Chapter 15
IFN-Based Therapy and Management of Patients

Victor C.K. Lo and Harry L.A. Janssen

Introduction

Interferon alfa (IFN) is an endogenously produced 128-amino acid cytokine that acts as an immunomodulator, enhancing cell-mediated immunity against viruses. Specifically, they are named because of their ability to interfere with viral replication. They also activate natural killer cells and macrophages, and upregulate antigen-presenting cells. Recombinant IFN alfa was approved in the 90s as the first agent for the treatment of chronic HBV. It is administered parenterally.

A study in 2014 investigated the mechanism by which IFN alfa induces a direct antiviral effect. It was found that interferon alfa and lymphotoxin-β receptor activation may induce non-cytolytic degradation of covalently closed circular DNA (cccDNA) via upregulation of proteins of the APOBEC3 family [1]. The degradation of intrahepatic cccDNA would prevent HBV reactivation. Since the genomic DNA was not affected, the authors suggest that the induction of nuclear deaminases, such as those induced by lymphotoxin-β receptor activation, may have potential as a new therapeutic for hepatitis B.

The pegylation of interferon (pegIFN), in which a polyethylene glycol is attached to the interferon protein, extends the half-life of IFN, stabilizes serum concentrations,

V.C.K. Lo, M.A.Sc., C.C.R.P.
Toronto Centre for Liver Diseases, University Health Network,
399 Bathurst Street, 6B Fell Pavilion, Toronto, ON, Canada, M5T 2S8
e-mail: victor.lo@uhn.ca

H.L.A. Janssen (✉)
Toronto Centre for Liver Diseases, University Health Network,
399 Bathurst Street, 6B Fell Pavilion, Toronto, ON, Canada, M5T 2S8

Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
e-mail: Harry.Janssen@uhn.ca

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and reduces the frequency of dosing and side effects, thereby improving patient compliance with treatment. Additionally, it was demonstrated that the use of pegIFN alfa leads to comparable or higher rates of HBeAg loss, HBV DNA suppression, and ALT normalization as conventional IFN [2]. Thus conventional (standard) IFN has largely been replaced with the use of pegIFN alfa. The treatment of chronic hepatitis B (CHB) uses recombinant pegIFN alfa-2a or 2b. PegIFN alfa-2a has a 40 kDa branched peg that is attached to IFN, whereas pegIFN-alfa-2b has a 12 kDa straight chain peg.

Interferon Monotherapy

The advantage of using IFN over oral nucleos(t)ide analogue (NUC) therapies is that treatment duration is finite, usually 48 weeks as recommended by current guidelines for treatment-naive patients, and there is no evidence for drug resistance. However, the frequency of adverse events is higher and is dose-dependent, and patient compliance may be lower due to the need for injection in contrast to the convenience of an oral agent. With the introduction of pegIFN alfa, injection schedules can be reduced from thrice weekly with conventional IFN to only once weekly.

While pegIFN alfa does not result in HBV suppression rates as great as NUCs, it has been shown that there exists post-treatment antiviral benefits which are more durable—a "delayed" effect. In patients with HBeAg-positive CHB, pegIFN alfa induces an early reduction of HBV replication, sometimes with a subsequent hepatitis flare. Using pegIFN alfa for a finite 1-year in HBeAg-positive patients resulted in HBeAg seroconversion rates of 32 % and 29 % respectively, found at 6 months post-treatment follow-up [3, 4]. These HBeAg seroconversion rates are significantly higher and more durable than what has been found with 1 year of NUCs such as LAM, ETV, or TDF. PegIFN alfa has also been shown to induce HBV DNA suppression, HBsAg clearance, normalization of ALT, and histological improvement [5]. Patients who achieve an IFN-induced HBeAg seroconversion also have a reduced risk of developing cirrhosis and HCC, leading to better clinical outcomes for patients.

