Evaluating the Antiviral Efficacy and Safety of pegylated Interferon-alpha 2a in Iraqi patients with Chronic Viral Hepatitis B: retrospective study

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ABSTRACT

Hepatitis B virus infection is a global health problem. It is the 10th leading cause of death globally with up to 1.2 million deaths each year from cirrhosis, liver failure, and hepatocellular carcinoma. Effective therapy is necessary to prevent the progression of chronic hepatitis B to cirrhosis, hepatocellular carcinoma, and death. This retrospective study aimed to investigate the efficacy and safety of Pegylated Interferon alpha-2a in Iraqi patients with chronic hepatitis B infection.The data related to current study were collected from patient medication records, stored in the gastrointestinal and hepatology teaching hospital/medical city/Baghdad. A total 73 patients treated by Pegylated Interferon- alpha-2a for 48 weeks consisting of 51 males (69.٩%) and 22 females (30.1%) were involved in this retrospective study. The age range of patients was from 17-79 years old with mean age of 39.2 ± 13.6 years. In addition to the demographic information, data related to the safety and efficacy of pegylated Interferon alpha-2a were collected at baseline, after 24 weeks of treatment, and after 48 weeks of treatment (end of course) as needed where safety and efficacy of pegylated interferon-alfa 2a were compared through those two periods.The patients were divided into 2 groups HBeAg positive [10 patients] and second group of HBeAg negative [63 patients]. Patients with HBeAg negative had significantly lower viral load (5.26± 1.01 $\log_{10}$ IU/ml) than HBeAg positive (7.18 ± .69 $\log_{10}$IU/ml). HBeAg positive patients had lower rate of viral suppression (20%) and only achieved it after 48 weeks of treatment, while for HBeAg negative the rate of achieving viral suppression after 24 weeks therapy was (38.1%) and significantly increased to (71.43%) after 48 weeks (p value < 0.05). Regarding rate of viral remission, 20% of HBeAg positive patients achieved viral suppresion and only after 48 weeks, while for HBeAg negative the rate of achieving viral remission after 24 weeks therapy was (31.75%) and significantly increased to (57.14%) after 48 weeks (p value < 0.05). HBeAg positive patients did not have loss in HBsAg in 24 and 48 weeks treatment, while patients with negative envelop antigen after 24 weeks 1 patient (1.59%) had a loss in HBsAg and 6 patients (9.48%) had loss in HBsAg after 48 weeks. Lower baseline viral load value associated with more suppression at the end of therapy. The rate of neutropenia was the same (6.94%) after 24 and 48 weeks while that of thrombocytopenia was increased from (16.44%) after 24 to (24.66%) after 48 weeks and that of anemia was increased from (16.44%) after 24 to (23.29%) after 48 weeks. However; both increments were non significant. In Conclusion HBeAg-Negative Chronic Hepatitis B patients had better therapeutic response (especially in term of viral suppression and viral remission) to Pegylated Interferon alpha-2a compared to HBeAg-positive patients with better response achieved after 48 weeks compared to 24 weeks therapy,yet statsitacally nt significant

Introduction:

Hepatitis B virus (HBV) infection is a global health problem [(1)]. It is the 10th leading cause of death globally with up to 1.2 million deaths each year [(2)] from cirrhosis, liver failure, and hepatocellular carcinoma [(3)].In Iraq, HBV infection has declined in the past few decades. This reduction is the result of the prevention and control programs adopted by the government, such as safe blood transfusion and safe injections in addition to introduction of the vaccination program[(2)]and It is transmissible through perinatal, sexual, or percutaneous exposure; close person-to-person contact with open cuts and sores;and sharing of household items such as razors and toothbrushes [(4)]. Infants born to mothers who are infected with actively replicating HBV have a 70% to 90% risk of becoming infected[(5)] . Seven therapies approved by the U.S. Food and Drug Administration (FDA) for the treatment of HBV: Interferon (interferon alfa-2b and pegylated interferon alfa-2a), nucleoside analogues (lamivudine, telbivudine, and entecavir) and the nucleotide analogues (adefovir and tenofovir) [(6)] and have been shown to delay the progression of cirrhosis, reduce the incidence of HCC and improve long-term survival [(7)] IFN-alfa therapy was the first approved therapy for treatment of HBV, it has antiviral, antiproliferative, and

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immunomodulatory effects in chronic HBV [8]. Pegylated interferon is interferon attached to a polyethylene glycol molecule that increases the half-life of the drug[5] .

