Descriptive study of incidence of side effects of Pegylated interferon alpha therapy and their relation to age, gender, duration of treatment and type of hepatitis in 50 Iraqi patients.

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Summary:

Background: Hepatitis C and B is common disease all over the world and their chronicity is a social and medical problem so medical treatment by alpha interferon can change the mortality and morbidity.

Object: Identify the incidence of the side effects of pegylated interferon alpha in a sample of Iraqi patients with chronic hepatitis B&C and their relation to age, gender, duration of treatment and type of hepatitis comparing them with the literatures from other countries.

Patients and methods: A descriptive case series study was conducted on 50 patients, 24 male and 26 female, with established diagnosis of hepatitis B(20 patients)and C(30 patients) who attend Baghdad Teaching hospital and Gastroenterology and Hepatology centre in Baghdad between the period of January 2009 and October 2010 with follow up over at least 3 months.

A direct interview with detailed history and thorough clinical examination with some simple laboratory investigation were done to determine any of the documented side effects of alpha interferon therapy or discover new side effects not elicited in the studies done on other populations.

Results: Flu-like illness is the most common side effect (84%), followed by fatigue, anorexia, local reaction and neuropsychiatric side effects while Neutropenia, lymphopenia and thyroiditis are rare.

There is no significant difference in the incidence of side effects between age groups with the exception of constipation which occurs more in younger age group. Arthralgia, palpitation, eczema, itching and rash increase in incidence with prolonged duration of treatment.

There is no significant difference in incidence of side effects between both genders apart from hypertension (more in female) and dizziness (more in male).

There is no significant difference in incidence of side effects between patients with hepatitis B&C but anemia occurs more in patients with hepatitis C and tremor reported more in patients with hepatitis B.

Conclusion: Almost all patients on treatment with interferon-based regimen will experience adverse events that can threaten good adherence. Flu-like illness is the most common side effect (84%), followed by fatigue, anorexia, local reaction and neuropsychiatric side effects (depression, nervousness, insomnia).

The higher incidence of anemia in patients with hepatitis C is mostly due to concomitant ribavirin therapy.

Age, gender, type of hepatitis and duration of treatment can affect the incidence of interferon therapy.

Keywords: hepatitis C and B, PG interferon alpha treatment.

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Introduction:

Interferons: Interferons comprise a group of related proteins whose effects include antiviral activity, growth regulatory properties, inhibition of angiogenesis and a wide variety of immunomodulatory activities. They are classified into:

-Leukocyte interferon is interferon alpha (IFNa)

-Fibroblast interferon is interferon beta (IFNb)

- Immune interferon is interferon gamma (IFNg) (4)

* Recombinant interferons have also been coupled to polyethylene glycol molecules (Pegylated interferon) to modify their pharmacokinetic properties and prolong their half-lives.

* It is assumed that increased expression of antiviral genes induced by type 1 interferons is an important factor in the elimination of hepatitis viruses.

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* Care of patients with chronic hepatitis depends upon recognition of those at increased risk for side effects, and appropriate response when they occur. (1, 2)

Side effects:

Flu-like illness: The most common side effects include myalgia, headaches and low-grade fevers, seen in over 80 %.

Hematological: include anemia, neutropenia and thrombocytopenia due to myelosupression and at certain levels it necessitates discontinuation.

Neuropsychiatric: carry significant impact on the patient and include depression, nervousness, insomnia and even suicide attempt or ideation.

Others: conjunctivitis, autoimmune thyroiditis, eczema, hearing loss. (3,5)

Patients and methods

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diagnosis of hepatitis B(20 patients) and C(30 patients) who attended Baghdad Teaching hospital and Gastroenterology and Hepatology centre in Baghdad between the period of January 2009 and October 2010 with follow up of at least 3 months.

All eligible patients had an established diagnosis of chronic hepatitis B or C based on clinical, biochemical and serological markers and polymerase chain reaction (PCR) studies.