PegIFN alfa has been used in the treatment of HBeAg-negative patients in whom HBV DNA continues to replicate despite the presence of anti-HBe immunity [6]. Treatment in HBeAg-negative patients with pegIFN alfa has shown a response (defined as HBV DNA below 400 copies/mL for up to 24 weeks after cessation of therapy according to the Peginterferon Alfa-2a Negative Chronic Hepatitis B Study Group) rate of approximately 20 % [5, 7], which is also durable and leads to better clinical outcomes [8]. Thus, a 48 week course of treatment with pegIFN alfa is currently recommended for HBeAg-negative CHB patients who have no contraindications to pegIFN alfa, as treatment is finite and virological response is durable.

A study in 2012 compared the treatment response between HBeAg-negative patients who received pegIFN alfa for 48 weeks with those who received pegIFN alfa for 96 weeks (with a dose reduction from 180 to 135 μg in the latter 48 weeks) [9].

This study examined a group of 128 patients with mostly HBV genotype D. It was observed that more than twice the number of patients who received pegIFN alfa for 96 weeks had a combined response of HBV DNA <3400 IU/mL and ALT normalization at 48 weeks post-treatment. Thus they concluded that extending treatment duration to 96 weeks improves sustained virological responses. However, it is important to consider side effects, as 12 % of patients withdrew from the extension group due to adverse events (AEs). The extended use of pegIFN alfa incurs a higher cost and risk of patient non-adherence, as well, so careful consideration is required before extending pegIFN alfa therapy. Nonetheless, pegIFN alfa is currently only therapeutic option that offers a reasonable chance of sustained off-treatment response.

Several studies examined the long-term effects of interferon use in CHB patients, particularly on survival and hepatocellular carcinoma (HCC). A placebo-controlled study analyzed 101 patients with a follow-up period of 1.1–11.5 years [10]. It was found that the cumulative incidence of HCC development was significantly higher, and the cumulative survival rate was lower in the placebo group compared to the treatment group. These findings were replicated in another study of 165 HBeAg-positive patients treated with IFN with a median follow-up period of 8.8 years [11]. Thus, the authors concluded that IFN results in long-term beneficial effects in terms of reduction of HCC and prolongation of survival.

Interferon Safety and Adverse Event Management

The most frequently reported side-effects associated with the use of conventional IFN were flu-like symptoms including: fever, fatigue, irritability, chills, headache, muscle aches, and local reaction at the injection site [12, 13]. Less common are: anorexia, nausea, insomnia, neutropenia, thrombocytopenia, alopecia, weight loss, and depression. A study in 2005 investigated the safety of pegIFN alfa for the treatment of CHB in 300 patients [13]. They found that all patients reported one or more of the adverse effects known to conventional IFN treatment with no reports of new adverse effects. The rate of dose reduction in the study was 22 % and therapy discontinuation was 9 %. The higher frequency of dose reduction using pegIFN alfa-2a compared to conventional IFN (rate of 10 %) was attributed to increased occurrence of neutropenia. However, while pegIFN alfa induced thrombocytopenia and neutropenia, it was found that the number of infections was low and relatively mild and that bleeding complications were also mild (epistaxis). Patients with liver cirrhosis should have more frequent monitoring, as they are at an increased risk of thrombocytopenia and bleeding complications.

Informing patients about adverse events and adequate treatment of symptoms, such as specific serotonin reuptake inhibitors (SSRIs) for depression, may lead to an increased proportion of patients capable of completing treatment without dose reduction. The use of anti-pyretics and analgesia may also help to relieve other side effects associated with the use of pegIFN alfa, such as flu-like symptoms.

Predicting Response to pegIFN Alfa

Since pegIFN alfa treatment is expensive and associated with considerable side effects, it is of clinical interest and significance to be able to predict which patients will have a high probability of response. Much investigation has been done on serum HBV DNA, ALT and HBsAg levels, HBV genotype and IL28B polymorphisms [14].

