WHO is feasible in European countries, and even planned for 2025 in France. It is achieved in Iceland, expected in Egypt but seems difficult in the US because of the epidemic HCV related to intravenous drug use and very challenging in sub-Saharan Africa.

## Compliance with ethical standards

**Conflict of interest** SP has received consulting and lecturing fees from Bristol-Myers Squibb, Janssen, Gilead, MSD, Abbvie and grants from Bristol-Myers Squibb, Gilead, Roche and MSD. The remaining author declares that she has no conflict of interest.



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