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Is it more cost effective for patients with chronic hepatitis B to have a trial of interferon before considering nucleos(t)ide analogue therapy?

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Both pegylated interferon (PEG-IFN) and nucleos(t)ide analogues (NUCs) are recommended as first line treatment options for patients with chronic hepatitis B (CHB).¹ In clinical practice however, NUCs are used as first line treatment in the majority of patients due to concern about side effects and the fact that only a small proportion of patients achieve durable response with IFN therapy. IFN therapy does offer a defined treatment duration and depending on the underlying hepatitis B virus (HBV) genotype, a higher chance of hepatitis B surface antigen (HBsAg) loss and durable hepatitis B e antigen (HBeAg) loss compared to NUC therapy.² If a response-guided approach for IFN therapy can be implemented in a manner similar to that used in hepatitis C, PEG-IFN therapy might be more attractive because patients who are unlikely to benefit can be spared from further side effects and costs.

Cost effectiveness analyses comparing different CHB treatment approaches show variable results depending on the study population, estimated rates of disease progression and treatment response, as well as costs of IFN and NUCs in each country. Thus far only one study has evaluated the cost effectiveness of IFN regimens with a 12 week response-guided stop rule. This study evaluated HBeAg-negative patients and found that first-line PEG-IFN strategies that applied either the 12 week stop rule or the full 48 week course were more cost-effective than NUCs, though the differences in quality adjusted life years (QALYs) were small.³

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In this issue of the Journal, Lo et al expanded on this work by evaluating the cost-effectiveness of response-guided IFN therapy for both HBeAg-positive and HBeAg-negative patients.⁴ They constructed a Markov model using Hong Kong population data and rates of disease progression and treatment response from data in the literature. The primary outcome variable was the cost effectiveness ratio (CER) of different treatment strategies based on QALYs compared to no treatment using a cost effectiveness threshold of 50,000 United States Dollars (USD)/QALY. The six different treatment strategies compared included: 1) PEG-IFN with 12 week stopping rule, 2) PEG-IFN for 48 weeks, 3) entecavir monotherapy, 4) tenofovir monotherapy, 5) telbivudine monotherapy, and 6) telbivudine roadmap with tenofovir switch. HBeAg seroconversion was used to define treatment response and HBsAg >20,000 IU/mL at week 12 as the stop rule for HBeAg-positive patients. For HBeAg-negative patients, response was defined as alanine aminotransferase >2 the upper limit of normal and HBV DNA >2,000 IU/mL and stop rule was no decline in HBsAg and <2 log decline in HBV DNA at week 12. The authors found that PEG-IFN therapy with a 12-week response-guided stop rule had the lowest CER (\$9501/QALY) compared to no treatment for HBeAg-positive patients, while entecavir had the lowest CER (\$34,310 /QALY) compared to no treatment for HBeAg-negative patients. They therefore recommended consideration of response-guided IFN as first line therapy for HBeAg-positive patients and supported the continued use of NUCs as first line therapy for HBeAg-negative patients.⁴

The impetus of this study is the recent proposal of response-guided IFN therapy for CHB; therefore, a critical issue is the validity of the 12-week stop rule. These stop rules were derived from retrospective analyses of data from large clinical trials and have never been tested prospectively.⁵⁻¹⁴ An ideal stop rule should have a negative predictive value (NPV) 95% for both intermediate and long-term response, and can be applied to all patients. As demonstrated in Table 1, the validity of a 12-week stop rule is difficult to assess because of the heterogeneity regarding treatment regimens, definition of treatment response, criteria for stopping treatment, and impact of HBV genotype. As an example, Sonneveld et al found that no decline in HBsAg at week 12 had a NPV of 97% for response at week 78 for HBeAg-positive patients based on data from a study with predominantly genotype A and D, but when Piratvisuth and colleagues applied this stop rule to two studies with predominantly genotypes B and C, the NPV decreased to 71-82%.^{9, 13} For HBeAg-negative patients, the stop rule of no decline in HBsAg and <2 log decline in HBV DNA was derived from studies with predominantly genotype D and the validity in patients with other genotypes remain to be confirmed.¹¹ Furthermore, different stop rules were identified for predicting long-term response indicating that some patients who meet criteria for stopping treatment based on low probability of intermediate response might have a late response with clearance of HBsAg. These data highlight that one universal stop rule is unlikely to yield sufficiently accurate predictions for response to PEG-IFN for it to be applied in clinical practice.

