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The Role of Interferon for the Treatment of Chronic Hepatitis C Virus Infection

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Contents

Abstract For many years the only available therapy for chronic hepatitis C virus (HCV) infection was interferon-based therapy. Interferons are a family of cytokines that are an essential part of the body's natural response to viral pathogens. In 1991, interferon-α (IFN-α) injections were first approved by the Food and Drug Administration for the treatment of HCV infection and remained the backbone of therapy until late 2014. As monotherapy, IFN-α injected thrice weekly yielded low sustained virologic response (SVR) rates. In 1998, the addition of ribavirin, a broad-spectrum, non-specific antiviral agent, decreased liver inflammation alone and, in combination with IFN-α, increased the SVR rate; however, the addition of ribavirin also increased side effects. In the early 2000s, IFN-α plus ribavirin combination treatment was further improved by the development of longer-acting pegylated IFN-α (PegIFN-α). While this reduced the need for subcutaneous injections from three times a week to

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once a week which improved patients' adherence, the increase in SVR with PegIFN-α over standard IFN-α was relatively modest. Further, drug-related side effects remained problematic, limiting HCV treatment uptake and effectiveness. In the early direct-acting antiviral (DAA) era, PegIFN-α and ribavirin were used in combination with DAAs to prevent drug resistance and increase the SVR rate. With the advent of combination DAA regimens, the role of IFN-α decreased dramatically and, in late 2017, IFN-α was no longer recommended by professional societies as a first-line treatment for any HCV genotype or patient population, marking the end of the IFN-α era.

Keywords Chronic infection, Hepatitis C virus, Inflammation, Interferon, Therapy

1 Introduction

Scientific discoveries related to the structure and replication of the hepatitis C virus (HCV) set the stage for the development of direct-acting antivirals (DAAs) for the treatment of HCV infection [1]. Prior to these breakthroughs, the foundation of HCV treatment was recombinant interferon alfa (IFN-α) which induce non-specific antiviral and immunologic activity against HCV in infected persons (Table 1).

Table 1 The timeline of interferon therapy for hepatitis C viral infection

Year	Therapeutic development
1986	IFN-α first used to treat "non-A, non-B hepatitis"
	Normalized ALT levels for 25–40% patients after 2–3 months
1989	HCV identified as the cause of most cases on non-A, non-B hepatitis
1991	FDA approval of IFN-α 3MU by subcutaneous injection thrice weekly for 24 or 48 weeks
	SVR of 12–16% for persons with HCV genotype infection
1999	The addition of ribavirin to IFN-α significantly improved rates of SVR to 35–45%
2001	PegIFN-α subcutaneous injection weekly plus ribavirin emerges as the standard of care for the treatment of chronic HCV infection
	SVR of 70–90% in genotypes 2 and 3 HCV infection
	SVR of 40–50% in other genotypes (including genotype 1)
2011	Boceprevir and telaprevir (NS3/4A protease inhibitor) approved by the FDA in combination with PegIFN-α and ribavirin
	Triple therapy introduced with PegIFN-α, ribavirin, and DAA
	SVR of 75% in genotype 1 HCV infection
2013	FDA approval of sofosbuvir (NS5B polymerase inhibitor) plus PegIFN-α and ribavirin as well as the first interferon-free regimen of sofosbuvir plus ribavirin
2017	AASLD/IDSA guidelines no longer recommend the use of interferon for any patient population or HCV genotype infection

IFN interferon, *HCV* hepatitis C virus, *ALT* alanine aminotransferase, *FDA* Food and Drug Administration, *SVR* sustained virologic response, *DAA* direct-acting antivirals, *AASLD* American Association for the Study of Liver Diseases, *IDSA* Infectious Diseases Society of America

While in the era of combination HCV DAA therapy the role of interferon has dramatically diminished, IFN-α was the cornerstone of HCV treatment from 1991 until late 2014 [2].