Patients and Methods:

Patients.

A total 73 patients consisting of 51 males (69.9%) and 22 females (30.1%) were involved in this retrospective study and collected during the period of 2011-2015. The age range of patients was 17-79 years old with mean age of 39.2 ± 13.6 years.

The data related to current study were collected from the liver and gastrointestinal diseases teaching hospital/Medical City/Baghdad.

Inclusion criteria

The patients were included in the current study if they meet the following criteria:

Having hepatitis B virus infection without regarding to age.

Treated by Pegylated Interferon-alpha 2a

Completed the total course of treatment (48 weeks).

Exclusion criteria

Patients were excluded if they had other concurrent chronic hepatitis (hepatitis C, hepatitis D), human immunodeficiency virus (HIV) or if they were treated by antiviral other than pegylated interferon-alpha 2a.

Methods:

The data were collected from patient medication records, stored in the liver and gastrointestinal diseases teaching hospital /medical city/Baghdad.

In addition to the demographic information, data related to the safety and efficacy of PEG-IFN a-2a were collected at baseline, after 24 weeks of treatment, and after 48 weeks of treatment were safety and efficacy of PEG-IFN a-2a were compared through those two periods. For each patient involved in the study the following information were recorded: Patient demographic information (name, age, gender), viral load or HBV DNA before and during treatment, HBs Ag (if positive or negative) and HBe Ag, complete blood picture.

(To detect anemia , thrombocytopenia and neutropenia), Serum Alanine aminotrasferase ALT, HBV treatment received by patient and Treatment outcome that include: Virological response (viral remission VR) when viral load <20 IU/ml (undetectable), viral suppression when viral load < 2000 IU/ml, biochemical response: normalization of ALT <40IU/L , HBsAg loss: clearance of HBV infection, HBeAg seroconversion: loss of HBeAg and development of anti-HBe, complete response when all target acheived (VR, viral suppression, HBsAg loss or HBeAg seroconversion in case of HBeAg positive).

Statistical analysis

Anderson darling test of normality was done to assess that continuous variables adhere to normal distribution, and all continuous variables found to be normally distributed. Mean and standard deviation was used to represent continuous data, while discrete variables represented by their number and percentage. Two sample t test was used to assess the statistical significance difference between the means of any two continuous variables. Chi square test was used to assess the statistical significance in distribution between different discrete variables, and Fisher exact methods used instead of chi square if the sample where below 20 subjects and if 2 expected frequency equal to or below 5 for 2x2 tables. Univariate binary logistics regression analysis was used to assess the relationship between viral suppression and variables predictors for response in 2 modules of prediction; OR (odd ratio) and its 95% confidence interval used to see the direction and magnitude of the relationship. Multivariate binary logistic regression analysis used to test whether the predictors are dependent or independent predictors for viral response. Level of significance (≤0.05) was chosenas cut off for p value in the calculations, all data analysis was done using SPSS version 23 software package and miniab version 17 LEAD Technologies, Inc, and excel Microsoft package used to draw histograms.

Results:

A total of 73 patients participate in the study , 51 were males (69.9%) while 22 were females (30.1%) after dividing the patients into 2 groups HBeAg positive [10 patients] and second group of HBeAg negative [63 patients] at baseline, there was no significant differences between their age and gender **(table 1)**, patients with negative envelope antigen had significantly lower viral load than positive antigen **(table 2).** HBV envelope positive had lower rate of viral suppression (and only achieve it after 48 weeks), for negative envelope antigen there was significant difference in rate of achieving viral suppression in 24 and 48 weeks (38.1%, 71.43% respectively) **(table 3, figure 1)**. Envelope antigen negative achieved higher rate of viral remission in both 24 and 48 weeks (31.75%, and 57.14% respectively) and was significant (p value = 0.004), while only 20% of patients with positive envelope achieve viral remission after 48 weeks **(table 4, figure 2).** One patient (10%) had seroconversion in 24 weeks, while 4 patients (40%) out of 10 patients had seroconversion in 48 weeks **(table 5).** Patients with positive envelop antigen did not have loss in HBsAg in 24 and 48 weeks treatment, while patients with negative envelop antigen after 24 weeks

