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*Original Research Article*

# Pegylated Interferon α-2a Therapy and Occurrence of Sinus Tachycardia in Chronic Hepatitis C Infected Patients

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**Pegylated interferon-α (Peg IFN-α) in combination with ribavirin is the backbone of treatment in patients with HCV infection that may produce serious adverse effects like arrhythmia and reversible hypertension. This study was carried out to determine whether there is any relationship between the use of pegylated interferon α-2a and sinus tachycardia (tachyarrhythmia) in chronic HCV infected patients treated with the combination of pegylated interferon α-2a and ribavirin. Also, to determine the effect of this pegylated interferon α-2a on blood pressure throughout three months period of treatment. In result, 19.67% of participants developed sinus tachycardia and 24.6% developed hypertension. We can conclude that there was a significant development of sinus tachycardia and hypertension three months after starting treatment with combination therapy with P < 0.001. On the other hand, each of pulse rate, systolic and diastolic blood pressures were significantly changed from pretreatment values with P = 0.000 for each parameter.**

**Keywords:** Pegylated interferon α-2a, Ribavirin, Sinus tachycardia, Chronic Hepatitis C infection, Reversible hypertension.

## INTRODUCTION

The recommended therapy of chronic hepatitis C virus (HCV) infection is the combination of weekly subcutaneous injection of pegylated interferon α (PegIFN α) and twice daily oral doses of ribavirin (RBV). The choice of this regimen was based upon the results of many clinical trials (Manns M *et al*, 2001). The recommended dose of PegIFN α-2a is 180 µg per week (Fried M *et al*, 2002b), and that of peginterferon alfa-2b is 1.5 µg per kilogram of body weight per week (Manns M *et al*, 2001).

Pegylated interferon-α (Peg IFN-α) in combination with ribavirin is the backbone of treatment in patients with HCV infection before direct-acting antiviral agents (DAAs) became available, and still is the optimal choice for the majority of patients with chronic hepatitis C infection (Zhao W *et al*, 2014). Cardiovascular complications caused by interferon consist mainly of arrhythmia, myocarditis, reversible hypertension, ischemic heart disease, pericarditis and pericardial effusion (Sonnenblick M and Rosin A, 1991, Teragawa H *et al*, 1996, Popescu C *et al*, 2011, Rauw J *et al*, 2012). Reversible hypertension means that upon cessation of the causative agent, the blood pressure will return back to normal level; here the causative agent is pegylated interferon α-2a. Torriani *et al* reported in their randomized, placebo-controlled trial, that ribavirin did not affect the frequency of adverse events in interferon therapy (Torriani F *et al*, 2004).

Although cardiovascular complications from interferon-α are almost rare, the growing number of patients receiving Pegylated interferon-α therapy will undoubtedly lead to an increasing number of patients with cardiotoxicity. Out of these complications, arrhythmia and ischemic heart disease are the predominant types, followed by myocarditis and reversible hypertension, while cardiomyopathy is rare (Sonnenblick M and Rosin A, 1991, Teragawa H *et al*, 1996)

Among the infrequently reported (1%) prominent serious adverse events associated with standard interferon therapy are retinopathy, retinal hemorrhage, visual loss, tinnitus, hearing loss, cardiac arrhythmias, congestive heart failure, interstitial pneumonitis, acute renal failure (Fried, 2002a).

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The term tachyarrhythmias typically refer to non-sustained and sustained forms of tachycardia originating from myocardial foci or reentrant circuits. The standard definition of tachycardia is a rhythm that produces a ventricular rate >100 beats per minute, this definition has some limitations in that atrial rate can exceed 100 beats per minute despite a slow ventricular rate (Marchlinski F, 2012). ECG characteristics for patients with sinus tachycardia include; rates greater than or equal to 100 beats/min, regular rhythm, upright, consistent P wave that's normal in morphology (if no atrial disease), P–R interval lies between 0.12–0.20 seconds and shortens with increasing heart rate and finally QRS complex will be less than 0.12 seconds, consistent, and normal in morphology (Jameson J *et al*, 2005).

