

Original Article

# Interferon-alpha reduced inflammatory effects of filgrastim (G-CSF) in the liver of Syrian mice

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## Abstract

**Introduction:** granulocyte colony-stimulating factor (G-CSF) has been widely used for the treatment of chemotherapy-induced neutropenia. One of the major side-effects of interferon- $\alpha$  (IFN- $\alpha$ ) therapy is neutropenia. Previous studies have confirmed the beneficial effects of co-administration of G-CSF and IFN- $\alpha$  on neutropenia in patients infected with hepatitis C. In this study for the first time, the effects of co-administration of type I IFNs and G-CSF on liver and liver enzymes investigated.

**Methods:** forty-two mice (male, eight weeks) were randomly divided into six groups of seven: distilled water, G-CSF (200 $\mu$ g/kg), IFN- $\alpha$  (200 $\mu$ g/kg), IFN- $\beta$  (200 $\mu$ g/kg), IFN- $\alpha$ +G-CSF and IFN- $\beta$ +G-CSF. After 28 days, blood was taken from the heart of each mouse and histological changes in the liver and liver enzymes including aspartate transaminase (AST) and alanine transaminase (ALT), as well as bilirubin, were measured.

**Results:** Surprisingly, in most cases, the G-CSF and type one IFNs alone or simultaneously reduced the levels of AST and bilirubin. The levels of ALT induced by IFN- $\alpha$ , the addition of G-CSF to IFN- $\alpha$  reduced the level of this liver enzyme. G-CSF induced cell infiltrations into the liver tissue, addition of IFN- $\alpha$  but not IFN- $\beta$  to G-CSF obviously reduced the cell infiltration into the liver.

**Conclusion:** Since the changes in liver enzymes and bilirubin were not at harmful levels, and the administration of IFN- $\alpha$  to G-CSF reduced the cell infiltrations into the liver, our results suggested that co-administration of type I IFNs and G-CSF had no harmful effects on liver histology and functions.

## Keywords:

Inflammation;  
IFN- $\alpha$ ;  
IFN- $\beta$ ;  
G-CSF;  
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## Introduction

Granulocyte colony-stimulating factor (G-CSF) and type one interferons (IFNs) are two groups of cytokines that play important roles in inflammatory

reactions. G-CSF is one of the hematopoietic cytokines, produce by monocyte-macrophages, fibroblast and endothelial cells. G-CSF causes the proliferation and differentiation of myeloid hematopoietic cells (Nakamura et al., 2000). Although the level of G-CSF in the serum is normally very low,

multiple reports indicated an increased expression of these factors in inflammatory diseases (Nakamura et al., 2000). G-CSF has been introduced in several studies as an inflammatory factor that plays a role in the inflammatory response (Eyles et al., 2008).

Pharmaceutical forms of this factor are filgrastim and lenograstim, which are widely used in cases of neutropenia following chemotherapy and bone marrow transplants and improve heart function after acute myocardial infarction. Filgrastim drugs may have several side effects such as allergic reactions, enlarged spleen, arrhythmia and vascular inflammation. Other known side effects of this drug are hepatomegaly (enlarged liver), transient hypotension, urinary disorders (such as hematuria), osteoporosis, thrombocytopenia, anemia, decreased transiently in blood glucose and increased uric acid (Dale et al., 2003; Renwick et al., 2009).

Interferons are produced by the host cells as a defensive response to pathogens such as viruses and tumors. Type I interferons are widely used in the treatment of leukemia, viral hepatitis and multiple sclerosis. Previous studies have indicated the anti-inflammatory properties of type I interferons (IFN- $\alpha$  and IFN- $\beta$ ). Type I IFNs down-regulate the formation of proinflammatory cytokines such as IL-1b and TNF- $\alpha$  in fibroblast-like synoviocytes (Palmer et al., 2004). IFN- $\beta$  inhibits the proliferation and the migration of T-cells (Stüve et al., 1996). The type one IFNs also induce the production of immunosuppressive cytokine of IL-10 that inhibits the pro-inflammatory gene (Benveniste and Qin, 2007).