1 patient (1.59%) had a loss in HBsAg and 6 patients (9.48%) had loss in HBsAg after 48 weeks **(table 6).** The number of the patients who has baseline high ALT were 15 patients among HBeAg negative and 6 patients among HBeAg positive. In the envelope antigen positive group only 1 patient (16.67%) had ALT normalization after 24 weeks, while after 48 weeks the 3 patients (50%) achieved ALT normalization. In the negative envelop antigen 4 patients (26.67%) after 24 weeks had ALT normalization while 6 patients (40%) had ALT normalization after 48 weeks **(table 7).** one patient (10%) with HBeAg positive achieved all target after 48 weeks as shown in table 3-9.while in HBeAg negative 4 patients (6.35%) achieved all targets (HBV DNA suppression, ALT normalization) after 24 weeks and 6 patients (9.52%) after 48 weeks **(table 8).** Regarding the predictive Factors for HBV DNA Suppression at end of treatment was found that lower baseline value associated with more suppression at the end of therapy **(table 9).** The rate of neutropenia was the same (6.94%) after 24 and 48 weeks while that of thrombocytopenia was increased from (16.44%) after 24 to (24.66%) after 48 weeks and that of anemia was increased from (16.44%) after 24 to (23.29%) after 48 weeks **(table 10, figure 3).**

Discussion:

PEG-IFN is an accepted as a first-line drug for the treatment of naïve CHB patients because it has both direct antiviral activity and immunomodulatory action [9]. In this study 73 patients were included 51 were males (69.9%) and 22 were females (30.1%). The number of male patients was more than female patients infected with HBV (~2.3:1 ratio male: female). According to a national survey for epidemiology of viral hepatitis B and C in Iraq (2005-2006) by Ata allah *et al*., Male gender significantly increases the risk of having positive HBs antigen by 41% compared to females [10]. Since several years, it is well known that men are more likely than women to be chronic carriers of Hepatitis B virus (HBV) [11]. Results comparable to the current study have also been obtained in Bangladesh where the researchers reported higher prevalence in males (67.86%) than females (32.14%) [12] and in Pakistan where the frequency distribution of hepatitis B infection was found as higher in males (78.5%) as compared to the females (21.5%) [13].The gender disproportion may be explained by the increased frequency of high risk jobs and behavior in men, like multiple sexual partners, drug use and unhygienic barber shaving practices [10]. In addition, females clear the HBV more efficiently as compared to males [14]. Despite that in this study males were about 2 folds more than females,the distribution of gender between HBeAg positive (70% were males) and negative (69.8% were males) were not significant. Similar non significant gender difference was reported by Y. E. Chon *et al*., among Korean patients where the frequency of male distribution among HBeAg positive patients was 55.6% and that among HBeAg negative patients was 63.3% [9].

HBeAg positive patients had significantly higher viral load compared to HBeAg negative patients, this observation is consistence with Y. E. Chon *et al.,* [9] and Alexander J.V. *et al.,* [15] where HBeAg positive patients had significantly higher viral load also.

Regarding the rate of viral suppression achieved in the current study, for HBeAg negative patients, treatment with PEG-IFN for 24 weeks resulted in viral suppression (<2000 IU/ml) among 38.1% of patients which increased to 71.43% after 48 weeks of treatment with a significant difference in the rate of viral suppression between the two periods of treatment. These results were not consistent with that obtained by Y. E. Chon *et al.,* where the rates of viral suppression were 81.2% and 87.8% after 24 and 48 weeks respectively with no significant difference between the two periods [9]. For HBeAg positive, treatment with PEG-IFN for 24 weeks did not result in viral suppression among all the patients. However, only 2 patients (20%) achieved viral suppression after 48 weeks of treatment with no significant difference in the rate of viral suppression between the two periods of treatment. These results were not in agreement with that of Y. E. Chon *et al.,* who reported a viral suppression rate of 36.7 % and 44.4% after 24 and 48 weeks respectively among HBeAg positive patients with significant difference between the two periods [9].