Normal rate for the sinoatrial (SA) node is 60 to 100 beats per minute; less than 60 beats/minute is considered as sinus bradycardia while greater than 100 beats/minute is considered to be sinus tachycardia (Patel A, 2010). According to the British hypertension society classification of hypertension, there are three categories for normal blood pressure; optimal, normal and high normal blood pressures. In optimal, systolic blood pressure will be less than 120 mmHg and diastolic blood pressure will be less than 80 mmHg. In normal, systolic and diastolic blood pressures will be less than 130 and 85 mmHg, respectively, while in high normal category; systolic blood pressure lies between 130-139 mmHg and diastolic blood pressure lies between 85-89 mmHg (Newby *et al*, 2014). In our study, we used high normal category as a normal range for systolic and diastolic blood pressures.

## METHODOLOGY

This study was conducted during the period from the 1st June 2015 till 1st December 2015, which was carried out in Gastro-enterology center at the General teaching hospital in Sulaimania city/ Kurdistan Region of Iraq.

### *The samples*

Sixty one (33 males and 28 females) chronic HCV infected patients with genotype one between ages 18-70 years old (43.67± 1.77) were included for the purpose of this study. Each one of them was treated with a combination of 180 µg pegylated interferon α-2a (Pegasys® by Roche pharmaceutical company, Switzerland) once, weekly by subcutaneous injection and different doses of oral ribavirin (Rebetol®) by Schering pharmaceutical company, USA), depending on body weight. Patients with body weights equal or greater than 75 kg, received 1200 mg/day of ribavirin, while those with body weights less than 75 kg, received 1000 mg/day of ribavirin.

### *Data collection*

After taking patient's concern, the data were obtained by direct interview with the patients twice for ECG monitoring and appropriate questionnaire to be filled at home by the patients themselves, including 12 blood pressure readings and 12 pulse rate readings throughout three months of treatment with the first-line combination therapy. For ECG monitoring, all the patients had at least 30 minutes rest, and were monitored before and after three months of treatment to determine if any sinus tachycardia or effect on the heart appeared throughout these months of treatment, then blood pressure and pulse rate were recorded again by health care professionals. The results of all three parameters should be normal in all patients before starting treatment with the first line combination therapy. The mean of blood pressure and pulse rate readings recorded by the patients were taken for the purpose of statistical calculations. The prevalence was monitored only in term of clinical aspect like ECG, blood pressure and pulse rate monitoring.

### *Inclusion criteria*

Patients included in this study were confirmed to have chronic HCV infection of genotype one, between 18-70 years old of both genders and willing to be treated and to adhere to treatment requirements. They were treatment-naive patients. Also the patients confirmed to have no cardiovascular problems before starting treatment with the first line combination therapy.

### *Exclusion criteria*

The HCV infected patients excluded from this study were those who were; with HIV or HBV co-infection, solid organ transplantation (heart, lung, liver, and kidney), decompensated liver disease, allergy to any one of the components of combination therapy, difficult to follow up (alcoholics, patients who travel frequently), breast feeding and pregnant or patients unwilling to comply with adequate contraception, or with thalasemia, cytopenia, severe anemia, renal failure, severe psychiatric disorder, severe immunosuppresion, heart failure or significant coronary or CVD, untreated thyroid disease.

### *Statistics*

Data are represented as mean ± SEM. Paired sample T-test is used to compare treatment groups, focusing on changes from pre-treatment values and after three months of starting treatment. Frequencies were calculated for categorical variables and $\chi 2$ test is used to compare categorical variables before and after starting treatment. $P < 0.05$ identifies significant difference between treated and pre-treated values.

## RESULTS

In all the sixty one patients, before starting treatment, the ECG reading was normal sinus rhythm (representing 100%), systolic and diastolic blood pressures were within the normal range (Systolic BP; 130.24± 1.4 mmHg, min= 90 mmHg, max= 139 mmHg, Diastolic BP; 76.8± 0.6 mmHg, min= 65 mmHg, max= 80 mmHg respectively), and the pulse rate reading was also within the normal range (81.37± 0.82 b/m, min= 60 b/m, max=94 b/m) as shown in table 1.