The liver plays a pivotal role in drug degradation as well as in the metabolism of carbohydrates, fats and protein. Changes in liver enzymes can indicate liver damage or changed bile flow. Transaminases are among of the most important enzymes of the liver that is interested in laboratory professionals. Two important transaminase enzymes often measured in clinical laboratories are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). One of the substances secreted by the liver is bilirubin and like other secretions such as alkaline phosphatase, cholesterol and products of cholesterol (bile acids) are excreted by the liver through the bile. Changes in liver enzymes along with other clinical investigations can be used to diagnose diseases (Giannini et al., 2005).

AST is currently used to diagnose liver disease. The

level of AST has greatly increased in liver parenchymal diseases such as viral hepatitis, toxic hepatitis and infectious mononucleosis. AST is also increased in obstructive liver disease (obstruction of the liver, both inside and outside). During the process of cirrhosis, AST levels could be higher than average (Sookoian and Pirola, 2015). The levels of liver enzymes such as AST and ALT can also indicate damage to the liver parenchymal cells in the inflammatory process. It has been suggested that the levels of AST and ALT in the serum can be used as markers for inflammation (except in cirrhosis) of the liver (Gaia et al., 2006).

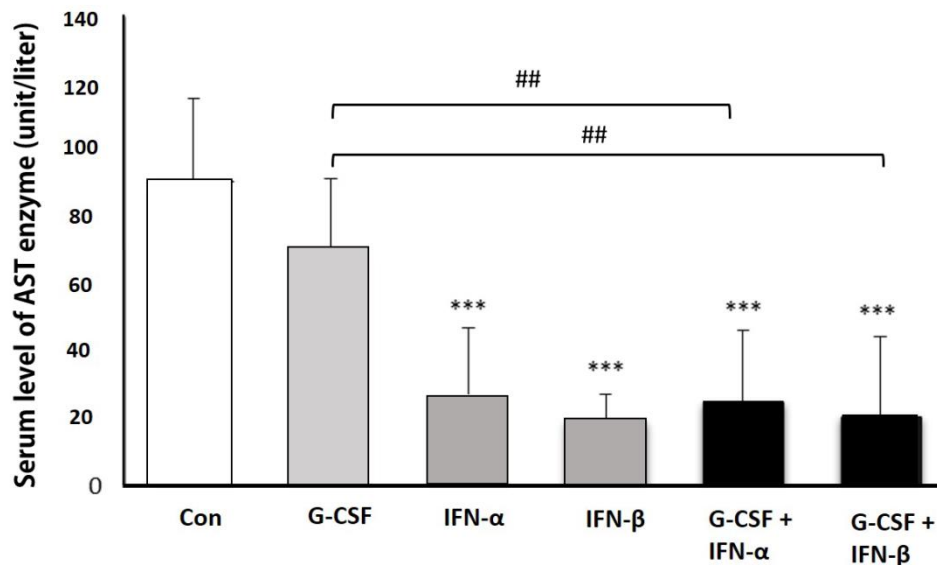
Neutropenia is a major side effect of IFN- $\alpha$  therapy which could be due to the suppression of G-CSF production in the presence of IFN- $\alpha$  (Tajuddin et al., 2010). Previous studies have confirmed the beneficial effects of G-CSF administration on neutropenia in patients with hepatitis C infections (Sharvadze et al., 2007; Koskinas et al., 2009). Since the co-treatment of G-CSF and IFNs could be beneficial, and due to the wide therapeutic use of these cytokines, in this paper for the first time we investigated the simultaneous effects of G-CSF and IFN- $\alpha$  or IFN- $\beta$  on liver and liver enzymes.

