Trakya Univ Tip Fak Derg 2010;27(3):261-264 • doi: 10.5174/tutfd.2009.02005.1

Original Article / *Klinik Çalışma - Araştırma*

Comparision of the Side Effects Due To Interferon Alpha 2A Plus Ribavirin and Pegylated Interferon Alpha 2A Plus Ribavirin Combinations For Chronic Hepatitis C Infection

Kronik Hepatit C İnfeksiyonda Pegileinterferon Alfa 2A ve Ribavirin Kombinasyonu ile İnterferon Alfa 2A ve Ribavirin Kombinasyonunun Yan Etkilerinin Karşılaştırılması

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***Submitted / Başvuru tarihi:** 26.01.2009 **Accepted / Kabul tarihi:** 03.04.2009*

Objectives: Comparision of the side effects due to interferon alpha 2a plus ribavirin and pegylated interferon alpha 2a plus ribavirin combinations for chronic hepatitis C infection.

Patients and Methods: In this study, 36 patients, who received interferon alpha 2a, 3 million U, subcutaneously thrice weekly plus oral ribavirin 1000-1200 mg daily were compared with 49 patients, who received pegylated interferon alpha 2a 180 μgr, subcutaneously once weekly plus oral ribavirin 1000-1200 mg daily with respect to side effects.

Results: Lack of appetite, headache and fatigue were more frequent in pegylated interferon alpha group, and these differences between groups were statistically significant ($p<0.05$).

Conclusion: In our study the treatment is discontinued in two patients who received interferon plus ribavirin (anemia in one, both anemia and thrombocytopenia in the other) and three patients, who were treated with pegylated interferon plus ribavirin (anemia in one, both anemia and thrombocytopenia in one and psychiatric problems in the other).

Key words: Pegylated interferon alpha 2a + ribavirin; interferon alpha 2a + ribavirin; side effects.

Amaç: Kronik hepatit C infeksiyonunda interferon alfa 2a ve ribavirin, pegile interferon alfa 2a ve ribavirin kombinasyonuna bağlı oluşan yan etkiler karşılaştırıldı.

Hastalar ve Yöntemler: Bu çalışmada, haftada üç kez 3 milyon U subkutan interferon alfa 2a ve 1000-1200 mg/gün oral ribavirin alan 36 hasta ile haftada bir subkutan 180 μgr pegile interferon alfa 2a ve 1000-1200 mg/gün oral ribavirin alan 49 hasta ile ilişkili yan etkiler karşılaştırıldı.

Bulgular: Pegile interferon alfa grubunda en sık görülen yan etkiler iştahsızlık, baş ağrısı, ve yorgunluktur. Bu fark gruplar arasında istatistiksel olarak anlamlıdır ($p<0.05$).

Sonuç: Çalışmamızda interferon ve ribavirin alan 2 hastada (bir hastada anemi, diğer hastada anemi ve trombositopeni) pegile interferon ve ribavirin alan üç hastada (bir hastada anemi, bir hastada anemi ve trombositopeni, diğerinde psikiyatrik problemler) tedavi kesildi.

Anahtar sözcükler: Pegile interferon alfa 2a + ribavirin; interferon alfa 2a + ribavirin; yan etki.

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Hepatitis C virus (HCV) is one of the most common causes of chronic hepatitis, liver chirrosis and hepatocelluler Ca. Viral replication and progression to fibrozis can lead to chirrosis and hepatocelluler Ca, like all viral hepatitis. Thus, the mean target of viral hepatitis treatment is to stop this progression by suppressing viral replication and diminish the complications due to progression.[1,2]

Interferon alpha is the unique agent that approved for chronic viral hepatitis treatment.[3] While interferon alpha (2a or 2b) and ribavirin combination had used in early 1990s, the current standard therapy for patients with chronic HCV infection is pegylaed interferon alpha (2a or 2b) and ribavirin combination.[1,4]

Sustained viral replication (SVR) rates ranges 53-64% with pegylated interferon alpha+ ribavirin combination.[5,6]

Numerous factors including, race, viral genotype, and viral load effect SVR.[5,7] For genotype I infections, while SVR rate is 63% in patients with complete treatment, it is found 34% in patients without complete treatment.[5,8]

Although interferon alpha is well-tolerated, it has a lot of side effects.[3] The most frequent side effect is flu-like syndrome, characterized with fever, shivering, myalgia, arthralgia, nausea and vomitting that begin 3-4 hours after injection. Early side effects are occurred in the first 1-2 weeks of the treatment and tolerance is developed by the time.[3] Late side effects are observed 1-3 months after the initial treatment and occurred in 3-10% of the patients.[9,10] Late side effects are fatigue, sleeplessness, hair loss, psychiatric problems including depression, granulocytopenia, thrombocytopenia, thyroid disorders, impotence, cardiotoxicity, anxiety and autoimmune events.[1,3,5]

The most important side effect owing to ribavirin is hemolytic anemia. Coughing, pruritis and sleep disorders have been reported, too.[6,7]

Treatment decision is important in high-risk group patients for side effects. Follow up without treatment is recommended. Giving information about side effects and costs is effective in reducing side effects.[5]

In this stduy, 36 patients received interferon alpha 2a plus ribavirin and 49 patients received pegylated interferon alpha 2a plus ribavirin combinations were compaired in terms of side effects.