Reduction in the level of serum HBV DNA or virological response (VR) is the earliest and perhaps most appropriate measure of treatment response [16]. the rate of viral remission (VR) achieved in the current study, for HBeAg negative patients, treatment with PEG-IFN for 24 weeks resulted in VR (defined as<20 IU/ml) among (31.75%) of patients which increased to (57.14%) at 48 weeks of treatment with a significant difference in the rate of VR between the two periods of treatment. The rate of VR achieved in the current study at 24 weeks was slightly lower than that reported by in P. Piccolo *et al* (33.3%) with a higher result at 48 weeks (36.7%) [17]. In HBeAg positive patients, treatment with PEG-IFN for 24 weeks did not result in VR among all the patients. However, only 2 patients (20%) achieved VR after 48 weeks of treatment with no significant difference in the rate of VR between the two periods of treatment. Like that observed in HBeAg negative patients, the rate of VR achieved in the current study at 24 weeks was lower than that reported by in Y. E. Chon *et al* (11.1%) with a comparable result at 48 weeks (22.0%) [9].

For HBeAg positive patients, the rate of seroconversion was 10% (1/10 patients) and 40% (4/10 patients) after 24 and 48 weeks respectively. Lower seroconversion rates were reported in previous studies. George K. *et al*., reported a seroconversion rate of about 27.0% among 271 patients after 48 weeks of PEG-IFN therapy [18]

HBsAg loss after therapy is considered the ultimate therapeutic goal of anti-HBV therapy, since it is associated with positive long-term clinical outcomes [18]. In HBeAg negative patients, only (1.59%) and (9.52%) of the patients had loss HBsAg after 24 and 48 weeks of treatment respectively, while patients with HBeAg positive did not have loss HBsAg neither in 24 weeks nor in 48 weeks of treatment. Comparable low rates of HBsAg loss were reported by Y. E. Chon *et al*., study in both HBeAg positive (0.4%) and negative (1.4%) patients which achieved only after 48 weeks of treatment[9].

ALT normalization rates in HBeAg negative patients were 26.67% and 40% after 24 and 48 weeks respectively. Comparable results were reported by Patrick M. *et al*., where the ALT normalization was achieved in 38% of HBeAg negative patients after 48 weeks treatment with PEG-IFN [19]. Also, rates of ALT normalization were reported by P. Piccolo *et al.*, where 26.7% and 30% of HBeAg negative patients achieved ALT normalization after 24 weeks and 48 weeks treatment with PEG-IFN respectively [17]. In case of HBeAg positive patients, the rates of ALT normalization were 16.67% and 50% after 24 and 48 weeks respectively which is similar to that reported by P. Korkmaz *et al.,* where ALT normalization was achieved in 50% of HBeAg positive patients 48 weeks of treatment with PEG-IFN [20].

In this study, achieving all targets in HBeAg negative patients (viral suppression, and ALT normalization) was reported in 4 patients (6.35%) after 24 weeks treatment and in 6 patients (9.52%) after 48 weeks treatment. These rates were lower than obtained by other studies (36.0% after 48 weeks [19], 31.3% and 47.3% after 24 and 48 weeks treatment with PEG-IFN [9]). Regarding HBeAg positive patients, achieving all targets (viral suppression,ALT normalization, and HBeAg seroconversion) was not reported in any patients after 24 weeks treatment, yet 1 patient (10%) achieved that target after 48 weeks of treatment. These low rates are comparable to that reported by other study (10.0% after 48 weeks treatment with PEG-IFN [18], 2.2% after 24 weeks, and 10.0% after 48 weeks [9]).

Studying predictive factors (Age, Baseline HBV DNA, Baseline ALT, and Treatment period) for HBV DNA suppression at end of treatment (ET) for patients involved in the current study was done only for HBeAg-negative patients as we could not do this prediction for HBeAg positive patients because limited sample of 10 patients.