Any patient with comorbidity (e.g. chronic renal failure, diabetes mellitus, connective tissue disease etc.) was excluded from the study because they may have clinical features that simulate side effects of interferon. Similarly any patient with regular multiple drug usage was excluded because they may share similar side effects with interferon with the exception of ribavirin in cases of hepatitis C which cannot be excluded for ethical issues as it essential part of hepatitis C treatment protocol and of proven efficacy.

Also, as the study deals with adult patients, patients younger than 18 year were excluded from the study.

All the patients were receiving the standard dose of interferon, pegylated interferon alpha 2b;100 µgm/ week subcutaneously, the same route at the same interval.

A direct interview of each patient and questioner was designed to name, age, residence, date of diagnosis and duration of treatment followed by questioner about variable symptoms involving each system, and specific questioner for depression (mood, talk, energy, ideas, cognition, physical and behavior).

Seventy side effects has been reported by history, examination and laboratory tests and each one was adhered separately to detect any relationship with age, gender, duration of treatment and type of hepatitis.

Anemia was defined according to the WHO definition as hemoglobin level <13 gm/dl in male and <12 gm/dl in female [20].

Neutropenia defined as absolute neutrophil count (ANC) of<1500/µl, lymphopenia as lymphocyte count <800/µl and thrombocytopenia as platelet count of <150 000/µl [21].

For ethical considerations the goals of the interview were explained to the patients and offered the choice to accept or refuse participation in the study.

Data Analysis:

Descriptive analysis was used to show the mean and standard deviation for age and duration. Number and percentage to describe the distribution of side effect, gender and type of hepatitis.

The chi-square (χ^2) test was used but when one of the expected values was less than 5, Fisher exact test or Mid-P exact test was used to calculate *P*-value.

The *t*- test was used to compare means of different groups for continuous variables. Study confidence interval was 95% and significant *P*-value was <0.05.

Statistical package for social sciences (SPSS) version 17(V17) was used for statistical analysis.

Results:

1-Fifty patient were included in the study, 24(48%) were male and 26(52%) were female, the youngest patient was 18 year old and the oldest was 71 year old, the mean age of the patients was (39.8).the duration of treatment was ranging from 2 months to 21 months.

The most common side effect was flu-like illness (84%) followed by fatigue 62%, anorexia 62%, local reaction 60%, depression 54% and arthralgia 50%.

Table (1) shows the prevalence of side effects of interferon therapy according to our study.

Table (1): prevalence of side effects of PG interferon alpha

	Side effect	No.	percentage		Side effect	No.	percentage
1	Flu-like illness	42	84%	29	Somnolence	5	10%
2	Fatigue	31	62%	30	Tremor	5	10%
3	Anorexia	31	62%	31	Stomatitis	5	10%
4	Local reaction	30	60%	32	Hair thinning	5	10%
5	Depression	27	54%	33	Menstrual disorder	5	10%
6	headache	27	54%	34	Thrombocytopenia	5	10%
7	Arthralgia	25	50%	35	Conjunctivitis	5	10%
8	Nausea	23	46%	36	Alopecia	4	8%
9	nervousness	22	44%	37	Irritability	4	8%
10	Abdominal pain	20	40%	38	Hypertension	4	8%
11	Insomnia	17	34%	39	Anxiety	4	8%
12	Weight loss	16	32%	40	Tinnitus	4	8%
13	Vomiting	15	30%	41	Thirst	4	8%
14	Anemia	14	28%	42	Parashesia	4	8%
15	Constipation	14	28%	43	Lymphopenia	3	6%
16	Eye pain	12	24%	44	Gingival bleeding	3	6%
17	Palpitation	12	24%	45	Chest pain	2	4%
18	itching	11	22%	46	Shortness of breath	2	4%
19	Vertigo	11	22%	47	Photosensitivity	2	4%
20	Increased sweating	10	20%	48	Eczema	2	4%
21	Diarrhea	9	18%	49	Loss of libido	2	4%
22	Rash	8	16%	50	flushing	2	4%
23	Cough	8	16%	51	Thyroiditis	1	2%
24	Dry mouth	8	16%	52	Dry skin	1	2%
25	Dyspepsia	7	14%	53	Suicide attempt	1	2%
26	Dysurea	7	14%	54	flatulence	1	2%
27	Neutropenia	6	12%				
28	rigor	6	12%				

2-There was no significant difference in the incidence of side effects between age groups with the exception of constipation occurring in younger age group, mean age of positive patients 30.79 year and *p*-value 0.001 (the mean age of negative cases is 44.09 years).

