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MINIREVIEWS

Factors associated with the response to interferon-based antiviral therapies for chronic hepatitis C

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Abstract

Hepatitis C virus (HCV) infection is a major health concern worldwide. Interferon-α (IFN-α) therapy has been the main antiviral treatment for more than 20 years. Because of its established antitumor effects, IFN-based treatments for chronic HCV infection still have a clinical impact, particularly for patients with high risk conditions of developing hepatocellular carcinoma, such as older age and advanced liver fibrosis. As a result of exhaustive research, several viral factors, including NS5A amino acid mutations such as the IFN sensitivity-determining region and the IFN/ribavirin resistance-determining region, and mutations of amino acids in the core protein region (core 70 and 91) were shown to be associated with the response to IFN-α treatment. In addition, among the host factors related to the response to IFN-α treatment, polymorphisms of the *interleukin-28B* gene were identified to be the most important factor. In this article, we review the factors associated with the efficacy of IFN-α treatment for chronic HCV infection. In addition, our recent findings regarding the possible involvement of anti-IFN-α neutralizing antibodies in a non-response to pegylated-IFN-α treatment are also described.

Key words: Anti-interferon-α neutralizing antibody; Interferon-α; Direct-acting antiviral; Interferon-free treatment; Chronic hepatitis C

Core tip: Interferon-α (IFN-α) therapy has been playing a central role in anti-hepatitis C virus (HCV) strategies, and several viral and host factors related to the treatment efficacy have been identified. After the development of pegylated-IFN-α (Peg-IFN-α), the clinical impact of anti-IFN-α neutralizing antibodies in the treatment for HCV infection has not been sufficiently addressed. We recently found that anti-IFN-α neutralizing antibodies were associated with a non-response to Peg-IFN-α treatment. Our findings provide important information for the treatment of chronic hepatitis C in the clinical setting.

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INTRODUCTION

HCV infection is a major health concern worldwide. Approximately 150-160 million individuals are assumed to be infected with hepatitis C virus (HCV), and chronic HCV infection causes fibrotic liver changes and cirrhosis[1,2]. Furthermore, HCV-associated cirrhotic patients are at a high risk of developing hepatocellular carcinoma (HCC). The eradication of HCV is considered to terminate the chronic liver inflammation and decrease the risk of cirrhosis-associated clinical complications. Therefore, the main goal of anti-HCV treatment has been focused on how to eradicated HCV and "cure" the patients. Interferon-α (IFN-α) therapy has been playing a central role in anti-HCV strategies. Exhaustive studies have been carried out to increase the efficacy of IFN-α treatment, and many viral and host factors have been identified that affect the response to treatment[3,4].

Recently, new agents which directly inhibit the replication of HCV have been developed [direct-acting antivirals (DAAs)], and new IFN-free regimens which include only DAAs have been introduced, with promising clinical efficacy. IFN-free treatments are currently approved as standard therapies in the recent guidelines of the American Association for the Study of Liver Disease and the European Association for the Study of the Liver[5,6]. However, even after a HCV infection has been resolved, elderly patients with advanced liver fibrosis still have a high risk at developing HCC, and many Japanese patients have these features[7,8]. Previous studies have shown that IFN therapy significantly reduces the risk for hepatocellular carcinoma in HCV-infected patients[9-11], while the antitumor effect of IFN-free treatment has not yet been sufficiently evaluated. IFN therapy is therefore still considered to have clinical significance, particularly in Japanese HCV-infected patients with a high incidence of HCC. In this article, we review the factors associated with the efficacy of IFN-α therapy for chronic HCV infection. In addition, we also discuss our recent findings regarding the role of anti-IFN-α neutralizing antibodies (NAbs) in IFN-α based therapy.

