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Pros and Cons of Peginterferon Versus Nucleos(t)ide Analogues for Treatment of Chronic Hepatitis B

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Abstract The emergence of new and more potent treatment options has markedly changed the treatment landscape of chronic hepatitis B. Both peginterferon and nucleos(t)ide analogues have considerable advantages and limitations, and current treatment guidelines refrain from clearly suggesting a first-line treatment option. Peginterferon offers the advantage of higher sustained response rates in both hepatitis B early antigen (HBeAg)-positive and HBeAg-negative patients, at the price of considerable side effects and high costs. Nucleos(t)ide analogues offer easy daily oral dosing, and newly registered agents can maintain viral suppression for prolonged treatment duration. However, relapse is common after therapy discontinuation and extended therapy therefore often necessary. Prolonged treatment with nucleos(t)ide analogues may enhance chances of virologic and serologic response at the potential cost of the emergence of viral resistance and side effects. Baseline and on-treatment prediction of response may help select patients for peginterferon therapy and can aid individualized treatment decisions concerning therapy continuation or discontinuation.

Keywords Peginterferon · Nucleos(t)ide analogues · Chronic hepatitis B

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Introduction

Chronic hepatitis B is a major health problem affecting more than 350 million people worldwide. Prolonged infection with the hepatitis B virus may result in severe liver-related morbidity and mortality, so treatment of chronic hepatitis B is indicated in patients with active liver inflammation [1, 2]. The introduction of nucleos(t)ide analogues (NA) changed the landscape of chronic hepatitis B management, because they have proven, at least in the short term, to be a safe and effective alternative to interferon (IFN). However, interest in IFN-based treatment regimens was renewed after the introduction of a pegylated form of standard interferon-α (PEG-IFN), which has better pharmacokinetic properties and higher antiviral potency than regular IFN [3]. Current guidelines recognize five NA for the treatment of chronic hepatitis B (lamivudine, telbivudine, adefovir, entecavir, and tenofovir), along with two formulations of PEG-IFN (peginterferon α-2a and α-2b) [4]. Both treatment modalities have proven to be effective, but clear recommendations as to which treatment strategy (NA or PEG-IFN based) should be used as first-line therapy are lacking. Choice of initial therapy should ideally be made considering the advantages and limitations of available therapy options and individual patient preferences.

In this review, we assess the pros and cons of the use of PEG-IFN as a first-line treatment option in chronic hepatitis B in the light of recent advances that have been made in the field.

Treatment End Points

Because complete eradication of the hepatitis B virus is only scarcely, if ever, achieved with currently available agents, the main goal of therapy is to halt the progression of liver inflammation to fibrosis, cirrhosis, or hepatocellular carcinoma [5]. Because these outcomes may not transpire until after decades of infection, surrogate measures are pursued during treatment. The most widely used end points of therapy are a reduction of HBV DNA to undetectable levels (virologic response), loss of hepatitis B early antigen (HBeAg) with or without the appearance of anti-HBe (serologic response), normalization of alanine transaminase (ALT) (biochemical response), and improvement of liver histology [6]. Sustained remission of the disease, whether treatment induced or not, is heralded by a loss of hepatitis B surface antigen (HBsAg) from serum accompanied by appearance of anti-HBs [7].

Both treatment modalities for chronic hepatitis B infection, NA and PEG-IFN, affect the host-virus equilibrium in different ways. PEG-IFN has an immunomodulatory and a direct antiviral effect, whereas NAs impede viral polymerase activity and prohibit viral replication [8]. These differences are reflected in the varying efficacy measures used during therapy.

In HBeAg-positive chronic hepatitis B patients treated with PEG-IFN, loss of HBeAg from serum accompanied by the appearance of anti-HBe (HBeAg seroconversion) is the primary treatment end point, because it is associated with a high probability of HBsAg seroconversion and increased survival [4, 6, 9–11]. In addition to HBeAg seroconversion, suppression of HBV DNA to undetectable levels until HBeAg seroconversion occurs is often used as efficacy measure for NA-based therapy.