3-Five side effects have been reported to be related to the duration of treatment including arthralgia, palpitation, eczema, itching and rash. Table (2) shows the statistical data of each one:

Table (2): the statistical data of side effects with significant relation to duration of treatment according to our study.

	Positive cases		Negative cases		*p*-value
	Mean of duration (months)	Standard deviation	Mean of duration (months)	Standard deviation	
1-palpitation	8.08	5.282	5.21	3.434	0.032
2-arthralgia	7.4	5.033	4.4	2.021	0.008
3-eczema	13.5	10.607	5.58	3.530	0.006
4-itching	8.18	5.115	5.2	3.567	0.035
5-rash	9.5	5.182	5.21	3.517	0.005

4-two side effects have been reported to be significantly related to gender; dizziness and hypertension. Dizziness has been reported in male more than female, 62.5% were male and 37.5% were female (χ^2=0.011). On the other hand all the four reported cases of new onset hypertension were female with a *chi-square* (χ^2) of 0.019. Below is a representing chart of these two side effects: (figure 1)

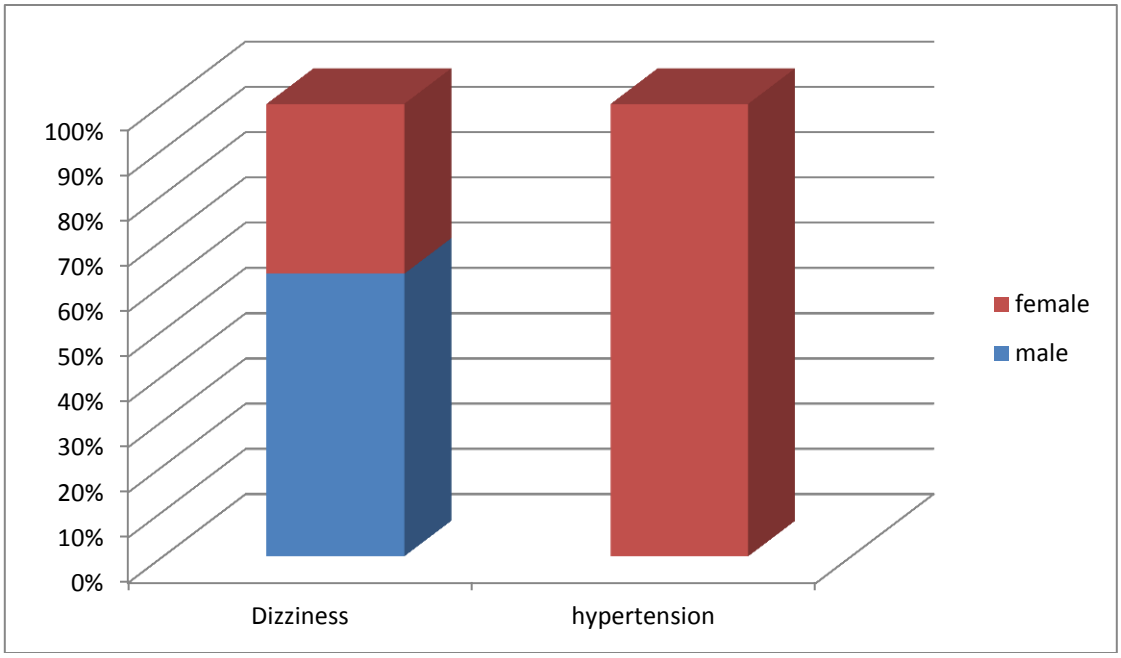

Figure (1): representing chart of dizziness and hypertension related to gender.

