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PREVALENCE OF FLU-LIKE SYNDROME AMONG CHRONIC HEPATITIS C INFECTED PATIENTS TREATED WITH THE FIRST LINE COMBINATION THERAPY (PEGYLATED INTERFERON A-2A AND RIBAVIRIN)

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ABSTRACT

Flu-like symptoms usually occur during the first weeks of treatment with administration of pegylated interferon α-2a and severity declines thereafter. These symptoms include fever, chills, headache, arthralgia, and myalgia. This study was carried out to determine the prevalence or frequency of this flu-like syndrome occurrences among chronic HCV-infected patients treated with the combination of pegylated interferon α-2a and ribavirin briefly after starting treatment as a practical tool for knowing the severity and how commonly are the incidence of these symptoms and comparing its occurrence to those patients who received a pretreatment with a suitable therapy. For this purpose, fifty chronic HCV-genotype one infected patients were included in this study. Each one of them treated with a combination of 180 µg pegylated interferon α-2a once weekly by subcutaneous injection and different doses of oral Ribavirin. The patients were divided into two groups; the first group consisted of 25 patients and only received the recommended first line combination therapy. The second group, which consisted of 25 patients, in addition to the recommended first-line combination therapy, they received acetaminophen 600 mg intramuscular injection prior to pegylated interferon injection as a prophylaxis for reduction of severity of flu-like syndrome. In the first group, 76% experienced one of the flu-like syndromes. In the second group, 12% experienced flu-like syndrome and the remaining 88% reported no symptom.

INTRODUCTION

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease (Williams R, 2006). First-line treatment for HCV includes pegylated interferon plus ribavirin. The dosing regimen varies with the specific product and the duration of therapy varies with the product and HCV genotypes (Wells B *et al*, 2006). There are different types of Interferon injection, but for the purpose of this study we used peginterferon α-2a. This peginterferon α-2a (Pegasys®, Hoffmann-La Roche) with a 40-kd branched PEG (Poly-Ethylene Glycol) covalently linked to the standard interferon α-2a molecule (Zeuzem S *et al*, 2003). The dose of this PegIFN α-2a is a fixed dose of 180 µg once weekly (Cornberg M *et al*, 2002). Ribavirin is a synthetic nucleoside in which ribose is linked to a triazole derivative. Like other nucleoside analogues it has to be activated intracellularly by phosphorylation (Greenwood D *et al*, 2007). Meta-analyses and systematic reviews confirm that a combination of Pegylated interferon with ribavirin is effective in treating patients with chronic hepatitis C (CHC), leading to high levels of SVR (Strader D *et al*, 2004). In general, the combination of ribavirin with α-interferons is associated with numerous adverse events to multiple organ systems, and these should be discussed with patients prior to initiation of therapy (DiPiro J *et al*, 2005). One of the most common adverse effects associated with the use of peginterferon α-2a is flu-like symptoms that usually occur during the first weeks of treatment and severity declines over time.

These symptoms include fever, chills, headache, arthralgia, and myalgia (Manns M *et al*, 2006). These symptoms usually occur with pegINF not with ribavirin. From ethical points of view, we used the combination of both two drugs because peginterferon alone is not effective and not recommended for eradication of the virus in patients infected with chronic HCV. For flu-like symptoms antipyretic drugs such as paracetamol or other non-steroidal anti-inflammatory drugs (NSAIDs) immediately before or after the injection of interferon can help to prevent or reduce these effects (Manns M *et al*, 2006).

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MATERIALS AND METHODS

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

The samples

Fifty chronic HCV-genotype one infected patients (26 males and 24 females) between ages 18-67 years old (44.6±1.8) were included for the purpose of this study. Each one of them 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), (1000 mg/day for those patients who weighed ≤ 75 kg and 1200 mg for patients with body weight > 75 kg). The patients were divided into two groups; the first group consisted of 25 patients (14 males and 11 females) between ages 21-67 years old (44.4 ±2.6). They only received the recommended first line combination therapy. The second group, which consisted of 25 patients (12 males and 13 females) between ages 18-65 years old (44.8±2.6), in addition to the recommended first-line combination therapy, they received acetaminophen (Paracetol®) 600 mg intramuscular injection prior to pegylated interferon injection as a prophylaxis for reduction of severity of flu-like syndrome. In this study, there was no observational group receiving placebo or conventional interferon because it would be against the ethics.