Interferons are soluble glycoproteins and cytokines, small proteins involved in cell signaling, that are an essential part of the body's natural response to viral infection [3]. There are many different interferons, and they are classified as types I, II, and III according to their receptor binding [3]. For HCV treatment, type I interferons are the most commonly used, mainly interferon-α (IFN-α) but also IFN-β [3], while the type III IFN-λ showed some promise [4].

Before HCV was identified as the agent mainly responsible for non-A, non-B hepatitis, IFN-α showed promise as an effective treatment [5]. However, early treatment regimens had some shortcomings; in many patients, the responses were disappointing, and as IFN-α has a short half-life, this meant patients needed subcutaneous injections three times a week. The addition of daily ribavirin, a broad-spectrum antiviral agent, improved the number of patients with a favorable response, however, at the expense of increasing side effects [6]. Moreover, the attachment of inert polyethylene glycol to create pegylated IFN-α (PegIFN-α) reduced the rapid degradation and clearance of IFN-α. Improved pharmacokinetics meant high levels of IFN-α could be sustained for extended periods of time, reducing the frequency of injection to once weekly [7]. However, even with these improvements, cure from HCV remained suboptimal with PegIFN-α and ribavirin, which lead to further research to discover more effective therapy with a better safety profile [3].

IFN-β has achieved excellent results for patients with genotype 1 infection who are mainly poor responders to standard treatment [8]. Receptors for type I interferons are expressed on all cells, whereas the expression of IFN-λ receptors is more localized. This observation suggests that IFN-λ is a useful alternative treatment for patients who experience severe side effects from interferon treatment [4]. Other recombinant interferon proteins have also been investigated including IFN-α2b fused with human serum albumin, known as albinterferon [9], and the consensus interferon (CIFN), an artificial interferon with the most common human IFN-α subtype amino acid at each position in the protein sequence [10].

As DAAs have become more widely available and less expensive, interferon alfa is no longer used to treat HCV infection in most regions, and very few persons with chronic HCV infection patients are expected to use this agent in the future [2]. This review aims to present the history of interferon therapy for patients infected with HCV.

2 Interferons

Interferons are a heterogeneous class of soluble glycoproteins that are expressed in response to viral or bacterial infection [3]. Interferons are released as the first line of defense by infected cells, and this then protects the neighboring uninfected cells against viral infection [11]. There are three types of interferon, types I, II, and III,

classified according to the structure of their membrane cell surface receptors. The antiviral properties of these proteins have led to the therapeutic use of recombinant interferons for viral infections including hepatitis C and B virus [11]. Also, interferon has broad application in treating various diseases including multiple sclerosis, leukemia, melanoma, human papillomavirus infection, chronic granulomatous disease, and malignant osteoporosis [12–14]. In many of these situations, they have been found to complement various antiviral drugs [11].

Type I interferons are cytokines that bind to the IFN-α/β-receptor (IFNAR). Type I interferons include multiple IFN-α subtypes and IFN-β, IFN-ε, IFN-κ, and IFN-ω [15]. For HCV infection, interferon therapy has mainly involved IFN-α, a type I interferon. When IFN-α binds IFNAR, this activates the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway. Several hundred interferon-stimulated genes are then stimulated by JAK/STAT to provide antiviral, antiproliferative, antitumor, or immunomodulatory actions [16]. Two subtypes of IFN-α were used to treat HCV infection, IFN-α-2a and IFN-α-2b; these are similar in structure but bind with different affinities to the IFNAR receptor subunits 1 and 2 [17]. In clinical trials, the efficacy and adverse profiles of IFN-α-2a and IFN-α-2b were similar and mostly indistinguishable from a clinical perspective [18].