Three months after starting treatment, twelve patients which represent 19.67% (7 males and 5 females) with mean age 53.5 ±2.46 reported sinus tachycardia with average pulse rate reading of (136.4 ±3.08 b/m, min= 122 b/m, max= 160 b/m), average systolic BP of (150.8± 5.96 mmHg, min= 130 mmHg, max=190 mmHg) and average diastolic BP (91.6±2.9 mmHg, min=80 mmHg, max=110 mmHg) readings, and all were significantly changed from the pretreatment values as shown in table 2. The remaining forty nine patients (which represent 80.33%) with mean ages 42.3 ± 1.9, reported normal sinus rhythm on ECG reading, average pulse rate of (83.95 ±1.02 b/m, min= 68 b/m, max=98 b/m), systolic BP (134.08 ± 1.54 mmHg, min= 110 mmHg, max=160 mmHg) and a diastolic BP (83.16 ±1.17 mmHg, min=65 mmHg, max=100 mmHg). Each of PR, SBP and DBP were again significantly changed from the baseline values as shown in table 3.

**Table 1.** Blood pressure (mmHg), pulse rate (beat/min) and ECG reading in all 61 patients before treatment and three months after starting treatment with combination therapy

| Parameters | Pre-treatment | Three months after starting treatment with 180 µg PEGIFN +RBV | P-value |
|---|---|---|---|
| **Blood pressure (mmHg);** | | | |
| **SBP** | 130.2 ± 1.4 | 137.4 ± 1.9 | 0.000 |
| **DBP** | 76.8 ± 0.6 | 85 ± 1.2 | 0.000 |
| **Transient hypertension** | 0 | 15 (25.6%) | < 0.001 |
| **PR (b/m)** | 81.37 ± 0.8 | 94.3 ± 2.9 | 0.000 |
| **ECG reading** | | | |
| **Normal** | 61 (100%) | 49 | |
| **Tachyarrhythmia** | 0 | 12 (19.67%) | < 0.001 |

*p < 0.05 significant difference between treated and pre-treated values.

**Table 2.** Blood pressure (mmHg), pulse rate (beat/min) and ECG reading in those 12 patients who developed sinus tachycardia before treatment and three months after starting treatment with combination therapy

| Parameters | Pre-treatment | Three months after starting treatment with 180 µg PEGIFN +RBV | P-value |
|---|---|---|---|
| **Blood pressure (mmHg);** | | | |
| **SBP** | 135.8 ± 1.9 | 150.8± 5.9 | 0.048 |
| **DBP** | 78.3± 1.1 | 91.3 ± 3 | 0.001 |
| **Transient hypertension** | 0 | 7 (58.3%) | |
| **PR (b/m)** | 75.8 ± 5.9 | 136.4 ± 3.1 | 0.000 |
| **ECG reading** | | | |
| **Normal** | 12 (100%) | 0 | -------- |
| **Tachyarrhythmia** | 0 | 12 | |

*p < 0.05 significant difference between treated and pre-treated values.

**Table 3.** Blood pressure (mmHg), pulse rate (beat/min) and ECG reading in the remaining 49 patients who showed normal sinus rhythm before treatment and three months after starting treatment with combination therapy

| Parameters | Pre-treatment | Three months after starting treatment with 180 µg PEGIFN +RBV | P-value |
|---|---|---|---|
| **Blood pressure (mmHg);** | | | |
| **SBP** | 128.9 ± 1.6 | 134.1± 1.5 | 0.001 |
| **DBP** | 76.4± 0.7 | 83.2 ± 1.2 | 0.000 |
| **Transient hypertension** | 0 | 8 (16.3%) | |
| **PR (b/m)** | 81.1 ± 0.98 | 83.96 ± 1.03 | 0.008 |
| **ECG reading** | | | |
| **Normal** | 49 (100%) | 49 | ------- |
| **Tachyarrhythmia** | 0 | 0 | |

*p < 0.05 significant difference between treated and pre-treated values.

Overall, three months after starting treatment, in all 61 patients, average blood pressure readings were SBP= 137.4 ± 1.9 mmHg, max= 190 mmHg, min= 110 mmHg, and DBP= 85 ±1.2 mmHg, max= 110 mmHg, min= 65 mmHg, PR= 92.6 ± 2.7 b/m, max= 144 b/m, min= 60 b/m.