Inclusion criteria

Patients included in this study were confirmed to have chronic HCV infection of genotype one, between ages 18-67 years old of both genders and willing to be treated and to adhere to treatment requirements. They were also treatment naïve patients.

Exclusion criteria

The HCV infected patients excluded from this study were those who were; diagnosed as having acute HCV infection, co-infected with HIV or HBV, or with either 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 pregnants or patients unwilling to comply with adequate contraception, with severe psychiatric disorder, severe immunosuppresion, heart failure or significant coronary or CVD, untreated thyroid disease, osteoarthritis, rheumatoid arthritis, or chronic pain disorders.

Patients were excluded from participation if they had an absolute neutrophil count (ANC) less than 1500 per cubic millimetre, platelet count less than 90000 per cubic millimetre, haemoglobin less than 12 g per decilitre in women and less than 13 g per decilitre in men, or a serum creatinine level more than 1.5 times the upper limit of normal. The study was approved by the Ethics Committee according to the Declaration of University of Sulaimani and ministry of health in Kurdistan Region of Iraq. All patients gave written informed consent prior to study enrolment. The mentioned excluding factors were investigated by comprehensive history taking and seeking in patients past medical records. In case of any suspicious finding, the patients were referred to specialist(s) to rule in/out the suspected disorder (such as major depression -----etc).

Data collection

This study is a prospective comparative study between two groups of patients, one without pre-treatment and the other with pretreatment with analgesic drug. After taking patient's concern, the data obtained by direct interview with the patients and appropriate questionnaire filled by patients themselves. For prevalence determinations, the patients in both groups interviewed before and one month after treatment to determine if any of flu-like symptoms appeared throughout this month and comparing the results of the two groups. The prevalence monitored only in term of clinical aspect.

Statistics

Data are represented as mean ± SEM. Paired sample T-test is used to compare treatment groups. 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 the first group, in which no pre-treatment with acetaminophen was used, among the 25 patients, 19 patients (10 males and 9 females) aging between 33-67 years old (48.7±9.8), which represent 76% (52.6% of males and 47.4% of females) of the first group, were experienced one of the flu-like syndromes and only 6 (4 males and 2 females) patients aging between 21-32 years old (21.7±4), which represent 24% (66.7% of males and 33.3% of females) of the group, were free from flu-like syndromes throughout one month of starting treatment. Among those 19 patients who experienced flu-like syndrome, two 37 and 39 years old male patients experienced fever/chill and headache for 20 minutes after first and second injections only, seven patients

Table 1. Comparison of flu-like syndrome occurrence between the two study groups

Symptoms	Group A 180 µg PegINF α-2a + RBV n=25	Group B 180 µg PegINF α-2a + RBV + 600 mg acetaminophen n=25
Symptom free	6 (24%)	22 (88%)
Flu-like syndrome;	19 (76%)	3 (12%)
fever/chill	2 (8%)	1 (4%)
headache	2 (8%)	1 (4%)
myalgia	7 (28%)	1 (4%)
arthralgia	10 (40%)	--------

(2 males and 5 females) experienced myalgia and muscle pain shortly after all 4 injections of peg interferon with the same severity with each injection. The remaining patients (6 males and 4 females) experienced arthralgia and joint pain for only 2 days after each peginterferon injection as shown in table 1. In the second group, who received 600 mg acetaminophen as intra-muscular injection prior to peginterferon injection, only 3 patients (2 females and 1 male aging 65, 63 and 60 years old, respectively) which represent 12% (66.67% of females and 33.33% of males) of the second group, experienced fever/chill, headache, myalgia and muscle pain respectively while the remaining 88% (22 patients) reported none of the flu-like symptoms as shown in table 1. The resulting difference between the two groups in the occurrence of flu-like syndrome was highly significant with $P < 0.001$

DISSCUSSION

Flu-like symptoms including fever, arthralgia and myalgia are the most common early adverse effects of pegylated interferon injection which appear a few hours after the injection and may last for up to three days. In order to increase patient adherence and prevent early treatment discontinuation, one common approach is the use of paracetamol or other NSAIDs immediately before or after the injection of interferon (Mauss *et al.,* 2012). Patients can be recommended for, injections on comfortable days, receiving acetaminophen or ibuprofen one hour before injection, hydration and basic physical exercises (Fried *et al.,* 2002a, Daryani *et al.,* 2004).