## Materials and methods

### Animals and treatments

Forty-two male Syrian mice (eight-weeks) were obtained from the animal house at the School of Pharmacy, Mashhad University of Medical Sciences, Iran. The whole process of the study was carried out in compliance with the guidelines for the care and use of Laboratory Animals published by the National Institutes of Health (NIH Publications No.8023, revised 1978) and was approved by the ethical committee of The Ferdowsi University of Mashhad. The mice had free access to food and water and were maintained on a 12h dark/light cycle in a room with controlled temperature (26-27°C) and humidity (60±10%). Recombinant human G-CSF and type one IFNs were purchased from Pooyesh Darou (Tehran, Iran) and were reconstituted in distilled water.

Mice were randomly divided into six groups which received intraperitoneal injection (n=7 in each group): group one (control): distilled water, group two: G-CSF (200µg/kg), group three: IFN- $\alpha$  (200µg/kg), group four: IFN- $\beta$  (200µg/kg), group five: same dosages of



**Fig.1.** The mean of AST enzymes in blood serum in six groups (units per liter). Data is shown as mean±SD. IFNs either alone or in combination with G-CSF significantly reduced AST enzyme compared to the control group ( $^{***}P<0.001$ ) or G-CSF ( $^{##}P<0.01$ ). Reduction of AST by G-CSF is not significant compared to the control group ( $n = 7$ ).

G-CSF + IFN- $\alpha$  and group six: same dosages of G-CSF + IFN- $\beta$ . After 28 days, the mice were anesthetized with ketamine and then, one ml of blood was taken from their heart with a syringe.

After collecting blood, serum was separated from blood cells using a centrifuge for 15 minutes at 4,000 rpm (Kakusan, Japan) and samples were sent to the medical laboratory of Veterinary Medicine of Ferdowsi University to measure serum levels of liver enzymes (AST and ALT) and bilirubin. In the next step to assess liver histology, small sample tissues were isolated and were maintained in 10% formaldehyde solution to fix it. After standard tissue processing, the samples were stained with hematoxylin-eosin.

### Statistical analysis

Differences among groups were assessed by two-way ANOVA with Tukey's post hoc analysis to identify statistical differences among the treatments when  $P$  was less than 0.05.

## Results

### G-CSF and IFNs reduced the level of AST

The results indicated that both IFN- $\alpha$  ( $25\pm 18$ ) and IFN- $\beta$  ( $20\pm 4$ ) significantly reduced the level of AST unit/l (U/l) in comparison to the control group ( $91\pm 27$ ) ( $P<0.001$ ). G-CSF ( $68\pm 25$ ) did not have a significant

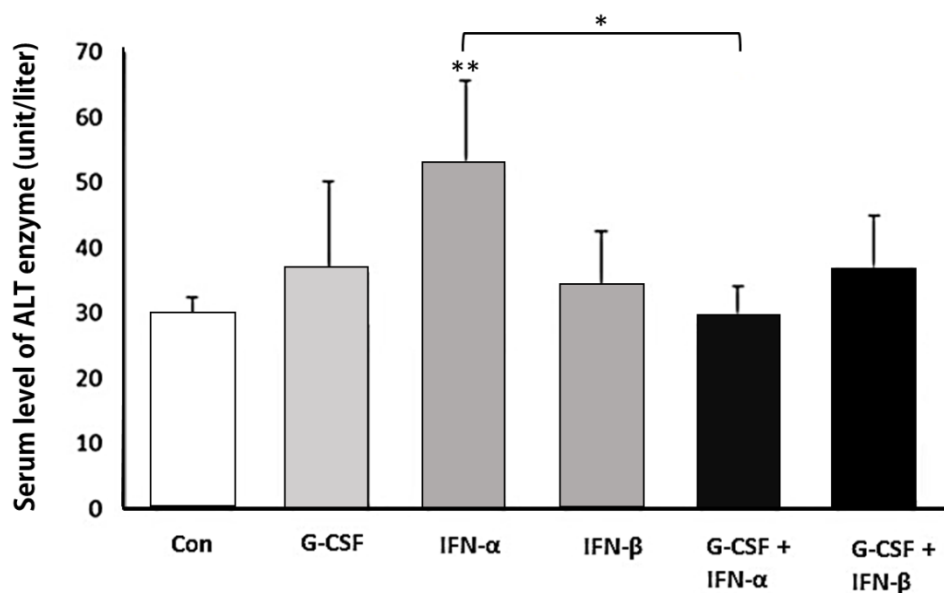
effect on the level of AST. When G-CSF was added to IFN- $\alpha$  ( $24\pm 21$ ) or IFN- $\beta$  ( $21\pm 24$ ), the level of AST was also reduced in comparison to the control group. The levels of AST in the groups of G-CSF + IFN- $\alpha$  and G-CSF + IFN- $\beta$  were significantly lower compared to G-CSF alone ( $P<0.01$ ). In other cases, the comparison between groups showed no significant difference (Fig. 1)