Pretreatment Response Prediction

Pretreatment virological, serological, and biochemical parameters such as viral load, HBsAg, HBeAg, and ALT levels as well as host and virus genetic factors have been investigated for their role in predicting response to pegIFN alfa. Being able to reliably predict and identify which patients will likely and unlikely benefit from pegIFN alfa or continuation of pegIFN will serve to increase cost-effectiveness and reduce patient side effects. Pretreatment ALT and HBV DNA levels have been demonstrated to be a reliable factor in helping clinicians form treatment plans [15]. Specifically, high pretreatment ALT levels and low HBV DNA were associated with a higher rate of sustained response to pegIFN alfa.

However, as viral load and ALT levels fluctuate throughout the natural course of disease, they are somewhat unreliable as predictive variables to treatment response. Thus, both host and viral genetic factors, like HBV genotype, have been investigated as a predictor of response to pegIFN alfa treatment. It has been found that CHB patients with HBV genotype A have the best response and that HBV genotype D is associated with poorer responses to treatment compared to other genotypes. Genotype A and D are more common among the Caucasian population, whereas genotypes B and C are more common among Asian populations [3, 16].

A 2012 study demonstrated that the presence of precore (PC) and basal core promoter (BCP) mutations in the viral genome affect the serological and virological response to pegIFN alfa [17] in HBeAg positive disease. Specifically, those with detectable mutant PC/BCP have a lower probability of response (HBeAg loss and suppressed HBV DNA) compared to those with wild-type, irrespective of HBV genotype. Thus, the authors conclude that the presence of wild-type virus is a strong predictor of response and HBsAg clearance. However, another failed to confirm these findings [18], suggesting that further investigation is needed to fully understand the effect of PC and BCP mutations and their predictive value to pegIFN alfa response.

Another study investigated the effects of host genetic polymorphisms on the interleukin 28B gene (IL28B, also known as IFN-λ-3) [19] on pegIFN alfa treatment response in 208 HBeAg-positive CHB patients. While the exact mechanism by which these genetic polymorphisms affect treatment response remain unclear, it was shown that there exists favorable IL28B genotypes (AA for rs12980275 and CC for rs12979860) which increase the probability of achieving a sustained HBeAg

seroconversion with pegIFN alfa. However, some patients maintain detectable HBV DNA and elevated ALT level despite HBeAg seroconversion [20]. While favorable IL28B polymorphisms were a strong predictor for serological response to pegIFN alfa in terms of HBeAg seroconversion, it was found that they are poor predictors for combined responses of HBeAg seroconversion and HBV DNA suppression (HBV DNA <2000 IU/mL). Thus, the authors recommend that genotypic variations in IL28B can be used in combination with other predictors of response such as HBV genotype and pretreatment HBV DNA and ALT levels, but not as a replacement. Another study in 2011 looked at other host genetic polymorphisms such as HLA-DPA1 and HLA-DPB1 as predictors to response to pegIFN therapy in HBeAg-positive patients [21]. Their findings suggest that genetic variations in HLA-DP regions may influence spontaneous and/or treatment-induced HBV clearance, but that further research is required to fully characterize the effects. Altogether, these studies provide evidence that host genetic factors are also important in the response to pegIFN alfa therapy, in addition to viral genotypic factors.

With regard to HBeAg-negative disease, a 2013 retrospective study also examined the effects of IL28B on pegIFN alfa response in CHB patients with mostly HBV genotype D [22]. They similarly found that particular IL28B genotypes are more favorable towards a positive response. Specifically, HBeAg-negative patients with HBV genotype D who carry the CC genotype of rs12979860 IL28B had an increased rate of sustained virological response and HBsAg clearance (3.9-fold higher) than those with the CT or TT genotype.

In contrast to the above two studies, other studies on CHB patients treated with pegIFN alfa demonstrated evidence that polymorphisms near IL28B gene were not associated with on- and post-treatment kinetics of HBV DNA and HBsAg levels [23, 24]. In light of conflicting results, further investigation is needed to fully characterize the effect of IL28B polymorphisms on pegIFN alfa response, particularly for HBeAg-negative patients, and its clinical relevance as a treatment predictor.