Lower baseline HBV DNA value was found to be associated with more suppression at the end of therapy (p value=0.002). On the other hand 48 weeks was better than 24 weeks; however, it was not statistically significant, while both age and baseline ALT were not predictor for viral suppression. The effect of baseline viral log as predictor of good response was maintained in multivariate analysis i.e. independent predictor for good viral suppression. Bonino *et al*., showed low baseline HBV DNA (similar to the current study), high baseline ALT, female gender, younger age, and genotype B or C (but not D) as independent predictors of a combined ALT and HBV DNA response at 24 weeks post-treatment [21].

Finally, regarding the rates of hematological side effects reported in the current study, the prevalence of neutropenia was (6.94%) after 24 and 48 weeks of treatment, prevalence of thrombocytopenia was increased from (16.44%) after 24 weeks to (24.66%) after 48 weeks and that of anemia was increased from (16.44%) after 24 weeks to (23.29%) after 48 weeks with no statistically significant difference between the two periods for any of these side effects. Buster EH *et al.,* found that the range of neutropenia was 25-26% and thrombocytopenia was 7-26% [22].

This study has some limitations. Genotyping was not done to assess the viral suppression and viral response, and no follow up after treatment was done to assess sustained viral response and antigen clearance from the patients.

4-2. Conclusions

According to the results of the current study, we can conclude that:

1-HBeAg-Negative Chronic Hepatitis B patients had better therapeutic response (especially in term of viral suppression and viral remission) to Pegylated Interferon-alpha 2a compared to HBeAg-positive patients with better response achieved after 48 weeks compared to 24 weeks therapy this may be due to the Lower baseline viral load (as a predictor factor for HBV DNA Suppression) associated with more viral suppression at the end of Pegylated Interferon-alpha 2a therapy.

2.Thrombocytopenia and anemia were more prevalent than neutropenia as hematological side effects among patients treated by Pegylated Interferon-alpha 2a.

4-3. Recommendations for future works

1. Another study to be followed with larger number of patients .

Effect of hepatitis B genotypes on drug response in Iraqi chronic hepatitis B patients treated by Pegylated Interferon-alpha 2a.

Appendix

Table 1: Demographic data of patients

	ÄHLÑÏÕÍÇÓÔ	ÊÅÍÄÎ ÑÑÓÍÕÕÏÇ	ÊÅÍÄÎ negative	ÊÖÏHÕÍ
ÈÕL·ÏÍÒ	WS	QP HQRNYE I	VS HKWKQE I	M
ÄÎÍ HÕI	SYNRq QSNV	SQNVq QUNR	TPNTq QSNQ	PNPUV[a]
ÇÍÑÏÍÒ (male)	UQ HVYNYE I	WHWPE I	TTHVYNXE I	PNYYR[b]
ï T test, b chi square				

Table 2: Log_{10} viral load

	ÄHLÑÏÕÍÇÓÔ	ÊÅÍÄÎ ÑÑÓÍÕÕÏÇ	ÊÅÍÄÎ ÑÍÎÏÕÍÇ	ÊÖÏHÕÍ
ÈÕL·ÏÍÒ	WS	QP	VS	M
ÐÑÎ ÖÍÇÏ ŁHÑÏÍ (IU/ml)	UNTYq QNQU	WQXq NVY	UNRVq QNPQ	ÁPNPPQ
ÔÛÍÓÔ				

Table 3: Log_{10} viral load

	ÄHLÑÏÕÍÇÓÔ	ÊÅÍÄÎ ÑÑÓÍÕÕÏÇ	ÊÅÍÄÎ ÑÍÎÏÕÍÇ	ÊÖÏHÕÍ
ÈÕL·ÏÍÒ	WS	QP	VS	M
ÐÑÎ ÖÍÇÏ ŁHÑÏÍ (IU/ml)	UNTYq QNQU	WQXq NVY	UNRVq 1.01	ÁPNPPQ
ÔÛÍÓÔ				