### IFN- $\alpha$ induced the level of ALT

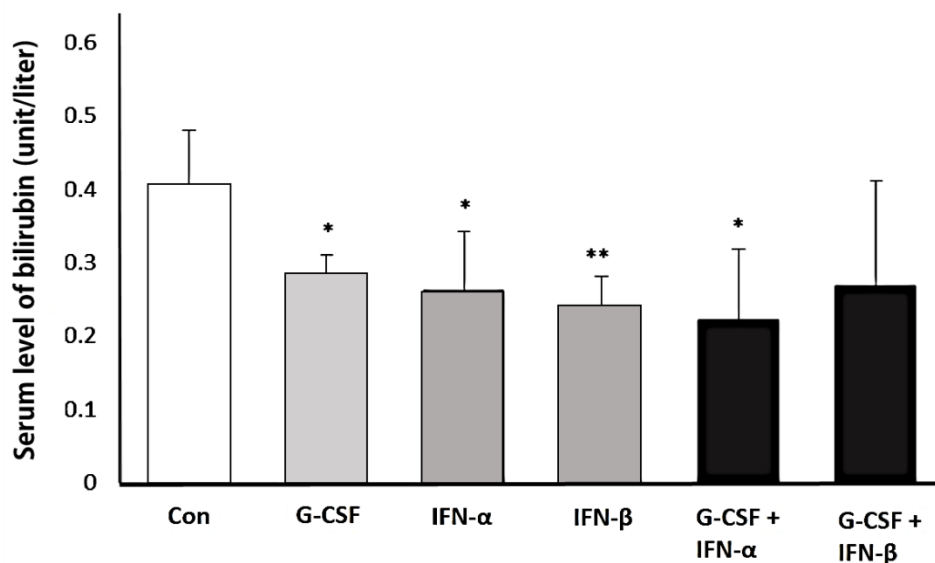
Examining the ALT level (U/l) after 28 days of injection with IFNs and G-CSF indicated that IFN- $\alpha$  ( $53\pm 12$ ) significantly induced this enzyme in comparison to the control group ( $29\pm 3$ ) ( $P<0.01$ ), whereas combination with IFN- $\alpha$  and G-CSF ( $30\pm 5$ ) significantly reduced the level of this liver enzyme ( $P<0.05$ ). In other cases, no significant changes in the level of ALT were observed (Fig. 2).

### G-CSF and IFNs reduced the level of serum bilirubin

Assessment of bilirubin (mg/dl) in the serum indicated that there was significant reduction, in the groups of: G-CSF ( $0.28\pm 0.03$ ) ( $P<0.05$ ), IFN- $\alpha$  ( $0.26\pm 0.08$ ) ( $P<0.05$ ), IFN- $\beta$  ( $0.24\pm 0.04$ ) ( $P<0.01$ ) and G-CSF + IFN- $\alpha$  ( $0.22\pm 0.1$ ) ( $P<0.05$ ) compared to the control group ( $0.41\pm 0.08$ ). The changes of bilirubin in the group of IFN- $\beta$  + G-CSF ( $0.26\pm 0.14$ ) was not significant (Fig. 3).