Besides concerns regarding validity of the 12-week stop rules in clinical practice, several aspects of the study design raise important questions. Inherent to any model are limitations that result from the accuracy of the estimates of rate of disease progression. The natural course of chronic HBV infection is characterized by fluctuations in viral replication and hepatitis activity and many factors (host, virus and environment) contribute to disease progression. Extrapolation of data from studies with short durations of follow-up or

combining data from multiple studies that focused on different subsets of CHB patients to provide estimates of disease progression may not apply to the base case model and can be misleading. For instance, the relative risk of decompensated cirrhosis and hepatocellular carcinoma (HCC) were abstracted in part from data from the REVEAL study which enrolled patients with a mean age of 43 years while the age of the base case model in this study was 35 for HBeAg-positive and 40 for HBeAg-negative patients.¹⁵ Similar concerns pertain to the accuracy of estimates of long-term treatment response rates since existing literature on response to HBV treatment beyond 5 years is limited. Lastly, a uniform value of 0.7 was used for utility estimates during PEG-IFN treatment, but tolerance to IFN is highly variable.

A more important limitation is the choice of outcome variable. The authors reported that their base case cohort represented a group of patients with indications for CHB treatment. As such, the outcome variable of interest would be the incremental cost effectiveness ratio (ICER) that compares response-guided IFN to 48 weeks of IFN without using a stop rule, or to NUC, and not the CER comparing individual treatment regimens to no treatment. Even focusing on the CER instead of the ICER, saving USD 1,000-3,000 in the setting of spending well over \$30,000/QALY may not be viewed to be significant enough of a cost saving to merit basing treatment decisions when viewed from the patient perspective. Limitations related to the variability in drug costs across countries also hinder broad application of these findings. Even within Asia the cost of HBV medications can vary considerably based on the availability of generic drugs and special price discounts negotiated between the manufacturer and the local health authority. Therefore, the results of this study may not be generalized outside of Hong Kong to other Asian countries and other parts of the world.

A major contribution of this study is to revive the debate regarding IFN vs. NUC as first-line treatment of CHB. Despite the limitations of this study, the CER data should reignite enthusiasm in considering a trial of PEG-IFN therapy with response-guided stop rule in patients who do not have medical or psychiatric contraindications, especially those who are predicted to have a high likelihood of response. This approach will allow a subset of patients (admittedly small) to derive a durable response with a defined course of treatment and spare nonresponders from continued side effects of IFN. Prospective studies validating the stop rules in diverse patient populations are needed before this approach can be endorsed.

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Abbreviations

CHB	chronic hepatitis B
CER	cost effectiveness ratio
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen

HBV	hepatitis B virus
ICER	incremental cost effectiveness ratio
NUCs	nucleos(t)ide analogues
PEG-IFN	pegylated interferon
USD	United States Dollars
QALYs	quality adjusted life years