4- Two side effects have been reported to be significantly related to the type of hepatitis, tremor and anemia.
Tremor is occurring more in patient with hepatitis B.80% of reported cases was in patient with hepatitis B with *chi-square* (χ^2) of 0.041. Anemia was seen in 14 patients, two of them hepatitis B, PCV drop from normal level to 28% - 30% , both of them the anemia was normochromic normocytic with retic count 1%. while in hepatitis C had been seen in 12 patients their PCV drop from normal to level range from 15-30% three of them their blood film normochromic normocytic , target cell and anisoparrocytosis their retic was increase between 4-6%. Other three patients were having hypochromic microcytic anemia. And 6 of them having normochromic normocytic anemia with normal retic count. Below is a representing chart of these two side effects: (figure 2)

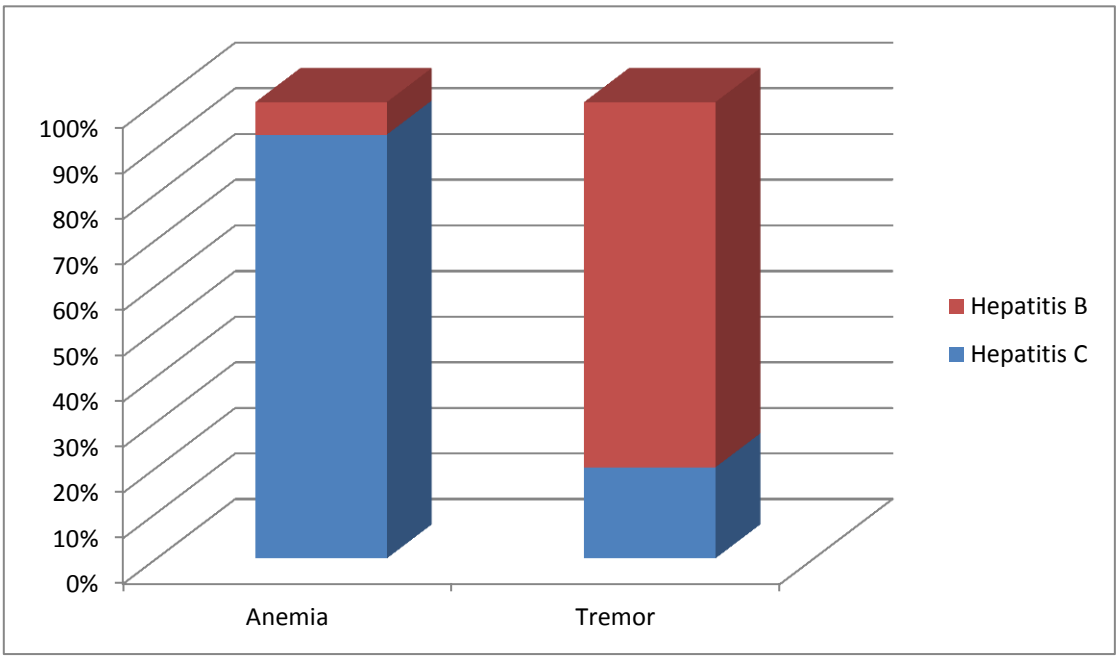

Figure (2): representing chart of anemia and tremor related to type of hepatitis.

Table (3) Incidence of depression in this study related to the type of hepatitis

	HBV	HCV	Total
Number of patients	10	17	27
%	20	34	54

This table showed the relationship between the depression as a complication of treatment in the both type of hepatitis B & C. depression seen in 10 patients with HBV and 17 patients with HCV.

Discussion:

Severe side effects may reduce adherence to therapy and may result in dose modifications that result in a less optimal response. Both IFN and ribavirin induce side effects that can impact the management of patients with chronic hepatitis C. IFN-related side effects can be divided into IFN-induced bone marrow suppression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes. The main adverse event of ribavirin is hemolytic anemia.