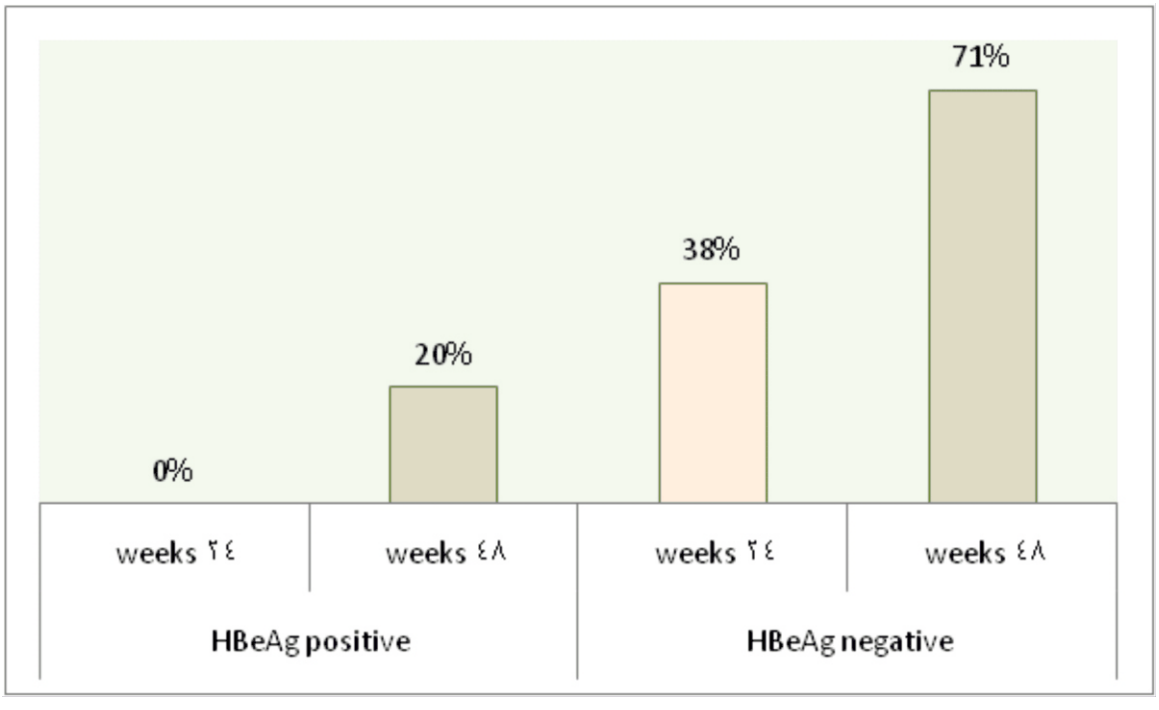

Figure 1: viral suppression according to HBeAg and duration of therapy

Table 4: Rate of viral remission according to envelope antigen

	ÇÅĮĂĴ ÑÑÓÍÓÖĮ (n=10)		Ê ÖÏ ĦÕĮ	ÇÅĮĂĴ ÑĮĴÏÓÍÓÖĮ (n=63)		Ê ÖÏ ĦÕĮ
Ĝ Į Į Ļ Ó	RT	TX	M	RT	TX	M
ĘÍÓÏ Ł remission	P (0%)	R (20%)	0.474[a]	RP (31.75%)	SV (57.14%)	0.004[b]
È ÑÔ	QP (100%)	X (80%)		TS (68.25%)	RW (42.86%)	