In HBeAg-negative chronic hepatitis B, suppression of HBV DNA to low or undetectable levels with normalization of ALT is currently the treatment goal of choice. Trials involving PEG-IFN have used, for unclear reasons, 20,000 copies/mL and ALT normalization as primary outcome measure [12], whereas trials investigating the potency of NA use improvement in liver histology and HBV DNA undetectability as primary outcome. Recent insight into the excellent prognosis of inactive hepatitis B carriers has led to the use of these criteria (HBV DNA <2,000 IU/mL and ALT normalization) as response parameters for PEG-IFN therapy in HBeAg-negative chronic hepatitis B [13•].

The disparities between treatment outcomes used for NA and PEG-IFN therapy show an important difference in treatment approach: during PEG-IFN treatment, viral suppression is secondary to achieving immunologic control over the virus and attaining a post-therapy sustained response. During treatment with NA, achievement of on-treatment maintained viral suppression to undetectable levels is always essential, for persisting viral replication will inevitably lead to resistance [2].

Other important considerations are the difficulties that arise when the effect of treatment on surrogate markers is extrapolated to clinical outcomes. Although sustained HBeAg and HBsAg seroconversion are associated with increased survival and lower incidence of hepatocellular carcinoma [10, 14, 15], an advantageous effect of viral load reduction by NA without sustained HBeAg or HBsAg seroconversion has only been shown convincingly in patients with advanced liver disease and is otherwise unclear [9, 16]. In addition, viral covalently closed circular (ccc-)DNA, the viral replicative intermediate at the basis of hepatitis B virus infection, persists in host cells even if HBV DNA levels are adequately suppressed [17]. Consequently, sustained off-treatment transition to the inactive carrier state should be used as primary end points during therapy for both HBeAg-positive and HBeAg-negative chronic hepatitis B. If this end point cannot be achieved, therapy-maintained HBV DNA suppression to undetectable levels is a secondary option.

HBeAg-Positive Chronic Hepatitis B

Patients with chronic hepatitis B may present in any one of four, not necessarily sequential, stages of infection. HBeAg-positive chronic hepatitis B is regarded as the earliest phase of infection, and patients commonly present with HBV DNA levels exceeding 20,000 IU/mL and with either normal or elevated ALT levels depending on whether the patient is in the immune tolerant or immune clearance phase of infection [10]. Current European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines propose active therapy of HBeAg-positive chronic hepatitis B patients who present with serum HBV DNA levels of over 2,000 IU/mL (20,000 IU/mL for AASLD) and elevated ALT levels or when liver biopsy shows at least moderate inflammation or fibrosis. The primary goal of therapy is achievement of HBeAg seroconversion and undetectable HBV DNA levels [4, 6].

All registered agents have been evaluated in large multinational randomized trials for treatment duration of 48–52 weeks; the serologic response rates are summarized in Table 1. After 1 year of treatment with PEG-IFN α-2b, 25% of patients achieved HBeAg seroconversion [18], whereas this was 27% in patients treated with PEG-IFN α-2a [19]. Six months after discontinuation of treatment, the rates were 29% and 32%, respectively. The ultimate surrogate end point of therapy, loss of HBsAg with appearance of anti-HBs, occurred in 4–6% of patients after 1 year of treatment and 6 months of post-treatment follow-up [18, 19]. In both studies, the addition of lamivudine to PEG-IFN monotherapy did not increase response rates, although on-treatment viral suppression was more vigorous in patients who received combination therapy [18, 19]. A representative cohort of 172

Table 1 Response rates for PEG-IFN and nucleos(t)ide analogues

Therapy	HBeAg-positive patients			HBeAg-negative patients		
	1y of therapy[a]	6mo post-treatment[b]	Long-term sustained[c]	1y of therapy[a]	6mo post-treatment[b]	Long-term sustained[c]
PEG-IFN	27%	32%	70%	36%	36%	43%
Tenofovir	21%	–	–	93%	–	–
Entecavir	21%	17%	–	90%	3%	–
Adefovir	18%	–	–	63%	–	–
Telbivudine	23%	–	–	88%	–	–
Lamivudine	20%	19%	64%	72%	7%	13%

Response rates per agent for HBeAg-positive and HBeAg-negative patients. Response is defined as HBeAg seroconversion in HBeAg-positive patients and as HBV DNA levels <20,000 combined with ALT normalization in HBeAg-negative patients treated with PEG-IFN. Response in HBeAg-negative patients treated with nucleos(t)ide analogues is defined as maintained viral suppression to undetectable levels. Data were derived from different studies, not head-to-head comparisons. Data on long-term sustained response were reported in populations different from those used to calculate response after 1 year of therapy and 6 months post-treatment

ALT alanine transaminase, *HBeAg* hepatitis B early antigen, *PEG-IFN* pegylated interferon

[a] Percentage of responders for 1 year of therapy

[b] Percentage of responders at 6 months after discontinuation.