Overall, side effects result in 10-20% premature withdrawals from therapy and an additional 20-30% of patients require dose modifications. These numbers are lower in recent studies, suggesting an improved understanding and management of adverse events which potentially may lead to higher SVR. (15) However, these percentages were recorded from registration trials using carefully selected patients. This may differ in general clinical practice, where patients with, e.g., history of depression, low platelets or thyroid disease are being treated (6).Our study has revealed that the side effects of interferon occur in significant percentage of treated patients. Nevertheless, our sample of patient which included 50 patients, only one patient(patient 3) discontinue treatment transiently because of severe depression and resumed treatment safely thereafter, a picture significantly lower than that of intolerance in western studies which approach 20% as mentioned above. This may be related to the pre-requisites of our study which exclude patients with major comorbidity or suggest better understanding and management of adverse effects.Table 4 shows comparison between results of our study and results of western studies. Comparing our study with studies done in western countries reveals some differences. Arthralgia, anorexia, weight loss, injection site inflammation, depression and nervousness were reported more frequently in Iraqi than western patients. On the other hand alopecia, dyspnea and irritability were lower in Iraqi than western patients. The remainder of the side effects were comparable in both studies. It is hard to compare results of the study with that of western trials owing to differences in socioeconomic and educational level. For example the incidence of depression and nervousness in our study is nearly double that of western studies which may reflect the depressed and/or nervous personality of Iraqi people.The incidence of side effects among different studies is difficult to compare since the studies had significant differences in genetic and socioeconomic backgrounds. Furthermore, there were methodological differences in assessing side effects. Patients were selected on the basis of well-defined inclusion and exclusion criteria(6). There is no similar study in the Middle East to compare with.

Table (4): comparison of the study results with the western results.

Side effect	Incidence in western patients(%) (Reddy 2007,Andriulli 2008, Zeuzem 2009) [8,7,9]	Incidence in Iraqi patients (%)
Headache	47-62	54
Pyrexia	40-46	52
Myalgia	37-56	52
Rigor	24-48	12
Arthralgia	24-34	50
Nausea	35-43	46
Loss of appetite	21	62
Weight loss	29	32
Diarrhea	22	18
Alopecia	21-36	8
Rash/dermatitis	20-24	16
injection site inflammation	25	60
Pruritus	25-29	22
Dyspnea	26	4
Fatigue	48-64	62
Insomnia	33-40	34
Irritability	24-35	8
Depression	22-31	54
nervousness	19	44

Flu-like symptoms usually occur during the first weeks of treatment and the severity declines over time. These symptoms include fever, chills, headache, arthralgia and myalgia. Antipyretic drugs such as paracetamol can help prevent or reduce these side effects[6].In our