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Table 1

12 week stop Rule for IFN therapy in CHB

Study	Study Population		Response Definition	Stop Rule	PPV	NPV
	N Treatment Regimen	HBV Genotype				
HBeAg Positive						
Sonneveld 2010 ¹³	N: 221 HBV 99-01 study PEG-IFN alfa 2b ± lamivudine for 52 wks	A: 35% B: 9.4% C: 15.1% D: 41.2%	HBeAg loss and HBV DNA <10,000 copies/mL at 1.Week 78 2.Mean of 3 yrs post-treatment (N=149)	No decline in HBsAg	1.25% 2.31%	1.97% 2.95%
Piratvisuth 2011 ¹⁰	N: 399 Phase 3 study PEG- IFN alfa 2a ± lamivudine for 48 wks	B: 32.6% C: 58.4%	HBeAg seroconversion 6 months post- treatment	HBsAg <1500 IU/mL	55%	72%
Liaw 2011 ⁵	N: 114 NEPTUNE study: PEG-IFN alfa 2a 180 µg/wk for 48 wks	A: 4.4% B: 33.8% C: 54.4% D: 7.4%	HBeAg seroconversion 6 months post- treatment	1.HBsAg <1500 IU/mL 2.HBsAg >20,000 IU/mL	1.58% 2.NR	1.84% 2.100%
Piratvisuth 2011 ⁹	N: 526 Combined analysis of Phase 3 study PEG- IFN alfa 2a ± lamivudine and NEPTUNE study ^	See above	HBeAg loss and HBV DNA <10,000 copies/mL 6 months post-treatment	No decline in HBsAg	NR	82% Phase 3 71% NEPTUNE
Sonneveld 2013 ¹²	N: 779 Combined analysis of Phase 3 study PEG- IFN alfa 2a ±lamivudine, NEPTUNE study ^, and HBV 99-01 study PEG-IFN alfa-2b ±lamivudine; With subanalysis of PEG- IFN monotherapy (N=465)*	A: 13% B: 25% C: 48% D:14%	HBeAg loss and HBV DNA <2,000 IU/mL 6 months post-treatment	1.No decline in HBsAg for Genotype A and D 2.HBsAg >20,000 IU/mL for Genotype B and C	NR	1.A: 88% 100%* D: 98% 97%* 2.B: 92% C: 98%
HBeAg Negative						
Marcellin 2008 ⁷	N: 160 Phase 3 study PEG- IFN alfa 2a ± lamivudine for 48 wks, subset with long-term follow up data	A: 8.4% B: 13.6% C: 32.4% D: 42.8%	Clearance of HBsAg by 4 years after end of treatment	HBsAg 1500 IU/mL	35%	97%
Moucari 2009 ⁸	N: 48 PEG-IFN alfa 2a for 48 wks	A: 27% B: 17% C: 12% D: 29%	Undetectable HBV DNA (<70 copies/mL) 6 months post-treatment	<0.5 log ₁₀ decrease in HBsAg	89%	90%
Rijckborst 2012 ¹¹	N:160 Phase 3 study PEG- IFN alfa 2a ± lamivudine for 48 wks, subset with PEG-IFN monotherapy (N=85) and PegBeLiver study PEG-IFN alfa 2a for 48-96 wks (N=75)	A: 9% B: 6.8% C: 13.7% D: 65.6%	HBV DNA <2000 IU/mL and normal ALT 6 months post- treatment	No decline in HBsAg and <2 log HBV DNA decline	41%	95%
Peng 2012 ¹⁴	N: 61 PEG-IFN alfa 2a for 48 wks	B: 79% C: 21%	Undetectable HBV DNA (<312	HBsAg <150 IU/mL	86%	85%

Study	Study Population		Response Definition	Stop Rule	PPV	NPV
	N Treatment Regimen	HBV Genotype				
			copies/mL) 6 months post-treatment			
Marcellin 2013 ⁶	N:120 Phase 3 study PEG-IFN alfa 2a ± lamivudine for 48 wks, subset with long-term follow up data	A:10% B:20% C:46% D:22%	HBV DNA 2,000IU/mL at year 5 post-treatment	10% log ₁₀ HBsAg decline	42%	87%

PPV: positive predictive value; NPV: negative predictive value;

[^] Analysis limited to the group who received full dose (180 µg/week) PEG-IFN alfa 2a for 48 weeks