On the other hand, 15 patients (8 females and 7 males) with mean age 48.7 ± 4.1 representing 25.6% of all patients developed hypertension three months after starting treatment. Ten of them (5 males and 5 females) developed isolated systolic hypertension while the remaining 5 patients (3 females and 2 males) showed elevation in both systolic and diastolic blood pressures. Among those patients who developed hypertension, 7 of them also developed sinus tachycardia; this means that 58.3% of those who developed sinus tachycardia also developed hypertension.

Finally, we can say that, there was a significant development of sinus tachycardia and hypertension three months after starting treatment with combination therapy with P < 0.001. On the other hand, each of pulse rate, systolic and diastolic blood pressures were significantly changed from pretreatment values with P = 0.000 for each parameter.

## DISCUSSION

Interferon therapy has been performed widely to treat chronic hepatitis C virus infection, which is associated with several side effects, such as fever, malaise, headache, blood cell count decrease, and depression. A small number of cases of suspected Interferon-induced cardiotoxicity have been reported in the literatures (Sakabe M *et al*, 2013). The most common manifestations of cardiotoxicity were tachyarrhythmias, such as paroxysmal atrial fibrillation, ventricular tachycardia and fibrillation, which were mostly observed in patients with underlying heart disease (Sonnenblick M and Rosin A, 1991).

In our study, 12 patients (19.67%) developed sinus tachycardia three months after starting treatment, this result means that the appearance of tachycardia was significant among our patients and particular attention is needed for cardiovascular complications.

Teragawa *et al* reported that 10 of 295 patients with chronic hepatitis C experienced cardiovascular adverse effects of interferon (Teragawa H *et al*, 1996). He studied 295 HCV-infected patients during their treatment course of interferon therapy and after one year. They found that 4 (1.4%) patients developed arrhythmias; this was only 40% of the overall cardiovascular complications of HCV treatment. The result of Teragawa's study is somewhat different from our results; this difference may be due to the difference in the demographic data of participants, larger sample size and longer duration of their follow up.

Fujiwara *et al* reported the case of a 64-year-old man infected with HCV. Seven days after starting interferon, the patient developed a giant T wave inversion visualized on a check-up electrocardiogram (ECG). In addition, ten days after interferon administration, the patient's clinical symptoms included fatigue, palpitations, a depressive feeling, tachycardia of 100 beats/min, supraventricular premature beats, atrial fibrillation, and septal and apical hypertrophy. At four days after cessation of interferon therapy, the patient's subjective symptoms improved and atrial fibrillation disappeared, however his giant T wave inversion and apical hypertrophy remained detectable several months after discontinuation of the drug (Fujiwara *et al*, 2001).

This result might be/not be achieved in our study and the sinus tachycardia and palpitations return back to normal/remain if we stopped interferon therapy. This case has shown that the discontinuation of pegylated interferon can revert some arrhythmic changes (Zhang R *et al*, 2010). In hemophilic patients simultaneously infected with HCV and HIV, therapy with interferon-alpha-2a has been associated with a 14% incident rate of tachycardia, leading to a decrease in the administered interferon dose (Zhang R *et al*, 2010) but in this case a blood disorder may also have a role in the development of tachycardia.

Transient sinus tachycardia has been observed in HCV infected patients undergoing interferon therapy (Karbasi-Afshar R, 2014). They have occasionally resulted in the cessation or dose reduction of the drug.

In another study done in Turkey by Ural *et al*, showed that 21.7% of participants who received a combination of pegylated interferon α-2a and ribavirin experienced palpitation throughout treatment period (Ural *et al*, 2010). This result is somehow close to our study's result, may be because of nearly the same sample size, similar demographic characteristics of the study participants and the use of the same brand of interferon injection (Pegasys®).