[c] Percentage of initial responders who sustain response through long-term follow up (>1 year after discontinuation).

patients treated with PEG-IFN α-2b ± lamivudine in the aforementioned study were enrolled in a subsequent follow-up study and revisited after a mean of 3 years. HBeAg seroconversion was sustained in 70%, and 11% of patients were HBsAg negative at the end of follow-up [20•].

The five NA registered for chronic hepatitis B have all been evaluated in large registration trials. Some (lamivudine, adefovir) against placebo, others (telbivudine, entecavir) against lamivudine or adefovir (tenofovir). The primary outcome in all studies was either improvement in Knodell inflammatory score at the end of treatment or a composite end point of HBV DNA suppression and improvement in Knodell score. The five agents differ considerably in their potency against the hepatitis B virus. Lamivudine suppresses HBV DNA to undetectable levels in 40% after 1 year of treatment [19], adefovir in 21% [21], telbivudine in 60% [22], entecavir in 67% [23], and tenofovir in 76% [24]. Because inclusion criteria differed between studies, and head-to-head comparisons between most agents are lacking, differences in antiviral potency should be interpreted with caution. Nevertheless, HBeAg seroconversion rates are rather homogeneous; approximately 20% of patients show HBeAg seroconversion after 1 year of treatment regardless of which NA was used (Table 1). HBeAg seroconversion rates increase during prolonged treatment with NA, reaching approximately 28% after 2 years of treatment with lamivudine, entecavir or tenofovir [25–27]. HBsAg seroconversion is rare during treatment with NA, in the order of 0% to 2% after 1 year of therapy, with an exception of 3% for tenofovir [24].

The durability of NA induced HBeAg seroconversion is doubtful, for studies report that HBeAg seroconversion is sustained in only 56–64% if treatment is stopped after lamivudine-induced seroconversion [28, 29]. Theoretically, NA therapy may be prolonged indefinitely, because side effects of treatment are generally mild during the first years of therapy [30]. However, prolongation of treatment comes at a price, because resistance rates increase with longer treatment duration: from 14% during the first year of treatment with lamivudine to 69% after 5 years of therapy. Resistance rates are lower for the most potent NA: 1.2% after 5 years of therapy with entecavir in treatment-naïve patients and 0% through 3 years of therapy with tenofovir. However, data beyond these time points are lacking and the safety of extended therapy remains to be determined [2].

HBeAg-Negative Chronic Hepatitis B

After loss of HBeAg from serum, viral replication may persist because of the presence of mutations in the viral genome. The most commonly encountered mutation is located within the pre-core region and prohibits the synthesis of HBeAg [10]. Current EASL and AASLD guidelines propose to consider active therapy of HBeAg-negative patients who present with levels of serum HBV DNA over 2,000 IU/mL with elevated ALT levels or when liver biopsy shows at least moderate inflammation or fibrosis [4]. Patients with HBeAg-negative chronic hepatitis B commonly present with slightly lower levels of HBV DNA and only moderately elevated levels of ALT when compared to HBeAg-positive patients. Because HBeAg seroconversion is no longer a feasible end point of therapy, suppression of viral replication, normalization of ALT, and ultimately HBsAg seroconversion are primary treatment outcomes [6, 10].