**Fig.2.** Mean of ALT enzyme in the blood serum of six groups (units per liter), ALT enzymes were significantly increased in the IFN- $\alpha$  group compared to control and G-CSF + IFN- $\alpha$ . Data are shown as mean $\pm$ SD. \* statistically significant ( $P<0.05$ ) and \*\* statistically significant ( $P<0.01$ ) compared to the control group ( $n = 7$ ).



**Fig.3.** Mean of bilirubin in the blood serum (mg/dl). Data is shown as mean $\pm$ SD. \* statistically significant ( $P<0.05$ ) and \*\* statistically significant ( $P<0.01$ ) compared with the control group. There was no significant difference between the groups in pairwise comparison ( $n = 7$ ).

### IFN- $\alpha$ but not IFN- $\beta$ inhibited the G-CSF-induced cell infiltrations in the liver

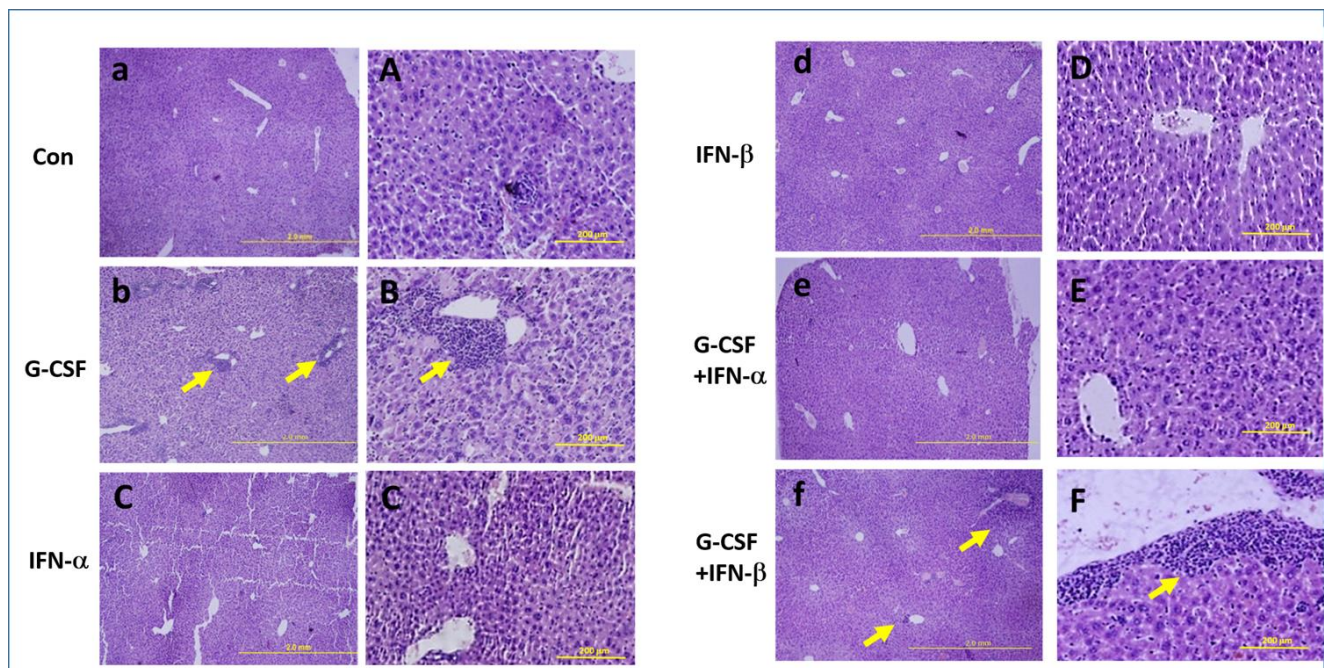
Examining microscopic sections indicated there was no fibrosis and severe disorders in liver tissues by G-CSF and IFNs. Therefore, quantitative evaluation, grading and staging of tissue changes were not necessary. Infiltration and migration of mononuclear cell were observed in the G-CSF groups. In the G-CSF + IFN- $\beta$  group, a relatively large volume of cell migration was also observed. When IFN- $\alpha$  was added

to G-CSF, the cell infiltration was reduced. No cell infiltration in either of the type one IFN injected groups, was observed (Fig. 4).