PATIENTS AND METHODS

Eighty-five patients, aged between 27-64 with chronic hepatitis C infection were enrolled this study, between January 1998 and June 2007. exclusion criteria were autoimmune diseases, immune suppressive therapy, serious co-morbidity and malignancy. Thirty-six patients were treated with interferon alpha 2a, 3 million U, subcutaneously thrice weekly plus oral ribavirin 1000-1200 mg daily, and 49 patients were administrated pegylated interferon alpha 2a 180 μgr, subcutaneously, once weekly plus oral ribavirin 1000-1200 mg daily for 12 months. Side effects were evaluated and recorded monthly.

Hemoglobin levels between 8.5-10 gr/dl required ribavirin dose reduction and 8.5 gr/dl levels are the discontinuation limit. Neutrophil count, below 750/mm^3 necessitates dose reduction and treatment had to stopped when neutrophil count is below 500/mm^3. Thrombocyt count, below 50 000/mm^3 necessitates dose reduction and treatment had to stopped when neutrophil count is below 25 000/mm^3.

RESULTS

Patient's demographics were similar between groups interferon alpha 2a plus ribavirin and pegylated interferon alpha 2a plus ribavirin (age 27-64 versus 21-64, F/M ratio 23/13 versus 27/22). Treatment was discontinued in two of 36 patients, who received interferon alpha 2a plus ribavirin, because of side effects (anemia in one, and both anemia and thrombocytopenia in the other). In three cases, who received pegylated interferon alpha 2a plus ribavirin we also discontinued the treatment for the same reasons (anemia in one, thrombocytopenia is one and psychiatric problems in the other). Side effects of the two treatment regimen are shown in Table 1.

Lack of appetite, headache and fatigue were found statistically higher in interferon alpha 2a plus ribavirin group ($p<0.05$). On the other hand, anemia and thrombocytopenia were statistically higher in pegylated interferon alpha 2a plus ribavirin group ($p<0.05$).

DISCUSSION

The current standard treatment for patients with chronic hepatitis C virus infection is pegylated interferon alpha in combination with ribavirin.[1,4] Treatment completement is changed SVR between 34% and 63%. The most common causes of uncompleted treatment are side effects due to drugs.[5,8]

The most frequent side effects seen, during interferon treatments are constitutional side effects, including fever, shivering, fatigue, artralgia, myalgia and headache. They generally begin 3-4 hours after injection and continue for 24-48 hours. Patients can be recommended for, injections on comforable days, receiving asetaminofen or ibuprofen one hour before injection, hydration and basic physical exercises.[5,11]

Thyroid disorders are observed in 1-6% of the patients during interferon treatment and a re higher in females than males. It is important to measure TSH levels before treatment, at the 12th month and at the end of the treatment cessation.

When hypothyroid is developed, treatment cessation is not indicated; thyroid replacement therapy is enough. However, hyperthyroidic patients had to consultated with an endocrinolog and treatment could be discontinued if necessary.[11,12] In our study 4.3-5.9% of the patients developed hypothyroidia, and hyperthyroidia is observed in 2.2-2.9% of them. In our study, thyroid dysfunctions were generally mild and not treatment-limiting.

Table 1. Side effects owing to interferon alpha 2a+ribavirin and pegylated interferon alpha 2a combinations

Side effects	SIFN RİBAVİRİN (n:34)	PeglaytedIFN RİBAVİRİN (n:46)	
Fever	%97.1	%91.3	
Myalgia	%91.2	%93.5	
Shivering	%88.2	%89.1	
Headache	%82.4	%58.7	***p*<0.05**
Distastefulness	%64.7	%82.6	
Arthralgia	%79.4	%73.9	
Dry mouth	%67.6	%80.4	
Fatigue	%64.7	%32.6	***p*<0.05**
Lack of appetite	%67.6	%45.7	***p*<0.05**
Weight loss	%57.6	%69.6	
Sleeplessness	%64.7	%67.4	
Irritability	%61.8	%76.1	
Forgetfulness	%55.9	%37	
Nausea	%50	%45.7	
Pruritis	%55.9	%58.7	
Hair loss	%52.9	%45.7	
Paraesthesia	%50	%41.3	
Palpitation	%26.5	%21.7	
Dispne	%11.8	%13.3	
Vomiting	%11.8	%10.9	
Chest pain	%6.1	%6.5	
Impotans	%6.1	%8.7	
Depression	%5.9	%6.5	
Diarrhea	%2.9	%4.3	
Herpes Labialis	%3	%6.5	
Suicide tendency	%0	%0	
Anemia	%47.1	%71.7	***p*<0.05**
Leucopenia	%14.1	%13	
Thrombocytopenia	%26.5	%50	***p*<0.05**
Hypothyroidism	%5.9	%4.3	
Hyperthyroidism	%2.9	%2.2	