study flu-like illness was the most common reported side effects occurring in 84% of patients, most of which occur in the first 48 hours after injection of interferon. The frequency and intensity of these symptoms decrease gradually after weeks of treatments. Some patients report amelioration of the symptoms with the ingestion of non-steroidal anti-inflammatory drugs (NSAID).Neuropsychiatric side effects such as irritability, severe fatigue, and apathy are frequent and pose a great problem for many patients, also affecting other family members. Severe depression can occur and even suicide has been reported [10]. Psychiatric care and the use of antidepressants, especially serotonin uptake inhibitors (SSRIs) may help reduce IFN-induced depression [11] and consequently improve adherence to therapy and the response rates [12]. [6]In our study neuropsychiatric side effects have been reported in high frequency. One patient (patient 3) develop severe depression that necessitate discontinuation of treatment and consult psychiatrist who kept him on antidepressant and after three months he resumed his treatment safely without recurrence. In spite of his severe depression, the patient denied any suicidal attempt or ideation.IFN has immunomodulatory properties, and treatment can induce autoimmune phenomena [22]. The most frequent problem is the development of autoimmune thyroiditis. In most cases thyroiditis starts with hyperthyroidism that later turns into hypothyroidism. Autoimmune thyroiditis has been reported in up to 20% of patients on or after IFN-based therapies. This may not be reversible upon stopping therapy [13]. Predisposed patients with pre-existing thyroid antibodies have a higher risk and it is possible that hepatitis C itself may be a cause of autoimmune thyroiditis [14]In our study we have one female patient with thyroiditis (patient 12), she has no history of thyroid disease and developed slight thyroid swelling and tenderness and thyroid function revealed slight elevation of thyroid hormone. Antithyroglobulin antibody comes to be positive with high ESR. Some of other reported side effects that can be explained by autoimmune mechanism include eczema (4%), itching(22%) and rash(16%).Interferon-based therapy is accompanied by a marked drop in white blood cells in general, neutrophils and absolute, although not relative, CD4+ cell count. This change of the cellular immune system does not result in an increased number of serious infections even in HIV-coinfected patients. In general the incidence of serious infections is low (<5%) in patients on interferon-based therapy[15,16,17]. Six patients in our study have documented absolute neutrophil count less than 1.5X109 /L with normal baseline leucocytes count. All of them have been sent for chest radiograph which revealed no abnormalities and ESR was persistently normal. None of them reported history of recurrent infection or febrile illness and no increase in the incidence of TB but none of them met the definition of profound or grade(4) neutropenia (i.e ANC <0.5X109/L). Regarding relation of the incidence of side effects to the duration of therapy, most of the reported side effects were unrelated to the duration. The exceptions were three skin manifestations: eczema, rash and itching which can be explained by autoimmune mechanism. On the other hand some side effects appear to wane with continuing treatment, the most obvious example is flu-like illness which is more marked early in the course of the treatment. This fall in the incidence of flu-like illness can be spontaneous diminution with ongoing treatment due to tolerance or reflect increased attention of the patient and doctor to this troublesome adverse effect and resolution with use of NSAIDs. Of note that low platelets are a contraindication for the use of acetylsalicylic acid, diclofenac or ibuprofen because of the inhibition of platelet aggregation. High doses of paracetamol may result in liver toxicity. Doses exceeding 2 g/day of paracetamol are not recommended[18]. By comparing the incidence of side effects between hepatitis B&C in our study there was considerable difference in the incidence of anemia with 92.9% of the reported cases were in patients with hepatitis C. This is most likely explained by the additive effect of hemolytic anemia induced by ribavirin to the myelosuppressive effect of interferon that inhibit compensatory reticulocytosis. In five patients out of thirteen (38.4%) with hepatitis C and anemia the anemia was severe enough to necessitate reduction in the dose of ribavirin. Of note fatigue was reported in 62% of our sample, 35.4% of them have concomitant anemia. Asthenia and fatigue are frequent complaints of patients that usually increase slowly in intensity over the first couple weeks of therapy. In patients with marked anemia these symptoms can be improved by raising low haemoglobin with the use of erythropoietin, reduction of ribavirin or red blood cell transfusion [19] By comparing the incidence of side effects between male and female, for unexplained reasons we have four patients who were normotensive prior to treatment developed grade (1) hypertension after treatment, all of them were female. Two of them have positive family history of hypertension. By relating the incidence of side effects to age most of them were unrelated but constipation was reported, paradoxically, in younger age patients.

Conclusion:

Good adherence is a key factor for success in the treatment of chronic viral hepatitis. However, almost all patients on treatment with interferon-based regimen will experience adverse events that can threaten good adherence. Therefore, proactive clinical management is crucial to avoid suboptimal therapy and treatment

discontinuations.The most common side effect is flu-like illness followed by fatigue, anorexia, local reaction and neuropsychiatric side effects. There are many differences in the incidence of side effects between Iraqi patients and results published in trials done on western patients. The higher incidence of anemia in patients with hepatitis C it may be due to concomitant ribavirin therapy. Age, gender, type of hepatitis and duration of treatment can affect the incidence of interferon therapy.

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