3 Standard Interferon Alfa Monotherapy

HCV cure is measured by the demonstration of a sustained virologic response (SVR) defined as undetectable HCV RNA by polymerase chain reaction (PCR) after cessation of antiviral therapy [19]. SVR was initially assessed at 24 weeks after stopping therapy but, more recently, undetectable HCV RNA 12 weeks (SVR12) after therapy has been accepted as evidence of HCV cure [19]. In 1986, IFN-α was first used as a monotherapy for HCV [5], before the discovery of HCV as the cause of disease in most persons with non-A, non-B hepatitis in 1989 [20]. In these early investigations, treatment efficacy was measured biochemically by testing alanine aminotransferase (ALT) level as a measure of ongoing liver injury from HCV [21, 22].

Initially, IFN-α monotherapy regimen was administered as IFN-α-2b three million units (MU) subcutaneous injections three times a week for 24 weeks; approximately, 25 to 40% of persons treated with this regimen achieved normalization of serum ALT level by the end of the treatment which was a significant advance for a disease with no prior therapeutic options [23, 24]. Unfortunately, the ALT response was only sustained in 8–9% of patients after stopping IFN-α monotherapy, and the most effective IFN-α regimens were prolonged courses of treatment over 12 to 18 months [25]. However, in those with sustained ALT normalization, later studies confirmed these outcomes were strongly associated with the absence of detectable HCV RNA and long-term follow-up of patients indicated improved clinical outcomes [26]. In addition to low and heterogeneous response rates, IFN-α monotherapy was also associated with adverse side effects including flu-like

symptoms, hematological toxicity, elevated liver enzymes, nausea, fatigue, and autoimmune, thyroid, and psychiatric sequelae [27]. In light of long treatment durations with a low likelihood of sustained response and nearly universal side effects, many patients did not initiate or failed to complete IFN-α monotherapy.

4 Standard Interferon Alfa and Ribavirin Combination Therapy

From 1991 until 1998, IFN-α monotherapy was the only treatment available for chronic HCV infection. Due to limited effectiveness, rates of treatment uptake and, among those treated, SVR were low during this period. The next breakthrough in HCV therapy was the addition of the non-specific antiviral ribavirin to IFN-α monotherapy. Discovered in 1970, ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) is a guanosine nucleoside analogue with broad-spectrum antiviral activity [28]. Even now, its full mechanism of action in the treatment of HCV is not fully understood [31–33]. Interestingly, ribavirin monotherapy did not demonstrate antiviral activity in persons chronically infected with HCV [29]; however, serum ALT levels and liver inflammation decreased in some patients while taking ribavirin [30, 31]. The observed biochemical response led to clinical trials of IFN-α alone and in combination with ribavirin. When used in combination with IFN-α, ribavirin achieved higher SVR than IFN-α alone resulting in a sustained virologic response in approximately 40% of persons receiving combination therapy [6, 32, 33]. On the basis of large randomized controlled trials, the combination of IFN-α-2b plus ribavirin was approved for the treatment of chronic HCV infection. In the first study, McHutchison and colleagues randomized 912 HCV treatment-naïve patients with HCV infection to receive the standard IFN-α-2b alone or in combination with ribavirin for 24 or 48 weeks. The SVR rate was markedly higher in persons who received combination therapy for either 24 weeks or 48 weeks (31–38%) compared to patients who received IFN-α-2b alone for either 24 weeks or 48 weeks (6–13%) [34]. In the second study, Poynard and coworkers randomized 832 treatment-naïve patients with HCV into three groups: IFN-α-2b plus ribavirin for 24 weeks, IFN-α-2b plus ribavirin for 48 weeks, or IFN-α-2b plus placebo for 48 weeks. SVR was achieved in 43% and 35% of patients treated with combination therapy for 48 weeks and 24 weeks, respectively, and only 19% of those treated with IFN-α-2b monotherapy [35]. In these studies, response to interferon plus ribavirin was associated with HCV genotype 2 or 3 infection, lower baseline HCV RNA level (<2 million copies/mL), younger age, female sex, and less liver fibrosis. While the mechanism of action of ribavirin was and is incompletely understood, the addition of ribavirin to IFN-α led to a substantial increase in SVR, largely by reducing the number of persons who experienced HCV relapse after stopping treatment. In one study, the magnitude of the biochemical response to ribavirin monotherapy appeared to predict the response to combination therapy [36]. Regardless of the mechanism,