[Ï] Fisher exact test, [b] chi square test

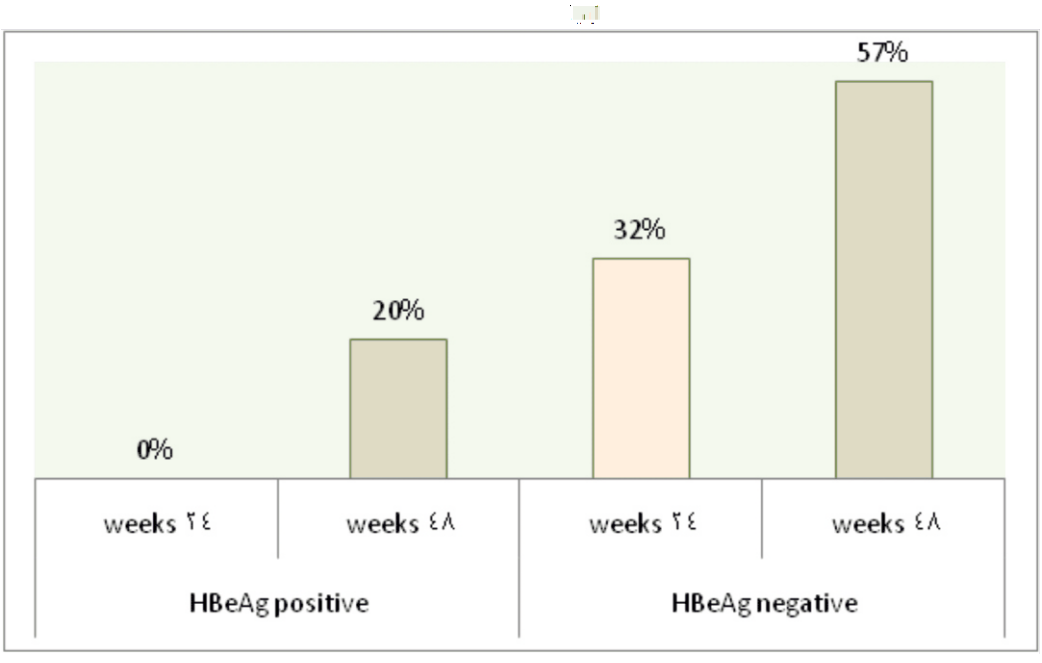

Figure 2: Viral remission according to HBeAg and duration of therapy

Table 5: Viral seroconversion of positive HBeAg

	ÇÅIÄJ ÑÑÓÍÔÖI (n=10)		Ê value	ÇÅIÄJ ÑIÎÏÔÖI (n=63)		Ê value
ĜIIĻÓ	RT	TX		M	M	M
ĒIÒÑÏÑÑÖIÒÓÍÑÑ	QHQPEI	THTPEI	PNSPSª	M	M	M
ÈÑÔ	YHYPEI	VHVPEI		M	M	M
ï Fisher exact test						

Table 6: Rate of viral loss of HBsAg

	ÇÅIÄJ ÑÑÓÍÔÖI (n=10)		Ê value	ÇÅIÄJ ÑIÎÏÔÖI (n=63)		Ê value
ĜIIĻÓ	RT	TX	M	RT	TX	M
ĘÍÖÏŁĿÑÓÓ	PHPEI	PHPEI	M	QHQNUYEI	VHYNUREI	PNQQUª
ÈÑÔ	QP (100%)	QP (100%)	M	VRHYXNTQEI	UWHYPNTXEI	
ï Fisher exact test						

Table 7: Rate of ALT normalization according to envelope antigen

	ĈÅĮĂĴ ÑŇÓĆĈĮ		Ê ÖĬĦÕĮ	ĈÅĮĂĴ ŃĮĴĬÖĈĮ		Ê ÖĬĦÕĮ
Ĝ ĮĮĻÓĤŇĜĬŁ no.)	RT (6)	TX (6)	M	RT (15)	TX (15)	M
ĂĎĚ normalization	Q (16.67%)	S (50%)	0.582[a]	T (26.67%)	V HTPE I	0.520[b]
ÈŇÔ	U (83.33%)	S (50%)		QQ (73.33%)	Y HVPE I	
Ï Fisher exact test, [b] chi square test						

Table 8: All targets achievement

	ĈÅĮĂĴ ÑŇÓĆĈĮÖĮ (n=10)		Ê value	ĈÅĮĂĴ ŃĮĴĬÖĈĮÖĮ (n=63)		Ê ÖĬĦÕĮ
Ĝ ĮĮĻÓ	RT	TX	M	RT	TX	M
ĂĬĶĹĮÖĮĬ	P HPE I	Q HQPE I	QNP[a]	T HVNSUE I	V HYNURE I	PNURP[b]
ÈŇÔ	QPHQPE I	Y HYPE I		UY (93.65%)	UW(90.48%)	
Ï Fisher exact test, [b] chi square test						

Table 9: Predictive Factors for the Suppression of HBV DNA (HBV DNA<2000 IU/mL) at the End of Treatment in HBeAg negative