Both PEG-IFN and NA have been evaluated in large multinational registration trials. In one such trial, patients were randomized to receive PEG-IFN α-2a alone, lamivudine alone, or the combination for 48 weeks of therapy. Patients were subsequently followed up for 24 weeks. Primary end point was suppression of HBV DNA levels to below 20,000 copies/mL and normalization of ALT. Response rate was 36% for the PEG-IFN monotherapy group both at the end of treatment and after 24 weeks of follow-up [12]. After 24 weeks of follow-up, 38% of patients treated with PEG-IFN had HBV DNA levels <10,000 copies/mL (the level below which the inactive carrier state is defined) [13•]. For lamivudine, the response rates were 69% at end of therapy and 23% after 24 weeks of follow-up. Addition of lamivudine to PEG-IFN increased the probability of an end-of-therapy response, but this difference was not sustained post-treatment [12]. In other trials, lamivudine treatment resulted in HBV DNA suppression to undetectable levels in 72% [23], adefovir in 63% [24], telbivudine in 88% [22], entecavir in 90% [23], and tenofovir in 93% [24] after 1 year of therapy (Table 1). The durability of post-treatment response to NA is generally low: 24 weeks after treatment discontinuation, lamivudine-induced HBV DNA undetectability was sustained in only 7% [12] and relapse rates increased further during prolonged follow-up [6, 31]. Despite the higher antiviral potency of entecavir, HBV DNA suppression to undetectable levels is sustained in only 3% of patients after 24 weeks of post-treatment follow-up [32]. By comparison, response to PEG-IFN, defined as post-treatment sustained HBV DNA levels <10,000 copies/mL, is durable in up to 43% of initial responders after 3 years of follow-up [13•].

Adverse Events

PEG-IFN and NA have vastly different side effect profiles. Treatment with PEG-IFN is associated with considerable side effects; the most frequently reported are a flu-like syndrome, headache, myalgia, fatigue, and local reactions at the injection site [12, 18, 19]. These symptoms typically present early during therapy, whereas neuropsychiatric side effects associated with PEG-IFN use, such as mood changes and irritability without depression, tend to present in the later stages [33]. Hepatitis flares have been reported to occur during PEG-IFN therapy. Especially host-induced flares with elevations in ALT and a decline in HBV DNA levels have been associated with a favorable outcome [34]. Patients with decompensated cirrhosis have an absolute contraindication to PEG-IFN therapy, but among patients with advanced fibrosis PEG-IFN is generally well-tolerated and effective [35]. PEG-IFN has mild myelosuppressive effects, but PEG-IFN-induced neutropenia and thrombocytopenia result in clinically significant symptoms, including bleeding and infections, in only a select group of patients [33].

NAs generally have favorable side effect profiles. Theoretically, all NA pose a risk of severe adverse events, for most inhibit not only viral polymerase enzymes but also host DNA polymerases [36]. Some agents also inhibit human mitochondrial DNA polymerases, which may result in a clinical syndrome including lactic acidosis, neuropathy and myopathy [36]. Fortunately, most NAs have had few adverse events during the first years of therapy. During a large randomized trial, adverse events did not occur more frequently during lamivudine treatment than with placebo [37] and the side effect profile of entecavir was indistinguishable from that of lamivudine [38]. Adefovir is known to be nephrotoxic in up to one third of patients [39] and renal toxicity is also a problem with tenofovir, although the latter seems relatively safe during the first year of therapy [24]. Tenofovir has been used extensively in HIV-treatment and renal toxicity has been described at length, necessitating creatinine monitoring especially during prolonged treatment [36]. In general, NA show favorable side effect profiles in comparison to PEG-IFN during the first year of therapy, but long-term safety data for the new agents are lacking.

Predicting Response to PEG-IFN

Because treatment with PEG-IFN is costly, comes with considerable side effects, and has only limited efficacy, tools have been devised to select patients with a high probability of response. So far, prediction of response to PEG-IFN at baseline has been challenging, which is reflected in the absence of clear recommendations regarding which patients should be considered as candidates for PEG-IFN therapy [4, 6]. Analysis of the two largest trials investigating the efficacy of PEG-IFN in HBeAg-positive chronic hepatitis B has shown that response rates are higher in patients with HBV genotype A and B compared to C and D and in patients with lower baseline HBV DNA levels or higher baseline ALT levels [18]. These findings were confirmed when data from the two studies were pooled and re-analyzed (n=721) [40••]. In addition to HBV genotype, lower HBV DNA levels, and higher ALT levels, female sex, older age, and no prior treatment with IFN were also recognized as significant predictors of response at baseline. A logistic regression model including these variables provided good discrimination between responders and non-responders. The authors advise consideration of PEG-IFN therapy in HBeAg-positive patients with a baseline probability of response >30%, calculated using their individualized PEG-IFN treatment index [40••].