In a 2013 study, it was found that baseline HBsAg was the only independent predictor of loss of HBsAg at week 144, after combination pegIFN + ADV treatment for 48 weeks [25]. Specifically, the authors noted that a low baseline HBsAg was a strong predictor for HBsAg loss for HBeAg-negative CHB patients. However, two large multinational studies of patients treated with pegIFN alfa-2a found that baseline serum HBsAg levels did not correlate with antiviral response, regardless of HBeAg status [26, 27]. These conflicting results suggest that further studies are required to validate the predictive value of baseline HBsAg levels for pegIFN alfa response.

Response-Guided Therapy

Strategies to evaluate the effectiveness of pegIFN alfa during the course of therapy is important as well, as stopping treatment early for patients whom it will be ineffective serves to improve cost-efficiency and reduce side-effects. A number of

studies have examined on-treatment parameters for their predictive value in determining treatment-response.

A study in 2013 analyzed the HBsAg levels of 803 HBeAg-positive patients treated with pegIFN [28]. The authors found that on-treatment levels of HBsAg could predict off-treatment response. Specifically, for patients who had serum levels of HBsAg <1500 IU/mL by week 12 of therapy, 45 % achieved response (defined as HBV DNA <2000 IU/mL and HBeAg loss). In contrast, only 14 % achieved a response in those who did not experience HBsAg decline, and only 6 % of patients responded if they had serum HBsAg levels >20,000 IU/mL by week 12. This effect was found to be HBV genotype-dependent, as response rates were low in patients with genotype A or D if there was no HBsAg decline, and B and C if HBsAg levels were >20,000 IU/mL by week 12. By week 24, nearly all patients with serum HBsAg >20,000 IU/mL failed to respond regardless of HBV genotype. This study demonstrates that on-treatment serum HBsAg can be used to guide treatment decisions, particularly with regard to discontinuing pegIFN when HBsAg levels remain >20,000 IU/mL after 24 weeks of therapy.

For HBeAg-negative patients, a study in 2009 observed that an on-treatment HBsAg decline of greater than 1 $\log_{10}$ IU/mL and <10 IU/mL at week 48 was significantly associated with sustained HBsAg clearance 3 years after pegIFN alfa treatment [29].

A 2010 study investigated early on-treatment kinetics of HBV DNA and HBsAg and their predictive power on pegIFN alfa treatment response in HBeAg negative patients [26]. It was found that patients with HBV genotype D who do not experience a decline in HBsAg levels and achieve <2 $\log_{10}$ copies/mL change in HBV DNA by week 12 of treatment do not achieve HBV DNA suppression or ALT normalization 6 months post-treatment. Follow-up studies were conducted to validate this finding, and thus the stopping rule for this study was incorporated into current treatment recommendations for patients with HBV genotype D [30].

Combination of IFN with NUCs for the Treatment of Chronic Hepatitis B

Combination therapy of IFN with NUCs has been investigated as an approach to treating chronic hepatitis B. Theoretically, the antiviral effects of NUCs would strongly suppress HBV DNA replication, and the immunomodulating effects of pegIFN alfa would enhance the host response to eliminate infected hepatocytes. However, the following sections on pegIFN alfa combination with specific NUCs demonstrate that the superiority of combination therapy to monotherapy is not well established. Thus current international guidelines do not support the use of pegIFN alfa in combination with NUCs for the treatment of CHB. However, studies investigating the use of more recently approved NUCs and their combination with pegIFN alfa are currently underway in both HBeAg-positive and HBeAg-negative CHB patients. Additionally, other strategies such as add-on or switch-over to pegIFN alfa from NUC have been explored as alternatives to concurrent pegIFN + NUC therapy.