Interferon can cause thrombocytopenia, neutropenia and anemia via bone marrow suppression. Anemia, a well-recognized effect of ribavirin is caused by its toxic effect on erythrocytes. During therapeutic period, anemia is reported in 20-25%, neutropenia in 18-20% and anemia in 3-6% of the patients[13-15] Neutrophil count, below 750/mm^3 necessitates dose reduction and treatment had to stopped when neutrophil count is below 500/mm^3. Some studies showed that, administration of granulocyte stimulating factor once or twice a week would increased neutrophil count. However, small study populations and granulocyte colony stimulating factor cost and side effects hinder its rutin use.[16-17] In our study, we observed in 13-41.1% of the patients, but no patients discounted therapy owing to neutropenia.

Hemoglobin levels below 12 gr/dl or a decrease more than 3 gr/dl is defined as anemia. Interferon causes anemia via bone marrow suppression and ribavirin causes anemia via hemolysis[18] Hemoglobin levels between 8.5-10 gr/dl required ribavirin dose reduction and 8.5 gr/dl levels are the discontinuation limit. It is known that a dose reduction in the first 12 week of the treatment is worsen SVR rates. Afdhal et al.[19] reported that, 40 000-60 000 U erythropoietin administration corrected anemia and improved life quality, in a double-blind randomized study. In our study, interferon treatment was discontinued owing to anemia in two cases and owing to both anemia and thrombocytopenia in one. Anemia and thrombocytopenia were statistically higher in pegylated interferon group ($p<0.05$).

Neuropsychiatric problems are more frequent among patients with chronic hepatitis C infection than normal population. Major depression rates were reported between 11% and 57%. Interferon reduces serotonin levels, by decreasing tryptophan synthesis and causes major depression. Treatment rate with selective serotonin reuptake inhibitor (SSRI) is approximately 90%.[5,20] Antidepressant therapy is initiated with small doses and is increased in a step by step manner. Antidepressants are continued with interferon treatment together and after interferon treatment is completed, they are stopped with dose reductions in 6-12 months.[20-22] Depression rates were 5.9% and 6.5% in own study. These patients were treated with SSRIs. Interferon causes some other psychiatric side effects, except depression. Treatment was discontinued in a patient who received pegylated interferon alpha 2a plus ribavirin, because of suicide tendency.

Alopecia is the most unwanted side effect during interferon treatment. It is frequent in the first 3-4 months of the treatment and is reversible.[5] Patients must be informed about this side effect and its reversibility and must be avoided using hair jelly and hard hair brushes. Alopecia was observed 45.7-52.9% of our patients.

Nausea and vomiting are the early side effects of interferon. Eating small amounts and frequently is recommended; antiemetic can be used in serious situations. [5] In our study, nausea rate were 45.7-50.0% and vomiting is observed in 10.9-11.8% of the cases.

Sleeplessness, irritability, forgetfulness, impotence, paraesthesia, distastefulness, dry mouth, dispne, coughing, pruritis, interstitial pneumonia is the other side effects owing to interferon. We also observed these, in different proportions.

In our study, we observed at least one of the side effects in our patients. Fever, myalgia, shivering, arthralgia, headache were the most frequent side effects. These complaints generally initiated after 3-12 hours of the injections, continued for 6-12 hours and were diminished with parasetamol.

Fried et al.,[4] Dinçer et al.,[5] and Manns et al.,[7] compared side effects due to interferon plus ribavirin and pegylated interferon plus ribavirin combinations and were not found any significant difference between groups. In our study while headache, fatigue and lack of appetite were statistically higher in interferon group;

anemia and thrombocytopenia were higher in pegylated interferon group. Higher headache, fatigue and lack of appetite rates were probably due to injections three times a week and higher anemia and thrombocytopenia rates were attributed to early discontinuations in interferon group owing to its side effects.

Phase 3 studies showed a 10-14% treatment discontinuation with pegylated interferon and 11-13% with interferon treatment. Dose reduction was needed in 33-42% of the cases, received pegylated interferon and in 32-34% of the cases, received interferon.[4,7] In our study treatment is discontinued in two patients, who received interferon plus ribavirin (anemia in one, both anemia and thrombocytopenia in the other) and three patients, who were treated with pegylated interferon plus ribavirin (anemia in one, both anemia and thrombocytopenia in one and psychiatric problems in the other).

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