	É Ë	YUE ÅČ	Ê ÖĬĦÕĮ
ĂĴĮ	PNYXS	PNYTT – 1.024	PNTQR
ÅĬÓĮĦŃĮ ĈÅĘ ĄÈĂ HĦŇĴ$_{10}$IU/mL)	PNSXX	PNRQT – 0.701	PNPPR
ÅĬÓĮĦŃĮ ĂĎĚ	QNPPQ	PNYYV – 1.006	PNVQY
ĚÒĮĬÔĽ·ĮŃÔŇĮÒĆŃĭ HTXÖÓRT weeks)	PNSQS	PNPYV – 1.014	PNPUS
ĖŃĹÖĬÒĆĬÔĮ Ï ŃĬĦŐÓĹÓ			

Table 10: Safety Profiles of Pegylated Interferon a-2a

ĚÑÖÏŁHŃÂWSI	RTĜ ĮĮĻÓ	TXŌĮĮĻÓ	ÊÖÏŁÕĮ
ÈĮÕÔÒÑÑĮŃÍÏ	UHVNTEI	UHVNTEI	QIP[a]
ĚĶÒÑL·ĪÑÏÓÔÑÑĮŃÍÏ	QRHQVNTEI	QX (24.66%)	PNRQY[a]
ĂŃĮL·ÍÏ	QRHQVNTEI	QW (23.29%)	PNSPP[a]
ï Fisher exact test			

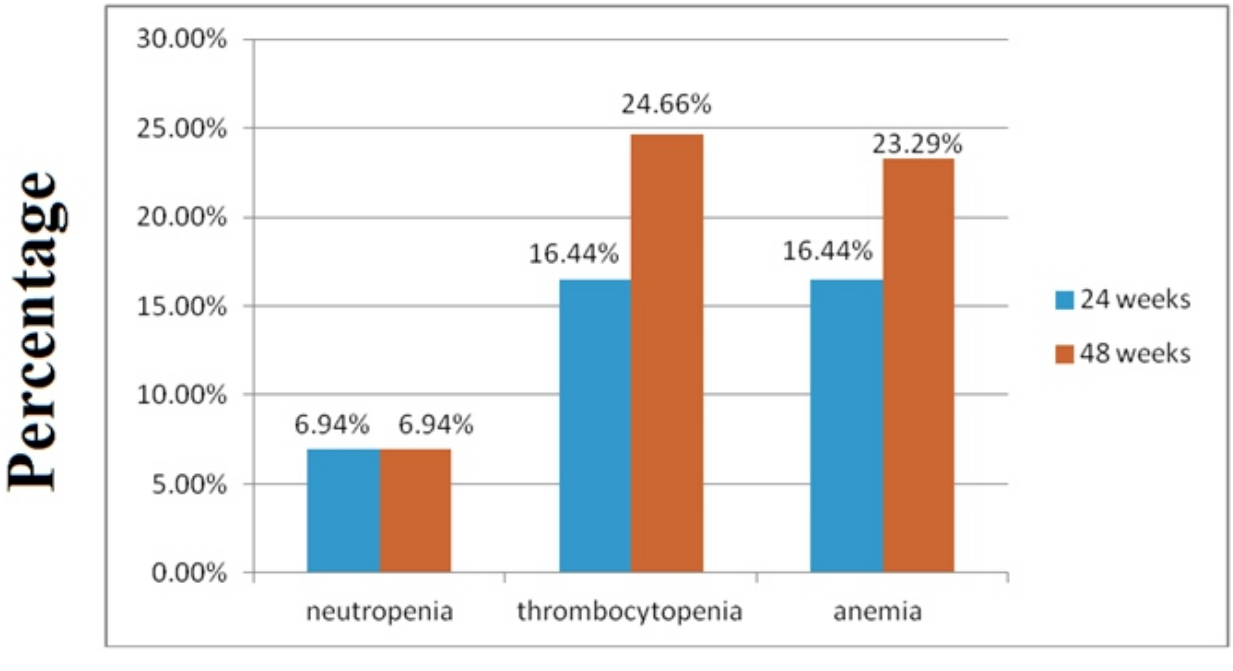

Figure 3: Safety Profiles of Pegylated Interferon a-2a

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