the combination therapy was a major advance in HCV therapy limited only by the adverse effects of the two-drug regimen [37]. Compared to placebo, the addition of ribavirin led to more side effects which were treatment-limiting for some patients, including hemolytic anemia hemolytic anemia, cough and dyspnea, rash and pruritus, and nausea. Also, ribavirin is teratogenic, bringing additional concern regarding pregnancy before and immediately after treatment with this agent [38].

The most significant adverse event related to ribavirin is dose-dependent hemolytic anemia, leading to a 2- to 3-g decline in hemoglobin in most persons. In some studies, persons with a greater magnitude of hemoglobin decline were more likely to achieve SVR, suggesting that the degree of anemia was associated with ribavirin exposure [39]. The mechanism of hemolytic anemia is thought to be related to phosphorylation of ribavirin inside the cells to ribavirin monophosphate [40]. Red blood cells lack 5′ nucleotidase and alkaline phosphatase needed to dephosphorylate and transport ribavirin monophosphate, so ribavirin monophosphate accumulates [41]. Ribavirin monophosphate is also phosphorylated further to ribavirin diphosphate and then ribavirin triphosphate. High levels of ribavirin triphosphate then interfere with the normal ATP-dependent systems within the red blood cells, which can result in hemolysis [42]. This anemia was managed with ribavirin dose reduction and, in some circumstance, epoetin alfa to stimulate the production of RBC from the bone marrow.

The approval of standard IFN-α-2b plus ribavirin by the US Food and Drug Administration (1998) marked a significant step forward in HCV treatment. The duration of combination HCV treatment was 24 weeks for persons with HCV genotype 2 or 3 infection and 48 weeks for those with HCV genotype 1 infection. In Europe, the EASL International Consensus Conference allowed for the use of IFN-α-2b plus ribavirin for 24 weeks in persons with HCV genotype 1 and low levels of HCV RNA at baseline ($<2 \times 10^6$ copies/mL) [43]. Of note, the next breakthrough in HCV treatment was nearly a decade later with the approval of the HCV NS3/4A protease inhibitors, telaprevir, and boceprevir, in 2008.

5 Pegylated Interferon Alfa Monotherapy

Before the approval of the first HCV DAAs, the field witnessed an incremental advance in HCV treatment with the development of longer-acting interferon alfa injections. In 1991, standard IFN-α-2b as thrice-weekly injections led to peaks and troughs in interferon exposure which contributed to lower efficacy and also increased side effects due to the fluctuating exposure. In 2000, the issue of short interferon half-life was addressed by the addition of inert polyethylene glycol (PEG) to IFN-α which resulted in decreased degradation and clearance, increasing the half-life of interferon and consequently permitting less frequent weekly dosing while maintaining higher and sustained interferon levels [44, 45]. Ultimately, two pegylated interferons or peginterferons (PegIFNs) were approved for use in patients with chronic HCV infection, PegIFN-α-2a (Pegasys®, Hoffmann-La

Roche, Nutley, NJ) and PegIFN-α-2b (Peg-Intron®, Schering-Plough Corp., Kenilworth, NJ). PegIFN-α-2a is formed by the addition of a 40-kDa branched PEG moiety covalently linked to the standard interferon alfa-2a molecule. This alteration created a molecule with a mean terminal half-life of approximately 80 h and allowed for once-weekly dosing with a fixed dose of 180 μg. PegIFN-α-2b is formed by the addition of a 12-kDa linear PEG moiety covalently linked to standard IFN-α-2b molecule [46]. This alteration created a molecule with a mean terminal half-life of approximately 40 h and allowed for once-weekly dosing with a weight-based dose of 1.5 μg/kg of body weight. PegIFN-α-2b and PegIFN-α-2a were approved by the US Food and Drug Administration in 2001 and 2002, respectively, and replaced standard interferon.