VIRAL FACTORS ASSOCIATED WITH THE RESPONSE OF HCV INFECTION TO IFN TREATMENT

It was known that there were patients who showed chronic liver damage irrespective of the absence of hepatitis A virus or hepatitis B virus infection (nonA-nonB hepatitis: NANB hepatitis). In 1986, Hoofnagle *et al*[12] reported that recombinant IFN treatment normalized the aminotransferase levels of patients with NANB hepatitis, and suggested the potential clinical utility of IFN treatment for NANB hepatitis. In 1989, HCV was identified by Choo *et al*[13], and many patients with NANB hepatitis were demonstrated to be infected with HCV. In 1992, IFN-α monotherapy was approved as the first antiviral therapy for chronic hepatitis C (CH-C) in Japan. At that time, the factors associated with the efficacy of IFN-α treatment were unclear, and IFN-α treatment was sensationally reported as a "dream" therapy that would cure about 30% of CH-C patients.

However, intensive research demonstrated several factors that were related to the efficacy of treatment[3,4]. Among these factors, serogroup 1 and a high viral load (100 KIU/mL: Currently 5.0 log copies/mL) were particularly associated with poor treatment efficiency, and most Japanese patients who achieved a sustained viral response (SVR) were infected with viruses of serogroup 2 or had a low viral load. Unfortunately, about 60%-70% of Japanese CH-C patients were infected with viruses of serogroup 1 (mostly genotype 1b) and had a high viral load (so-called "1b/high" patients), and fewer than 5% of these patients experienced a successful eradication of HCV by the IFN-α treatment. Therefore, many Japanese "1b/high" patients showed unfavorable outcomes despite their high expectations to be free from HCV infection, and a few years after the approval of IFN-α treatment for CH-C, the "1b/high" patients came to be considered patients who should not be treated using this regimen, because they were predicted to be at risk for experiencing adverse events without achieving a SVR.

Although only a small percentage of patients with 1b/high disease obtained a SVR, this finding indicated that there were patients who achieved a SVR irrespective of infection with "1b/high" viruses. In 1996, Enomoto *et al*[14] compared the amino acid sequences of HCV between patients with a SVR and those without a SVR. They found that the amino acids sequence of the NS (non-structural) 5A region was closely related to the eradication of HCV genotype 1b in response to IFN-α monotherapy. They named the specific region (NS5A 2209-2248) the interferon sensitivity determining region (ISDR). The identification of the ISDR had a high clinical impact; however, the HCV phenotype with many mutations of amino acids in the ISDR was observed in only in a small percentage of "1b/high" patients, and HCV eradication remained a major challenge for Japanese clinicians.

In 2000, ribavirin (RBV) became clinically available, and about 20%-30% of "1b/high" patients succeeded in obtaining a SVR following RBV treatment. This gave physicians the impression that they could also cure patients infected with "1b/high" viruses even without mutations of the ISDR. However, because of the presence of an ISDR-independent response, the identification of additional factors that were associated with the response to IFN-α plus RBV combination therapy was needed. Akuta *et al*[15]

reported that mutations of amino acids in the core protein region (core 70 and 91) were significantly associated with a non-response to combination therapy. Subsequently, a specific region other than the ISDR (NS5A 2334-2379) was found to be related to the treatment response to IFN-α plus RBV therapy, and was reported as the Interferon/Ribavirin Resistance-Determining Region (IRRDR)[16,17]. Overall, the most important viral factors associated with the response to IFN-α treatment for HCV were determined to be the amino acid sequences in the core region and NS5A region, such as mutations of core 70, core 91, ISDR and IRRDR.

HOST FACTORS ASSOCIATED WITH THE RESPONSE TO IFN TREATMENT FOR HCV INFECTION

From 2004, when pegylated-IFN-α (Peg-IFN-α) became available, Peg-IFN-α plus RBV combination therapy came to be a standard treatment, which provided a SVR in about 40%-50% of the patients with "1b/high" infections. Since IFN-α treatment depends on the immune response of patients, the characteristics of HCV-infected patients were considered to affect the treatment efficacy. Some host factors such as aging, sex, and the degree of liver fibrosis, had long been known to be related with the treatment efficacy. However, the major predictive factors for the response to IFN-α treatment were the amino acid sequences of HCV in the NS5A and core regions, and no decisive host factor had been discovered.