Combination IFN and Nucleoside Analogues

Lamivudine (LAM)

Many studies have been conducted on the use of pegIFN alfa combined with LAM for the treatment of chronic hepatitis B, as LAM is the first approved NUC for the treatment of chronic hepatitis B. A number of pivotal studies on both HBeAg-positive and HBeAg-negative disease have been described in this section in chronological order respectively.

In a study published in 2005, 307 HBeAg-positive patients were randomized to either pegIFN alfa-2b with LAM or with placebo for 52 weeks [3]. At the end of the follow-up period of 26 weeks, it was found that combination pegIFN + LAM therapy was not superior to pegIFN alfa monotherapy in terms of achieving a sustained response. Specifically, while combination therapy initially had higher response rates on-treatment (lower HBV DNA, higher rates of HBeAg seroconversion), the rates of HBeAg seroconversion, ALT normalization, HBV DNA suppression, and HBsAg clearance at the end of follow-up were similar between the two treatment groups. It was also observed that patients with HBV genotype A and B had a higher response rate than those with HBV genotype C and D. The authors concluded that combined pegIFN alfa-2b + LAM therapy is not superior to pegIFN alfa-2b monotherapy.

Another study in 2005 examined pegIFN alfa-2a monotherapy, LAM monotherapy and combination pegIFN alfa-2a + LAM, for 48 weeks of treatment with a 24 week follow-up [4]. They examined 814 HBeAg-positive patients, mostly infected with HBV genotype B or C. Those who received pegIFN alfa-2a + LAM or pegIFN alfa-2a alone had higher rates of HBeAg seroconversion (32 and 27 % compared to 19 % on LAM monotherapy) and also HBV DNA suppression (32 and 34 % compared to 22 % on LAM monotherapy). Furthermore, 16 patients who received pegIFN alfa-2a had HBsAg seroconversion, whereas none of the patients on LAM monotherapy did. The authors concluded that pegIFN alfa-2a offered superior efficacy over lamivudine in the treatment of HBeAg-positive CHB, on the basis of HBeAg seroconversion, HBV DNA suppression, and HBsAg seroconversion.

A large registration trial for HBeAg negative disease investigated the efficacy and safety of pegIFN alfa-2a alone, LAM alone, or a combination of the two for 48 weeks with a 24 week follow-up [5]. Their trial was placebo-controlled and had approximately 180 patients in each of the three treatment groups. It was observed that pegIFN alfa-2a monotherapy alone or in combination with LAM yielded higher rates of ALT normalization (59 and 60 %) compared to LAM alone (44 %) after follow-up. A similar finding was observed with respect to HBV DNA suppression (<20,000 copies/mL), where rates were higher in pegIFN alfa-2a monotherapy and combination (43 and 44 %) compared to LAM alone (29 %). Using a threshold of HBV DNA <400 copies/mL, the rates were 19 and 20 % compared to 7 % with LAM alone. Thus, while adverse event rates were higher in patients taking pegIFN alfa-2a, such as pyrexia, fatigue, myalgia, and headache, these patients also achieved a higher combined response, which was sustained at least up to 24 weeks post-treatment. The authors also concluded that the addition of LAM to pegIFN alfa-2a

did not improve response rates. This study provides support for the use of pegIFN alfa-2a monotherapy for HBeAg-negative CHB patients over LAM.

The study investigating the treatment responses of pegIFN alfa-treated patients for 48 versus 96 weeks of treatment also found that the concurrent administration of LAM during the first 48 weeks did not improve outcome in HBeAg negative patients [9].

These studies taken together suggest that the concurrent administration of LAM or monotherapy of LAM does not have superior rates of response compared to pegIFN alfa in both HBeAg-positive and HBeAg-negative CHB patients. Other treatment strategies such as add-on or switch-over could be investigated for benefit as well, but as LAM resistance has been well-established, future research may utilize more recent and potent NA like ETV and TDF.