The basis for the shift from standard to long-acting pegylated IFN was randomized studies comparing the formulations. Several clinical trials demonstrated higher rates of SVR in persons receiving PegIFN monotherapy versus standard IFN monotherapy [7, 47, 48]. In one study, Zeuzem et al. [7] randomized 531 HCV treatment-naïve patients to receive either PegIFN-α-2a weekly or IFN-α-2a thrice weekly for 48 weeks; the SVR rate was 39% in patients randomized to PegIFN group compared to only 19% in those who received standard IFN. In a dose-finding study, Reddy and colleagues found that PegIFN-α-2a 180 μg weekly was the optimum dose for efficacy, safety, and tolerability in patients without advanced liver disease [47]. In another phase 3 trial, PegIFN-α-2a was evaluated in persons with compensated cirrhosis for whom safety and efficacy of interferon were generally worse than was observed in other patient population [49]. The cirrhotic patients were randomized to receive IFN-α-2a thrice weekly, PegIFN-α-2a 90 mcg weekly, or PegIFN-α-2a 180 mcg weekly with SVR rates of 8%, 15%, and 30% in each group, respectively [49]. These studies demonstrated that PegIFN was more effective than standard IFN, leading the way for the use of PegIFN plus ribavirin for most patients. However, PegIFN monotherapy was the standard of care for persons who were not able to take ribavirin including those not able to tolerate hemolysis such as persons with renal insufficiency, hemoglobinopathies, and cardiovascular disease.

6 Pegylated Interferon Alfa and Ribavirin Combination Therapy

The next step in HCV drug development was the combination of PegIFN plus ribavirin therapy which was the part of the standard of care for the treatment of chronic HCV infection for more than a decade from 2001 to October 2014. In phase 3 clinical trials of PegIFN-α-2a and PegIFN-α-2b in combination with ribavirin, persons with HCV genotype 1 infection had SVR rates of 46% and 42%, respectively [50–52]. However, the cross-study comparison of these combination treatments was difficult because the studies used different doses of ribavirin. The trials of PegIFN-α-2a were conducted with weight-based dosing of ribavirin (1,000 mg/day

for persons less than 75 kg and 1,200 mg/day for persons greater than or equal to 75 kg) which was the standard dosing schema with standard interferon. In contrast, the trials of PegIFN-α-2b were conducted with fixed-dose ribavirin (800 mg/day) for all participants. Since SVR rates were generally higher in persons with greater ribavirin exposure (ribavirin mg per kilogram), this led to uncertainty as to the efficacy of the two types PegIFN in combination with ribavirin. Also, differences were observed concerning the SVR rates achieved in patients enrolled in the United States and Europe with higher response rates in the non-US patient population. This uncertainty prompted the conduct of the largest HCV clinical trial ever conducted, the IDEAL study. The study was a large, multicenter, prospective, randomized, controlled study performed in the United States to provide a head-to-head comparison of the antiviral efficacy and adverse events of PegIFN-α-2a and PegIFN-α-2b [53]. Overall, 3,070 patients with HCV genotype 1 infection were randomized to 48 weeks of treatment with 1 of 3 PegIFN plus ribavirin regimens: PegIFN alfa-2b standard-dose (1.5 mcg/kg) plus weight-based ribavirin (800–1,400 mg/kg), PegIFN alfa-2b low-dose (1.0 mcg/kg) plus weight-based ribavirin (800–1,400 mg/kg), or PegIFN-α-2a 180 mcg plus weight-based ribavirin (1,000–1,200 mg/kg). The SVR rates achieved in all three groups were similar: 39.8% with the standard-dose PegIFN-α-2b, 38.0% with low-dose PegIFN-α-2b, and 40.9% with PegIFN-α-2a. The safety profile was also similar among the three groups; serious adverse events occurred in 8.6 to 11.7% of patients [53]. In contrast, two studies in Europe showed better efficacy for PegIFN-α-2a compared to PegIFN-α-2b in combination with ribavirin, mostly in HCV genotype 1 [54, 55].