A similar analysis was performed using the data from a large trial comparing PEG-IFN ± lamivudine with lamivu-

dine alone in HBeAg-negative chronic hepatitis B. Baseline factors associated with response in this group were similar to those identified in HBeAg-positive patients: ALT, HBV DNA level, age, and sex [41].

However, considerable uncertainty remains whether an individual will actually benefit from PEG-IFN therapy, even if baseline probability of response is high. Extension of baseline prediction of response with on-treatment parameters may help refine individualized treatment decisions. Frequent assessment of HBV DNA levels during treatment is therefore recommended in recent guidelines [4]. Different patterns of viral decline during treatment with PEG-IFN-α2b with or without lamivudine treatment have been described in HBeAg-positive patients. Nevertheless, prediction of response based on viral decline during the first months of therapy is difficult, because on-treatment kinetics of HBV DNA provide only limited discrimination and predictive values are low [42].

Because on-treatment HBV DNA kinetics do not adequately predict response, focus has changed to other measures of viral replicative status, such as HBeAg and HBsAg levels in serum. The latter may provide new insight into the host-virus equilibrium considering its close correlation with intrahepatic cccDNA levels [17].

Baseline HBsAg levels appear to be similar in HBeAg-negative patients who show a decline in HBsAg while on-treatment and those who do not. However, patients who developed a sustained response to treatment with PEG-IFN (HBV DNA undetectability 24 weeks after treatment discontinuation) experienced a significant decline in HBsAg levels, whereas patients who did not respond showed little or no decline [43]. Patients who experienced a decline in HBsAg levels >0.5 logIU/mL after 12 weeks of treatment had an 89% probability of sustained response, whereas patients who did not undergo such a decline had a 90% probability of not responding. Similar observations were made for a decline of 1 logIU/mL after 24 weeks of treatment: the positive predictive value was 92%, the negative predictive value 97%. [43]. However, these results were reported from a small study including only a limited and possibly selected group of patients, and should therefore be interpreted with caution. Other observations were reported after analysis of data from the PEG-IFN registration trial in HBeAg-negative subjects. Patients who had a decline in HBsAg level of less than 0.46 logIU/mL from pretreatment to end of therapy had a 95% probability of not having a sustained response 3 years post-treatment. [44••] Definitive data in HBeAg-positive chronic hepatitis B are still pending, but preliminary results show considerable promise [45].

Quantification of HBeAg in patients with HBeAg-positive chronic hepatitis B has also proven worthwhile. Patients who experience a limited decrease in HBeAg levels during the first 4–8 weeks of treatment have a significantly lower chance of HBeAg seroconversion [46]. These results were confirmed in a large study, which also showed that quantification of HBeAg may provide more discriminatory power than HBV DNA levels [47]. Prospective studies are required to confirm these results and compare the predictive and discriminatory values of HBeAg and HBsAg kinetics.

Augmenting Response to PEG-IFN

The majority of patients do not experience a sustained response after 1 year of PEG-IFN therapy; consequently, investigators have attempted to increase response rates using alternative administration strategies. Because lower baseline HBV DNA levels are associated with a higher probability of response [40••], it has been hypothesized that lowering HBV DNA levels with NA before commencing PEG-IFN therapy could increase response rates. So far, results of studies attempting to test this hypothesis have been conflicting [48, 49], and definitive data from an adequately powered trials are still awaited. Additionally, the effects of extending the duration of PEG-IFN therapy have been investigated in pilot studies, and have shown hopeful results [50].

Table 2 Pros and cons of PEG-IFN versus nucleos(t)ide analogues

PEG-IFN	Nucleos(t)ide analogues
Pros	*Pros*
Finite duration of therapy	Daily oral dosing
Absence of viral resistance	Potent HBV DNA suppression
Response durable post-therapy	Minimal side effects in the short term
Proven effect in general patient population	Proven effect in patients with advanced liver disease
Increase in HBsAg seroconversion rate	Less expensive during first year, possibly equally or more costly after long-term therapy
Cons	*Cons*
Frequent side effects	Risk of resistance
Weekly subcutaneous injection	Limited increase in HBsAg seroconversion rate
Less effective HBV DNA suppression	Response less durable post-therapy
Expensive	Long-term or indefinite therapy may be required

HBsAg hepatitis B surface antigen, *HBV* hepatitis B virus, *PEG-IFN* pegylated interferon.