Telbivudine (LdT)

A large randomize-controlled trial performed in HBeAg-positive CHB patients investigating the combination of pegIFN alfa-2a with LdT was published recently [31]. A total of 159 patients were randomized to LdT monotherapy, pegIFN alfa monotherapy, or pegIFN alfa + LdT combination therapy. Although HBV DNA reduction was more pronounced and rapid in the combination therapy group, the rate of occurrence of serious peripheral neuropathy was also significantly higher in this treatment group (7 cases in 50 patients, compared to 1 in 109 in the monotherapy groups). Thus, the trial was terminated prematurely due to these severe side effects, and the authors concluded that the combination of pegIFN + LdT should not be used.

Entecavir (ETV)

There have been few studies on the combinatory use of pegIFN alfa and ETV, a third generation NUC with more potent antiviral activity and lower incidence of resistance compared to older NUCs. ETV is currently recommended by AASLD, EASL, and APASL guidelines for treatment-naive chronic hepatitis B patients, so it is certain that new studies will be published on its use in combination with pegIFN alfa.

A study published in 2014 investigated the serological response rates of add-on pegIFN to ETV therapy in 175 HBeAg-positive CHB patients [32]. Add-on pegIFN treatment (180 μg/week) during weeks 24–48 was associated with a higher rate (19 %) of HBV DNA reduction to <200 IU/mL, compared to patients who continued ETV monotherapy (10 %). Therapy was also discontinued in patients who achieved HBV DNA <200 IU/mL, and it was found that 13 % of patients receiving add-on pegIFN achieved remission compared to 2 % of patients on ETV monotherapy. At 96 weeks post-treatment follow-up, those in the combinatory treatment group also experienced a higher rate of HBeAg seroconversion than those on ETV

monotherapy (26 % compared to 13 %). Thus the authors conclude that the addition of pegIFN to patients already on ETV monotherapy could be a useful strategy to further reduce viral load, prevent relapse, and facilitate the discontinuation of ETV therapy. Unfortunately, this study lacked a pegIFN monotherapy arm.

Another recent study from Asia investigated the efficacy and safety of switching long-term ETV therapy to pegIFN alfa-2a therapy [33] in highly selected patients with low HBeAg levels. A total of 192 HBeAg-positive patients on ETV for 9–36 months were randomized to either switch-over to pegIFN for or continued ETV monotherapy for 48 weeks. It was found that patients who switched to pegIFN achieved higher rates of HBeAg-seroconversion than those who continued on ETV monotherapy (14.9 % vs. 6.1 %), and that the only occurrences of HBsAg loss were confined to the pegIFN treatment group, at a rate of 8.5 %. Thus the authors concluded that switch-over to pegIFN after long-term viral suppression with ETV could be a viable strategy for inducing HBeAg seroconversion and potentially HBsAg loss.

In another 2014 study, 218 treatment-naive, HBeAg-positive Chinese patients were randomized to either pegIFN alfa-2a monotherapy for 48 weeks, concurrent ETV and pegIFN alfa-2a treatment during weeks 13–36, or lead in treatment with ETV for 24 weeks followed by pegIFN alfa-2a [34]. Response rates were evaluated at the end of pegIFN alfa-2a treatment and also at the end of 6-months follow-up. While the addition of ETV suppressed HBV DNA during treatment, the response was not sustained off-treatment at the end of 6-months follow-up. Although therapy was effective, as all three treatment groups achieved significant reduction rates in HBeAg, there was no evidence that combination treatment in either of the treatment sequences yielded superior benefit compared to pegIFN alfa-2a monotherapy in terms of immunological response. Rates of HBeAg seroconversion, HBsAg clearance or seroconversion were also similar between the three groups. Thus, in contrast to the above two studies, the authors concluded in that ETV add-on or pretreatment with ETV was not superior compared to pegIFN alfa-2a monotherapy, and that further investigation on the optimal combination of NUC with pegIFN alfa was required. However, it should be noted that ETV pretreatment in this study was 24 weeks, a shorter duration than the aforementioned studies.