In 2009, findings regarding the gene polymorphisms of interleukin 28B (IL28B) were reported[18-20]. A genome-wide analysis showed that patients with a risk allele had about 40-fold higher resistance to Peg-IFN-α plus RBV combination therapy. These three papers were extremely important, because these studies included various races of patients from different counties, thus demonstrating that the involvement of IL28B in the treatment response to the Peg-IFN-α plus RBV combination therapy was not limited to patients with a specific ethnic back ground. In Japan, the *IL28B* gene polymorphism rs8099917 is commonly assessed, and patients with the G allele are predicted to show a poor response to Peg-IFN-α plus RBV combination therapy. Among the host factors associated with the response to the IFN-α treatment for HCV, the IL28B sequence is considered to be the most important factor.

MUTATIONS OF HCV RESULTING IN RESISTANCE TO DAAS

As described above, the Peg-IFN-α plus RBV treatment increased the rate of HCV eradication in patients with "1b/high" infection; however, more than half of the patients with "1b/high" infections still experienced treatment failure. In order to provide a higher SVR rate than Peg-IFN-α plus RBV treatment, DAAs which directly inhibit the replication of HCC were developed, and triple therapy (the Peg-IFN-α plus RBV plus a DAA) became available in Japan. In 2011, telaprevir, which inhibits the activity of the protease in the NS3/4A region, was first approved for clinical use in Japan, and the combination of telaprevir with Peg-IFN-α plus RBV increased the SVR rate of the "1b/high" patients over 60%[21,22]. Recently developed drugs such as simeprevir[23,24] and vaniprevir[25,26] were shown to provide a SVR in over 80% of the "1b/high" patients when one of these agents was administrated in combination with the Peg-IFN-α plus RBV. Although the DAAs showed strong anti-HCV effects, DAA monotherapy induced viruses with drug-resistant mutations, and the main role of a DAA has thus been to increase the treatment efficacy of Peg-IFN-α and RBV. Many viral mutations associated with resistance to DAAs have been reported[27,28]; however, factors associated with the response to the IFN treatment are also considered to be important in the efficacy of DAA-containing triple therapy. Table 1 summarizes the various factors associated with the efficacy of interferon-based treatment.

THE ROLE OF ANTI-IFN-α NEUTRALIZING ANTIBODIES IN IFN-α TREATMENT

Since IFN treatment involves the exogenous administration of the antiviral drug, patients who receive IFN sometimes develop anti-IFN NAbs. Anti-IFN NAbs inhibit the interactions between IFN and its receptor, and diminish the biological activity of IFN. Anti-IFN NAbs were reported to be associated with a poor response of CH-C treated with IFN, particularly in patients treated with non-natural recombinant IFNs[29-32]. With regard to HCV-infected patients receiving rIFN-α, several previous studies have suggested that anti-IFN-α NAb were more frequently detected in the sera of non-responders than in that of responders[29-32]. Because of the difficulty in obtaining a SVR, Japanese HCV-infected patients with "1b/high" sometimes received multiple kinds of IFN therapy, and frequently develop anti-IFN-α NAbs.

Since non-pegylated IFN-α products were unstable in human sera, the administrated non-pegylated IFN-α has a short plasma half-life (3-8 h), and becomes undetectable within one day[33]. Peg-IFN-α maintains serum concentrations that show antiviral effects for a long time (Peg-IFN-α 2a: 168 h and Peg-IFN-α 2b: 80 h) for two reasons. One reason is that the clearance of IFN-α is decelerated because of the biding of the IFN-α with a high weight molecule agent (polyethylene glycol), and the other is that the Peg-IFN-α product, which is enclosed in polyethylene glycol, can escape from recognition and attack by the host immune system[34].

Since Peg-IFN-α products were designed to be protected from the host immune system, the anti-IFN-α NAb were no longer believed to be of clinical significance after Peg-IFN-α was used as the first-line drug. In 2010, Halfon *et al*[35] measured anti-IFN-α NAbs with a