The most important contribution of the IDEAL study was the identification of host genetic polymorphism by a genome-wide association study (GWAS) that explained much of the heterogeneity observed in viral response to interferon, namely, the lower SVR rates observed in persons with African ancestry compared to those with European or Asian ancestry. Ge and colleagues performed genotyping on 1,671 patients who were treated in the IDEAL study and consented to genetic testing; all were HCV treatment naïve and had HCV genotype 1 infection [56]. The researchers found that a polymorphism on chromosome 19 (re12979860) located upstream of the gene for interleukin28B (IL28B) was strongly associated with SVR in all patient populations. The presence of the IL28B CC genotype was associated with an approximately twofold higher SVR rate compared to the presence of the CT or TT genotype. Interestingly, the frequency of the CC genotype was highest in persons of Asian ancestry and lowest in those of African ancestry and explained 56% of the observed lower SVR rates in persons with African ancestry. Thompson and coworkers incorporated this single-nucleotide polymorphism into models of existing baseline predictors of SVR following PegIFN plus ribavirin treatment and found that IL-28B genotype had the highest odds ratio favoring SVR (CC vs non-CC: odds ratio, 5.2; 95% CI, 4.1–6.7; $P < 0.0001$) [57]. After adjustment for IL28B status, other independent predictors of higher SVR were lower HCV RNA level (<600,000 IU/mL), Caucasian or Hispanic ethnicity, minimal liver fibrosis (METAVIR stages 0–2), and lower fasting blood glucose. Factors associated with SVR following PegIFN plus ribavirin are summarized in Table 2. In addition to the

Table 2 Factors related to response to treatment of HCV with PegIFN and ribavirin

Factor	Influence on treatment
HCV genotype	Genotypes 1 and 4 have decreased response compared to genotypes 2, 3, and 5
Baseline viral level	Patients with a low level (less than six million U/mL) show a better response
Race	Caucasians show a better response. This is related to interleukin-28B genotype and HCV-specific immune response
Host polymorphism near the gene for interleukin-28B	The chance of cure is more than doubled with homozygosity for the C allele at the rs12979860 SNP
Liver fibrosis/cirrhosis	Minimal fibrosis predicts a better response
Body weight	Patients weighing less than 85 kg have a better response
Age	Patients younger than 40 years have a better response
Gender	Females have a better response to treatment than males
Alanine aminotransferase level	Patients with ALT quotient of 3 or more (mean serum ALT level/upper limit of the normal range) have a better response
HCV-specific immune response	Patients with a high CDC+ T cell count have a better response
Insulin resistance and steatosis	The absence of these both predicts a better response
Statin use	Statin use before treatment predicts a better response to treatment
Response during treatment	Patients with either a rapid or early virologic response have a better overall response to treatment
Adherence to treatment	Patients who do not adhere to treatment (less than 80% total doses of IFN and ribavirin received less than 80% of the expected duration of therapy) have a poor response