These large studies taken together indicate that there is potential benefit in either switching over or adding-on pegIFN to prior long-term ETV monotherapy, but that the optimal combination or timing has yet to be determined.

Combination IFN and Nucleotide Analogues

Adefovir (ADV)

Relatively fewer clinical trials have been conducted on the use of pegIFN alfa in combination with ADV for the treatment of chronic hepatitis B. As with LAM, ADV is an older generation of NUC, and is likely to see less frequent use for the

treatment of CHB. Studies on both HBeAg-positive and HBeAg-negative CHB patients have been conducted and discussed here.

A study published in 2006 investigated cccDNA change after 48 weeks of combined pegIFN alfa-2b + ADV and its correlation to serological, virological, and histological markers [35]. Twenty-six HBeAg-positive patients were involved in this single arm study, and had biopsies done at baseline and end of treatment. They observed a 2.4 $\log_{10}$ decrease in cccDNA and 2.2 $\log_{10}$ decrease in intrahepatic HBV DNA after 48 weeks of combination treatment, along with a reduction in the number of HBsAg- and HBcAg-positive hepatocytes by 2.5- and 2.3-fold, respectively. Additionally, it was found that serum HBV DNA became undetectable in 13 (54 %) of the patients, 8 patients lost HBeAg with 5 of those patients experiencing HBeAg seroconversion, and 4 patients developed anti-HBsAg. Those who had lost HBeAg had significantly less intrahepatic cccDNA than those who did not. There was also a strong correlation between intrahepatic HBV DNA and serum HBsAg titre. Thus the authors concluded that the combination of pegIFN alfa-2b + ADV can effectively diminish intrahepatic cccDNA, HBV DNA, reflected by a reduction in serum HBsAg levels, and induce a positive serological, virological and histological on-treatment response.

A 2013 study investigated the sustained curative efficacy of ADV add-on therapy to HBeAg-positive patients already on pegIFN alfa-2a monotherapy with poor virological response [36]. They examined a total of 85 patients, with 34 receiving add-on ADV therapy and the remainder continuing on pegIFN alfa-2a monotherapy, both for 6 months. At the end of treatment, it was found that the addition of ADV significantly improved sustained virological and biochemical responses, and higher rates of HBeAg loss (55.9 % vs. 19.6 %) and seroconversion (41.2 % vs. 13.7 %). Thus, they concluded that add-on ADV was beneficial for patients experiencing poor virological response to pegIFN alfa-2a monotherapy. However, this study does not include a follow-up period after treatment, so it is uncertain what the sustained response and relapse rate is.

A study in 2014 investigated a small group of 61 HBeAg-positive CHB patients, randomized to receive either pegIFN alfa-2b alone or pegIFN alfa-2b + ADV for 52 weeks [37]. Analysis at the end of treatment revealed no significant differences in the HBeAg seroconversion rate, but that the rates of undetectable HBV DNA was significantly higher in the combination group. It was also found that thyroid dysfunction was significantly higher in patients receiving combination therapy. However, this study also does not include a follow-up period after treatment and had a relatively small sample size, so it remains to be determined if these findings are sustained in the long-term.

A prospective, randomized trial published in 2009 investigated the safety and efficacy of pegIFN alfa-2a + ADV compared to pegIFN alfa-2a monotherapy in 60 HBeAg-negative CHB patients [38]. Patients received therapy for 48 weeks and follow-up was conducted at 24 weeks post-treatment. It was found that combination therapy resulted in greater on-treatment viral suppression and ALT normalization rates, but that they were not sustained upon treatment cessation at 24 weeks post-treatment. Thus they concluded that while combination pegIFN alfa-2a + ADV

is safe, it was not superior to pegIFN alfa-2a monotherapy in terms of sustained virological and biochemical response.