Table 1 Factors associated with the efficacy of interferon treatment

Factors	Main findings	Ref.
Classically identified viral and host factors		
Age, HCV genotype, Viral load, Liver fibrosis	Older age, HCV genotype 1, high viral load, and advanced liver fibrosis were associated with poor treatment results	[3,4]
Viral factors		
ISDR	Mutations of the ISDR (NS5A 2209-2234) were positively related to the HCV eradication with IFN-α monotherapy	[14]
Amino acid mutations of the core region (Nos. 70 and 91)	Mutations of amino acids were associated with a poor response to IFN-α plus RBV treatment	[15]
IRRDR	Mutations of the IRRDR (NS5A 2334-2379) were associated with a favorable response to the IFN-α plus RBV treatment	[16,17]
Drug resistant mutation[1]		[27,28]
Host factors		
IL28B SNPs	The hero/minor allele of IL28B SNPs was related to a poor response to Peg-IFN-α plus RBV treatment	[18-20]

[1]Resistant mutations to DAAs are only associated with the treatment efficacy of DAA-containing triple therapy. HCV: Hepatitis C virus; ISDR: Interferon sensitivity-determining region; IRRDR: Interferon/ribavirin resistance-determining region; RBV: Ribavirin; SNPs: Single nucleotide polymorphisms; Peg-IFN-α: Pegylated-interferon-α; IL28B: Interleukin 28B; DAA: Direct-acting antiviral.

quantitative sandwich enzyme-linked immunosorbent assay and reported that the presence of anti-IFN-α NAb was not associated with an early viral response (≥ 2 $\log_{10}$ copies/mL reduction in HCV-RNA at week 12 relative to baseline values). However, Peg-IFN-α agents are artificially generated drugs as well as conventional IFN agents, and we therefore asked whether anti-IFN-α NAbs were associated with the treatment efficacy of Peg-IFN-α using an antiviral biological assay method[36].

ANTI-IFN NEUTRALIZING ANTIBODIES IN PEG-IFN-α TREATMENT WITH THE ANTIVIRAL BIOLOGICAL ASSAY METHOD

We studied a total of 129 patients who had received Peg-IFN-α plus RBV treatment at our institute, and evaluated the involvement of anti-IFN-α NAb in the response to the Peg-IFN-α plus RBV treatment. An antiviral biological assay revealed that none of the 82 end-of-treatment responders had developed anti-IFN-α NAbs, while anti-IFN-α NAbs were detected in seven of the 47 NR patients (7/47: 14.9%). When we examined the sera of an additional 83 NR patients who had received Peg-IFN-α treatment at other institutions, 12 patients were proven to be anti-IFN-α NAb-positive (12/83: 14.5%). The patients who had IFN-responsive factors, such as HCV serogroup 2 and major allele homozygotes for the *IL28B* gene, were included in the 19 anti-IFN-α NAb-positive patients; however, all of them were non-responders, suggesting that the presence of anti-IFN-α NAb contributed to the non-response to the Peg-IFN-α treatment[36]. Table 2 shows the published reports regarding the possible involvement of anti-IFN-α neutralizing antibodies in the response to IFN-α treatment for chronic hepatitis C.

Since patients with a non-response to Peg-IFN-α plus RBV therapy often show a poor response to robust triple therapy (Peg-IFN-α plus RBV plus a DAA), the factors associated with the response to IFN treatment were also suggested to have an impact on the new DAA-containing therapy. We recently used the HCV-replicon system with genotype 1b to assess the potential role of anti-IFN-α NAb in the response to DAA-containing triple therapy[37]. Although telaprevir (TVR) monotherapy rapidly reduced the HCV-RNA level *in vitro*, the HCV-RNA level was increased again with the emergence of TVR-resistant viruses. Combination treatment with TVR and IFN-α successfully inhibited the replication of HCV for more than 30 d. However, in the presence of anti-IFN-α NAb-positive sera, the levels of HCV-RNA showed a time course similar to that with TVR monotherapy, and TVR-resistant viruses were detected in the conditioned medium. Our findings suggest that the anti-IFN-α NAb decreased the antiviral effects of IFN-α and caused treatment failure even when used in DAA-containing triple therapy. Indeed, we recently experienced a patient who achieved a SVR with an IFN-free regimen, despite that the patient developed the anti-IFN-α NAb and resulted in NR to the triple therapy. The role of anti-IFN-α NAb in triple therapy (Peg-IFN-α plus RBV plus a DAA) should be clarified in further clinical studies.