IFN interferon, *HCV* hepatitis C virus, *Peg* pegylated, *ALT* alanine aminotransferase, *SNP* single-nucleotide polymorphism

factors identified in the IDEAL study (limited to genotype 1 infection), patients with HCV genotype 2 or 3 infection are more responsive to PegIFN plus ribavirin than those with HCV genotype 1 infection. For example, patients with genotype 2 or 3 infection achieved SVR rates between 70 and 80% following treatment of 24-week duration with a lower dose of ribavirin (800 mg daily); in contrast, those with HCV genotype 1 infection achieved SVR rates of 40% following treatment of 48-week duration with higher-dose ribavirin (1,000 or 1,200 mg daily) [58]. On-treatment HCV RNA kinetics was a significant predictor of SVR; for example, persons who failed to achieve decline from baseline in HCV RNA level > two log10 IU/mL (null response) were found to have a low likelihood of achieving SVR with continued treatment. This observation led to the widespread adoption of HCV RNA monitoring at treatment week 12 and the early discontinuation of PegIFN plus ribavirin for futility in persons with a null response. Similarly, the achievement of rapid virologic response (RVR) which is defined as undetectable HCV RNA after 4 weeks of PegIFN plus ribavirin was strongly associated with SVR. In a randomized controlled trial by Moreno et al. [59], it was suggested that HCV genotype 1 patients with low

baseline HCV RNA level (400,000 IU/ml) and undetectable HCV RNA at week 4 can achieve SVR with shorter duration of therapy of 24 weeks which was helpful for patients having a better side effects profile compared to patients who received extended therapy of 48 weeks [59]. In the study by Thompson et al., the achievement of RVR was not predictive of SVR in persons with the favorable IL28B CC genotype but was strongly associated with SVR in those with non-CC genotype [57]. In a model that included baseline predictive factors and RVR, RVR had the largest odds ratio for SVR (odds ratio, 9.1; 96% CI, 5.8–14.0 vs non-RVR non-CC genotype reference). Based on these findings, IL28B genotype and RVR were widely used in clinical practice to manage patients with HCV genotype 1 infection in whom treatment was considered (IL28B) or initiated (RVR) to limit the exposure to PegIFN plus ribavirin to the subset of persons most likely to achieve SVR.

7 Other Types of Interferons

Because of the limited response to PegIFN-α treatment in some patient populations with HCV and unpleasant side effects, alternative treatments have been investigated to different extents. In some Asian countries, IFN-β therapy, a type I interferon with similar antiviral activity to IFN-α, has been utilized, especially for patients who found adherence to standard IFN-α regimens difficult or who had encountered treatment failure [8, 60, 61]. Recombinant IFN-β monotherapy or in combination with ribavirin was suggested for patients intolerant to IFN-α [62]. Natural IFN-β monotherapy used short term has been shown to be useful for patients with acute HCV infection and patients infected with HCV genotype 2 with low HCV RNA levels. Its use in combination with ribavirin for 48 weeks or for 24 weeks was also effective for some patients with HCV genotype 1 or HCV genotype 2 infection and for patients who had been challenging to treat with standard PegIFN-α plus ribavirin therapy [63]. The efficacy of IFN-β therapy in persons who did not respond to IFN-α may have been due to the development of anti-IFN-α associated with non-SVR in some patients treated with this agent [64].

The systemic side effects of IFN-α may in part be due to their general expression in most cells in the body that is typical of type I interferons. IFN-λ is a type 3 interferon with more restricted tissue expression. PegIFN-λ was investigated in persons with chronic HCV infection and found to have similar rates of SVR to PegIFN-α with less systemic side effects and bone marrow suppression. However, this agent was also associated with emergent elevations in serum ALT levels; this hepatotoxicity led to the discontinuation of the development of this agent for chronic HCV infection [65]. The single-nucleotide polymorphisms (SNPs) in the IL28B gene and associated with treatment outcome in HCV patients treated with PegIFN-α/ribavirin have also been identified for IFN-λ [66]. Interestingly, studies are ongoing with PegIFN-λ as a potential treatment for chronic hepatitis D virus infection [67].

Other recombinant interferon fusion proteins have also been investigated. For example, IFN-α2b fused with human serum albumin, known as albuferon, had

similar antiviral properties to IFN-α in cultured cells and in HCV-infected patients [9]. This albumin fusion also prolonged the half-life of albuferon compared to PegIFN-α [68]. Clinical studies showed that albuferon had similar antiviral effects to PegIFN-α [69, 70]. But concern over serious pulmonary adverse events resulted in the discontinuation of this agent.