A study published in 2011 assessed the virological and serological impact of sequential ADV therapy followed by pegIFN alfa-2a in 20 HBeAg-negative patients [39]. Patients received 20 weeks of ADV, followed by 48 weeks of pegIFN alfa-2a with an overlap of 4 weeks, and were then followed up at 24 and 48 weeks post-treatment. It was found that ten (50 %) of the patients experienced a sustained combined response (ALT normalization and suppressed HBV DNA). However, the authors acknowledge their limited sample size and lack of a control group. Thus, they suggest further investigation is needed to fully evaluate the strategy of sequential therapy.

In conclusion, these studies suggest that the use of ADV with pegIFN alfa has potential beneficial on-treatment serological and virological effects, but there is evidence that such benefits are not sustained in the long-term.

Tenofovir (TDF) Therapy

There have not been many clinical trials published on the combinatory use of TDF with pegIFN alfa yet as TDF is the most recent NUC approved for the treatment of CHB. However, as with ETV, TDF is recommended by AASLD, EASL, and APASL guidelines for treatment-naive CHB patients, more studies will inevitably be published on its use in combination with pegIFN alfa.

Preliminary data from a prospective, global randomized controlled trial investigating HBsAg loss using the combination of pegIFN alfa-2a + TDF have been recently published [40]. A total of 740 HBeAg-positive and HBeAg-negative patients of varying HBV genotypes were randomized to four treatment groups: concurrent pegIFN + TDF for 48 weeks, concurrent pegIFN + TDF for 16 weeks followed by TDF monotherapy for 32 weeks, TDF monotherapy for 48 weeks, or pegIFN monotherapy for 48 weeks. At the end of 48 weeks of treatment, it was found that combined pegIFN + TDF for 48 weeks resulted in a higher rate of HBsAg loss (7.5 %) compared to either TDF or pegIFN monotherapy (0 % and 2.4 % respectively), and also a higher rate of HBsAg seroconversion (5.9 %) compared to all other treatment arms (0.6 %, 0 % and 1.8 % respectively). Of the patients who experienced HBsAg loss, 73 % were HBeAg-positive, and most had HBV genotype A or B (A: 31.8 %, B: 36.4 %, C: 18.2 %, D: 13.6 %). Rates of HBeAg loss were also higher in combination treatment arms (24.3 % and 20.2 % respectively) compared to monotherapy arms (8.3 % and 12.5 % respectively). HBV DNA suppression (<15 IU/mL) was significantly higher in the TDF-treated patients (69.2 %, 71.2 %, 60.5 % compared to 20.8 % respectively). Thus, the authors concluded that the combination of pegIFN + TDF for 48 weeks is superior to either treatment given alone at the end of 48 weeks of treatment. It remains to be seen if these effects are sustained at a longer 72 weeks timepoint.

Conclusion

New antiviral agents against chronic HBV infection have resulted in significant advances but disease control and clearance is still difficult to attain due to persistent HBV replication from cccDNA in infected hepatocytes. While NUC therapy is safe, effective in suppressing HBV DNA, and convenient for patients, immune-based antiviral strategies are likely needed for the immune-mediated clearance of infected hepatocytes. Thus at the current time, the antiviral and immunomodulating effects of pegIFN alfa make it an important tool for clinicians to consider in treating their chronic hepatitis B patients, as it is practically the only licensed therapeutic option that can offer off-treatment, sustained response. Sustained off-treatment response can be achieved in about 20–30 % of HBeAg positive or negative patients. Pretreatment prediction rules using in particular HBV genotype, ALT and HBVDNA levels as well as response-guided therapy using quantitative HBsAg can optimize treatment response and help to individualize therapy. Further research into both viral and host genetic factors will also lead to better identification of patients likely to benefit from pegIFN alfa and minimize the number of patients receiving pegIFN alfa with little clinical benefit. Future studies on the use of pegIFN alfa in combination with newer antiviral agents, such as ETV and TDF, are required to determine which treatment regimens lead to the best clinical outcomes.

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