CONCLUSION

Although IFN-free treatments are currently recommended in the USA and Europe[5,6], the guideline of the Asian Pacific Association for the Study of Liver Disease[38] includes IFN-based antiviral treatments for CH-C. Because of its antitumor effects, IFN treatment is still important in HCV-infected patients, particularly in Japanese patients who are at a high risk of developing HCC. Viral factors (such as serogroup, viral load, mutations of core 70, core 91, ISDR and IRRDR) and host factors (such as aging, sex, the degree of liver fibrosis and IL28B SNPs) have been identified to be

Table 2 Possible involvement of anti-IFN-α neutralizing antibodies in the response to interferon-α treatment for chronic hepatitis C

Treatment	Cohort	Main results	Ref.
IFN-α monotherapy	47	Fifteen of 47 patients (31.9%) developed detectable levels of NAbs within two to eight months after starting treatment. Patients who developed anti-IFN NAbs showed poor responses to IFN (4/15: 26.6%) compared to antibody-negative patients (26/32: 81.3%) (P = 0.0009)	[29]
IFN-α monotherapy	63	Fifteen of 63 patients were positive for neutralizing anti-IFN-α NAbs. The responsive rate of all patients was 60.3% (38/63), while that of patients with anti-IFN NAbs was 13.3% (2/15), showing that NAbs development could significantly affect the therapeutic efficacy of IFN (P < 0.01)	[30]
IFN-α monotherapy	28	Among 28 patients treated with recombinant IFN-α-2a, anti-IFN-α NAbs were detected in 75% (6/8) of the patients who did not respond to IFN therapy. During IFN treatment, the mean ALT level of anti-IFN negative patients was decreased and continuously suppressed during treatment with the 3 MU of IFN-α-2a, while that of anti-IFN positive patients was reelevated without a dose-reduction of IFN	[31]
IFN-α monotherapy	84	In 84 patients with initial responses to IFN-α treatment, anti-IFN-α NAbs developed in 38.5% (5/13) of patients with breakthrough, as compared to 2.8% (2/71) of complete-responder patients (P < 0.0005) The emergence of anti-IFN-α NAbs three months after the initiation of therapy was the only factor to be predictive of breakthrough (RR = 9.5, 95%CI: 1.6-64.7, P = 0.007)	[32]
Peg-IFN-α plus RBV	42	A total of 42 non-response patients to previous conventional IFN treatment were re-treated with Peg-IFN-α-2a plus RBV. A decrease in HCV-RNA greater than 2 log10 copies/mL at week 12 relative to baseline values was not associated with the presence of anti-IFN-α NAbs (7/19, 36.8% in responders *vs* 6/23, 26.1% in non-responders at week 12; P = 0.73)	[35]
Peg-IFN-α plus RBV	129	A total of 129 patients who received Peg-IFN-α plus RBV were studied. Of the 47 patients who did not achieve an end of treatment response, seven patients (14.9%) were positive for anti-IFN-α NAbs, while no anti-IFN-α NAbs were detected in the 82 end of treatment responders (P = 0.0001). Anti-IFN-α NAbs were associated with a non-response to Peg-IFN-α plus RBV treatment, regardless of the patient IL28B-type and other treatment response-related characteristics	[36]

IFN: Interferon; Peg-IFN-α: Pegylated-interferon-α; RBV: Ribavirin; NAbs: Neutralizing antibodies; ALT: Alanine aminotransferase; RR: Relative risk; HCV: Hepatitis C virus; IL28B: Interleukin 28B.

associated with the response to IFN treatment for HCV infection. In addition, viral mutations resistant to DAAs have become problematic in recent triple therapies.

After the development of the Peg-IFN-α, the clinical impact of anti-IFN-α NAb in the treatment of CH-C was no longer considered. Due to the discrepancy in the results of our study[36] and a previous study[35], perhaps because of different detection methods of NAbs, the association between anti-IFN-α NAbs and a non-response to Peg-IFN-α therapy has not been fully confirmed. However, our recent findings suggest that anti-IFN-α NAb abolished the antiviral effects of Peg-IFN-α, and this finding provides important information for the treatment of CH-C in the clinical setting.

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