In a case study in Egypt done by Atrebi K and El-Bassyouni H, a 55-years-old Egyptian woman with chronic hepatitis C, with no cardiac abnormalities and normal ECG, treated with Peg-IFN-a2b at a dose of 1.5 mg/kg per week subcutaneously (150 mg/week) and ribavirin 1200 mg/day. On week 12, she complained of two attacks of palpation followed by syncopal attacks. ECG holter revealed ventricular ectopic activity in the form of unifocal ventricular extrasystoles (VES) and sinus tachycardia (Max HR was 156 beats/min). Follow up did not show any more palpitation, syncopal attacks or other side effects (Atrebi K and El-Bassyouni H, 2009), this exactly what happened for majority of our patients who developed sinus tachycardia on ECG monitoring three months after starting treatment, and if Atrebi K and El-Bassyouni H, had studied more cases throughout three months of starting treatment with combination therapy the same results as in our study may be obtained, although the source for interferon was different because they used pegylated interferon α-2b instead of pegylated interferon α-2a.

Actually, the appearance of cardiac arrhythmia after interferon therapy is reported only in the Peginterferon product information (Atrebi K and El-Bassyouni H, 2009) and one big study conducted on 441 chronic HCV patients reported that unexplained syncopal attacks occurred in 11 patients resulting in discontinuation of the treatment (HCV advocate, 2002). Also a recent series has reported the discontinuation of interferon in 17% of HCV-infected patients happens, mainly due to cardiovascular complications (Giannini E *et al*, 2010).

Apart from one report from a large population, much lower frequencies of cardiovascular complications of interferon [7 out of 11241 (0.06%)] in patients with chronic hepatitis have been reported (Fattovich G *et al*, 1996). These complications have been reported as case reports and series from different centers; however, to the best of our knowledge till now, there is no article that has comprehensively reviewed the existing data to provide clinicians with an inclusive view on this subject, this is may be due to the suggestions that HCV-infected patients are mostly complicated with several other disorders, and a cardiovascular complication may be associated with these disorders and not be considered as a side effect to interferon therapy alone (Karbasi-Afshar R, 2014).

Several reports indicated an association between interferon therapy in HCV-infected patients to arrhythmias, either directly or secondary to endocrine or pulmonary system disturbances. Hiramatsu *et al*, in a cohort of 22 patients, suggested that arrhythmias which developed as a consequence of interferon therapy in patients with active hepatitis were reversible and subclinical with no sustained ventricular arrhythmia detected throughout the follow-up period (Hiramatsu *et al*, 2005). However, their cohort consisted of a limited number of patients with a very small sample size and serious arrhythmias could happen occasionally.

Secondary hypertension is elevated blood pressure that results from an underlying, identifiable, often correctable cause. Only about 5 to 10 percent of hypertension cases are thought to result from secondary causes (Onusko E, 2003). This reversible hypertension usually has secondary causes that upon the removal of causative agent the blood pressure will return to normal. Here pegylated interferon is a causative agent for elevating blood pressure.The first, most practical step in evaluating an elevated blood pressure reading is to investigate its accuracy.

White-coat hypertension (blood pressure that is elevated in the physician's office but normal at other times) accounts for about 20 percent of patients with elevated readings (Setaro J, 2000). JNC-VI (the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) recommends confirming high blood pressure readings outside of the office setting (Onusko E, 2003), that's why we provided our patients with a questionnaire to report their blood pressure and pulse rate by themselves at home at least twelve times throughout the study period. Despite all these precautions from recording falsely-elevated blood pressures, 15 patients (25.6%) developed hypertension three months after starting treatment.

Ten of them developed isolated systolic hypertension while the remaining 5 patients showed elevation in both systolic and diastolic blood pressures. Among those patients who developed hypertension, 7 of them also developed sinus tachycardia; this means that 58.3% of those who developed sinus tachycardia also developed hypertension. This significant elevation in blood pressure three months after starting treatment, despite interferon therapy, may be due to several factors, the most important one is the psychological status of

the patients because after our interview with each one of them, we realized that they consider their disease as a social stigma.

## CONCLUSION

In conclusion, we can say that, there was a significant development of sinus tachycardia and hypertension three months after starting treatment with combination therapy and each of pulse rates, systolic and diastolic blood pressures were significantly changed from pretreatment values.

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