Discussion

Considerable advances have been made in the treatment of chronic hepatitis B over the past decade. With the availability of new and highly efficacious agents, the choice of first-line therapy has become increasingly complex. Both treatment modalities—NA and PEG-IFN—have substantial advantages and limitations (Table 2). In HBeAg-positive patients, PEG-IFN results in post-treatment sustained HBeAg seroconversion in 32% of patients after 1 year of treatment and 6 months of follow-up [18, 19], and this response is sustained in more than 70% [20•]. Response to PEG-IFN also increases survival and decreases the incidence of hepatocellular carcinoma [15]. Direct inhibition of viral polymerases using NA results in viral suppression in most patients, but HBeAg seroconversion occurs in only 20% of patients after the first year of therapy, irrespective of antiviral potency [2]. Although HBeAg seroconversion rates increase during prolonged treatment and may eventually equal or surpass those of a 1-year course of PEG-IFN, cessation of therapy results in relapse in a considerable proportion of patients [28]. Prolonged therapy also increases the chance of the emergence of viral mutants resistant to current NA and the emergence of NA-related side effects [36]. Sustained serologic response, preferably after a finite duration of treatment, should therefore be pursued in HBeAg-positive patients.

In patients with HBeAg-negative chronic hepatitis B, PEG-IFN results in suppression of HBV DNA and ALT normalization in 36% of patients after 1 year of treatment [12]. After 6 months of post-treatment follow-up, this percentage is still 36%, but only 43% of these patients will have sustained this response through 3 years of follow-up [13•]. The most potent NAs, entecavir and tenofovir, can suppress HBV DNA levels to undetectable levels in more than 90% of patients, but only a few patients sustain the response after 6 months of treatment discontinuation [32]. Achieving a post-therapy sustained response thus seems more difficult in HBeAg-negative patients, but because indefinite treatment is often required in HBeAg-negative patients treated with NA and emergence of resistant mutants and side effects of prolonged NA treatment may occur, PEG-IFN is still a first-line therapy option for these patients.

Considering that the limited probability of sustained response to PEG-IFN is offset by high costs and side effects, only patients who have a good chance of response should be considered for this therapy. A prediction model for HBeAg-positive patients provides good discrimination between responders and non-responders, and may help clinicians to choose patients for PEG-IFN therapy based on readily available data such as genotype, ALT, sex, and HBV DNA levels [40••].

On-treatment monitoring of patients treated with PEG-IFN using HBV DNA, HBsAg, and perhaps HBeAg levels may optimize individualized prediction of response and can help decide which patients are to benefit from (dis-) continuing PEG-IFN therapy. If patients are not eligible for PEG-IFN based on their baseline characteristics or must discontinue for reasons of inadequate response, patients should be started on NAs that offer the highest antiviral potency, the least chance of resistance, and a favorable side effect profile, because prolonged or indefinite treatment may be necessary.

Additional research will have to show whether alternative strategies of PEG-IFN administration, such as continuous subcutaneous dosing, lowering HBV DNA levels using NA before PEG-IFN is started, or prolonging PEG-IFN therapy beyond 1 year, will lead to higher rates of sustained response.

Conclusions

The advantages and limitations of PEG-IFN and NA should be weighed for every individual patient. PEG-IFN offers a higher chance of post-therapy sustained response at the cost of higher treatment price and considerable side effects. NA provide easy daily oral dosing and can maintain adequate viral suppression for prolonged periods, but post-treatment sustained response can probably not be achieved in a majority of patients. Prolonging treatment with NA may enhance chances of HBeAg and HBsAg seroconversion. We propose that only patients who have a high baseline probability of response to PEG-IFN should be considered for this therapy regimen, because the potential benefits may offset the higher costs and side effects. Non-eligible patients or non-responders to PEG-IFN should be treated with the most potent NA, but long-term or indefinite therapy is often necessary, posing considerable risk of viral resistance and long-term side effects.

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- •• Of major importance

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