Finally, consensus interferon (CIFN) is an artificial interferon designed to have the most common human IFN-α subtype amino acid at each position in the protein sequence [10]. In treatment-naive patients with chronic HCV, CIFN plus ribavirin showed high SVR, and it also showed positive results in nonresponders [71–73]. However, a short half-life meant CIFN required daily injection, and therefore, this interferon was not widely adopted in clinical practice.

8 The Addition of HCV Direct-Acting Antivirals to Peginterferons Plus Ribavirin

As molecular biological methods have provided a better understanding of the viral protein structure and the life cycle of HCV, drugs that act against specific viral targets, HCV DAAs have been developed [74]. Early studies of the first-generation DAAs, the HCV NS3/4A protease inhibitors telaprevir and boceprevir, demonstrated the rapid emergence of HCV drug resistance. This observation led to the combination of these drugs with PegIFN and ribavirin, increasing the SVR to as high as 75% for persons infected with HCV genotype 1 [75–77]. However, these combination therapies were problematic in clinical practice due to the marked increase of side effects with the addition of the DAAs to PegIFN plus ribavirin. These added side effects included severe anemia (telaprevir and boceprevir) and severe skin rash (telaprevir) and coupled with a high daily pill burden led to poor patient compliance and limited uptake in clinical practice [78]. Not unexpectedly, SVR with these triple-combination therapies was also influenced by the patient and virus characteristic that had been identified in the PegIFN plus ribavirin studies. For example, the HCV RNA response to a 4-week lead-in phase of PegIFN-α plus ribavirin was highly predictive of SVR following the addition of boceprevir. Further, studies also confirmed the impact of the patients' IL28B genotype on the likelihood of SVR; in some studies persons with the favorable IL28B CC genotype could be treated for shorter durations of therapy with boceprevir triple therapy [79]. These first-generation HCV NS3/4A protease inhibitors were replaced by the safer, more effective HCV NS5B inhibitor sofosbuvir; however, the initial approval of this DAA for genotype 1 patients included the combination of sofosbuvir plus PegIFN and ribavirin [80]. Subsequently many DAAs have been approved for treatment of HCV as part of interferon-sparing regimens [81]. Currently, interferon-containing regimens are not recommended for use in clinical practice because of the excellent efficacy and safety of pan-genotypic DAA regimens; the use of these regimens has expanded dramatically with the reduced cost of the DAAs due to commercial competition and generic

manufacturing [82]. In the United States, the interferon era officially ended in September 2017 when the HCV treatment guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America removed interferon as a recommended therapy for any patient population or HCV genotype [83]. The last indication for its use had been for persons with advanced renal disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2) and HCV genotype 2 or 3 infection; this recommendation was dropped in favor of treatment with the pan-genotypic DAA combination of glecaprevir/pibrentasvir which includes DAAs that are not cleared by the kidneys [84].

9 Conclusions

Interferon was the backbone of HCV treatment for nearly 25 years (1991 until 2014), and, in the United States, interferon-based therapy remained a recommended HCV treatment for a least one patient population (HCV genotype 2 or infection plus advanced renal insufficiency) until September 2017. The removal of interferon from HCV treatment has had the combined effect of increasing antiviral efficacy since the response to interferon was heavily influenced by patient and virus characteristics and increasing effectiveness with the elimination of the severe side effects associated with interferon which increased the number of people eligible and willing to be treated for chronic HCV infection. Indeed, the removal of interferon has paved the way for efforts to eliminate HCV infection globally using safe, tolerable, and effective oral DAA regimens to cure persons living with chronic HCV infection.

Compliance with Ethical Standards

Conflict of Interest Author declares that he has no conflict of interest.

Ethical Approval Not applicable.

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