## Discussion

Histopathology and serum biochemistry serve as an initial indicator of the physiological function of the liver (Sookoian and Pirola, 2015). Liver damage is associated with elevated transaminases like AST and





**Fig.4.** Histological sections of the liver at day 28. The sections were stained with hematoxylin-eosin. Cell infiltration in the group of G-CSF and G-CSF + IFN- $\beta$  was observed. Arrows show cell infiltrations. Scale bar: a-f 2mm and A-F 200 $\mu$ m

ALT (Dkhill et al., 2014). High level of AST and ALT may indicate damage to the liver parenchymal cells (Giannini et al., 2005). Similar to the previous study, we have shown that administration of G-CSF did not raise the level of ALT (Todriia and Kaplanskaia, 2006). However, unlike, Todriia and Kaplanskaia (2006) study which reported that short-term administration of G-CSF in mice caused a 2-3-fold increase in the level of AST, we did not see any induction of ALT in our results.

Some controversy exists regarding the effects of IFNs on the level of serum enzymes. In the current study, IFN- $\alpha$  induced the level of ALT and reduced the level of AST. This reduction of AST had previously been reported in the IFN- $\alpha$  therapy of a patient with chronic hepatitis type C but in their research, IFN- $\alpha$  significantly reduced the level of ALT (Ameli et al., 2008). On the other hand, another study reported that IFN- $\alpha$  does not cause a persistent elevation of liver enzymes in chronic hepatitis C patients (Refaat et al., 2015).

This controversy persists in IFN- $\beta$  treatments as well. Increase in the liver enzymes has been reported as a side effect of IFN- $\beta$  in patients with multiple sclerosis (Francis et al., 2003). In the present study, IFN- $\beta$  reduced the level AST and did not significantly alter the level of ALT. Given these controversies surrounding the effects of G-CSF or IFNs on the liver enzymes, this effect could depend on various

parameters such as dosage and the period of using these factors. In addition, most of the previous researches have been done on patients whose disease complications could affect the outcome.

In this study, IFN- $\beta$  or IFN- $\alpha$  in combination with G-CSF reduced the level of AST in the serum. Although elevated levels of AST in serum is one of the major signs of health problems, the causes of low AST levels (below 10 U/l) remains unclear and has not been associated with any serious health problems (Gowda et al., 2009). Therefore, co-administration of G-CSF and IFNs did not seem to have any damaging effects on AST levels.

In the current study, the changes in ALT in the presence of G-CSF and/or IFN- $\beta$  were not significant. Only when IFN- $\alpha$  injected, the induction of ALT observed. Any types of parenchymal cell damage of the liver can increase ALT levels (Marcellin, 1999). Moreover, increased ALT levels were associated with reduced insulin sensitivity, adiponectin and glucose tolerance as well as increased free fatty acids and triglycerides (Burgert et al., 2006). However, the harmful level of ALT has been considered five times higher than the normal level (Giannini et al., 2005). Therefore, the simultaneous administration of G-CSF did not seem to alert the liver enzymes.

The results of this study indicated type one IFNs (with or without G-CSF) significantly reduced the amount of bilirubin compared to the control group. Bilirubin is a