According to a study done by Daryani *et al.,* one of the most frequently observed adverse effect with administration of pegylated interferon was flu-like symptoms (74%) that fortunately were self-limiting and rarely existed more than a few weeks from the first administration of the study drug. This problem was helped a lot by limited use of acetaminophen or ibuprofen tablets just before injection of interferon (Daryani *et al.,* 2004). If we closely look at the percent of patients who experienced flu-like symptoms in Daryani's study (74%) is similar to the percentage of patients who experienced the symptoms in our study which was 76% but in the second group who received pre-treatment with acetaminophen it reduced to only three elderly patients (12%) whom experienced at least one of the flu-like symptoms. This similarity between the results of our study with Daryani's may be due to the demographic characteristics of study subjects that were so close from each other and using the same brand drug (Pegasys®).

Another study done by Ural *et al.,* state that; the most frequent side effects with pegylated interferon are constitutional side effects like flu-like syndrome, characterized with fever (91.3%), shivering (89.1%), headache (58.7%), myalgia (93.5%), and arthralgia (73.9%) that begin 3-4 hours after injection and continue for 24-48 hours. In their study, they observed at least one of the side effects in all patients. Fever, myalgia, shivering, arthralgia, headache were diminished with paracetamol (Ural *et al.,* 2010). In our study, we only observed fever/chill (8%), headache (8%), myalgia (28%) and arthralgia (40%) but in the second group the percentage of patients experienced these symptoms reduced to 4% (only one patient for each symptom) for fever/chill, headache and myalgia but none of them experienced arthralgia. The difference in this study's first group's result from that in Ural's may be due to the fact that Ural counted one patient for different symptoms (for example one patient experienced fever, headache, myalgia at the same time but fever was the most prominent and the two other symptoms were mild), so Ural counted this patient for each of the presenting symptoms that's why the percentage are so high. In the other hand, in our study, we only counted and reported the most prominent symptoms and ignored the mild one (in the above example, we only reported fever). In a retrospective multicenter study done in Argentina, 92.7% of study subjects reported at least one of the influenza like symptoms ((Ridruejo *et al.,* 2010). Also in a prospective study done in Italy by Ascione *et al.,* the appearance of flu-like symptoms were in order of arthralgia 36.6%, fever 23.7%, myalgia 15.1%, and headache 15.1% (Ascione *et al.,* 2010). The different results of these studies from our study may be due to difference in demographic characteristics or difference in races or due to the bigger sample sizes enrolled in the two previous studies but somewhat the results of Ascione's study is near to our first group's results and the first study did not individualized the symptoms instead only stated that 92.7% of study subjects reported at least one of the symptoms. Flu-like symptoms usually diminish spontaneously over the first weeks of treatment.

According to previous studies flu-like symptoms may develop in virtually all cases treated with interferon but fortunately these symptoms resolve or become less severe after the first month of therapy. Also acetaminophen or ibuprofen taken at a time of injection may resolve these symptoms (Manns *et al.,* 2001, Fried *et al.,* 2002a, Fried *et al.,* 2002b, Daryani *et al.,* 2004). We observed similar results in our studied patients.
Early side effects are occurred in the first 1-2 weeks of the treatment and tolerance is developed by the time (Gürel S, 1998) this may also be true for our study subjects especially for the young patients in the first group who reported the symptoms only after the first two injections that lasted only for several hours but later no symptoms reported with continued injections. However we should state that, despite the short duration of the symptoms and development of tolerance with time to these symptoms, the pretreatment with analgesic or NSAID produces a significant improvement or reduction in the appearance of these symptoms and is a right choice for patients who cannot tolerate these symptoms especially elderly patients or those with co-existing medical conditions that will be worsening upon these symptoms.

Conclusion

Flu-like symptoms including fever/chill, headache, myalgia and arthralgia are the most common early adverse effects of interferon injection which are short-living and disappear soon with continued injection but can also be significantly reduced by pre-treatment with acetaminophen.

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