natural product of heme catabolism that indicates both anti-inflammatory and anti-oxidative activities, and can be involved in the improvement of inflammatory conditions (Zhu et al., 2010; Huang et al., 2012). During the inflammation, several methods control the secretion of bilirubin. It has been shown that heme oxygenase increases in response to various inflammatory conditions that limits the speed of catabolism and production of bilirubin, free iron and carbon monoxide (Huang et al., 2012). It has been shown that IFN- $\alpha$  reduces bilirubin to less than half in the treatment of chronic hepatitis B (Malekzadeh et al., 2004). On the other hand, induction of bilirubin (hyperbilirubinemia) has been reported in the inflammatory conditions (Pascussi and Vilarem, 2008). Lower serum bilirubin could be associated with parenchymal liver diseases or incomplete extrahepatic obstruction, that could be due to tumors and granuloma (Gowda et al., 2009). In the current research, the reduction of the level of total bilirubin by G-CSF and/or IFNs although significant was not at harmful levels. The cell infiltration did not seem to have any effect of this reduction since the cell infiltration occurred only in the G-CSF group but the level of bilirubin has been reduced in IFNs as well. This reduction could be a result of the induction of heme oxygenase as it has been shown previously for IFNs (Ghezzi et al., 1986) and G-CSF (Wei et al., 2011).

In this study, distinct behavior of IFN- $\beta$  and IFN- $\alpha$  has been observed. The different effects of IFN- $\beta$  and IFN- $\alpha$  in inflammatory conditions have been previously reported. It was reported that IFN- $\alpha$  therapy in some cases leads to autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. While, it has been shown that anti-inflammatory properties of IFN- $\beta$  have beneficial effects in the treatment of multiple sclerosis and rheumatoid arthritis (Crow, 2010). In the stellate cells of the rat's liver, IFN- $\alpha$  and IFN- $\beta$  showed different biological effects on cell proliferation and activation (Shen et al., 2002). This difference can possibly be due to their affinity with their receptors and diverse signaling events between them. Accessibility and the availability of pathway members of JAK-STAT can affect the incorporation of the IFNs with their receptors. For example, lack of tyrosine kinase inhibits IFN- $\alpha$  signaling but does not change IFN- $\beta$  signaling (Crow, 2010). In this study, neither IFN- $\alpha$

nor IFN- $\beta$  seemed to have any effect on liver morphology, but when G-CSF was administered, a significant amount of cell infiltrations into the liver was observed. Administration of IFN- $\beta$  with G-CSF did not reduce these cell infiltrations. However, when IFN- $\alpha$  was added to G-CSF, no cell infiltrations were observed. These results suggested that IFN- $\alpha$  reduced the inflammatory effects of G-CSF in the liver and confirmed the distinct behavior of IFN- $\alpha$  and IFN- $\beta$ .

In our study, G-CSF or IFNs did not seem to cause any the harmful effects in liver such as necrosis or fibrosis, but G-CSF enhanced the infiltration of cells into the liver. Many studies have been conducted on the effects of G-CSF on the structure and function of the liver. Different side effects of G-CSF on rat liver were reported, including: necrosis of hepatocytes, congestion veins and red blood cell hemolysis (Todriia and Kaplanskaia, 2006). On the other hand, other studies have shown that G-CSF therapy significantly improves chemical or radiation damaged-liver tissue of mice. (Li et al., 2010). Clinical studies in humans suggested that G-CSF plays a protective role in liver damage and its administration is beneficial after surgery (Fiuza et al., 2002). The cell infiltration into the liver by G-CSF in the current study suggested mild liver inflammation, which can be one reason for liver enlargement caused by filgrastim. When IFN- $\alpha$  is administered with G-CSF, it can reduce these cells. Since, administration of IFN- $\alpha$  with G-CSF did not affect the reduction in AST, ALT and bilirubin, our results suggested that the simultaneous use of IFN- $\alpha$  and G-CSF could be beneficial for reducing side effects of G-CSF in the liver.

## Conclusion

In summary, this research was a preliminary study for investigating the effects of simultaneous treatment of G-CSF and IFNs on the liver enzyme and liver histology. Our data suggested that not only simultaneous use of G-CSF and IFNs had no harmful effects on liver histology and function, but also, IFN- $\alpha$  reduced the inflammation in the liver produced by G-CSF.

## Acknowledgments

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## Conflict of interest

There is no conflict of interest in this study.

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