International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

The Common of Side Effects of Pegylated Interferon Treatment in Hepatitis B and Hepatitis C Patients: Systematic Review

Rachellita Pujadimarta[a], Ummi Maimunah[b]*, Maftuchah Rochmanti[c]

[a]*Faculty of Medicine, Airlangga University, Surabaya, Indonesia*
[b]*Division of Gastroenterology and Hepatology, Dr. Soetomo General Hospital, Surabaya, Indonesia*
[c]*Departement of Pharmacology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia*
[b]*Email: ummima@gmail.com*

Abstract

Pegylated Interferon (Peg-INF) therapy which has various side effects and is relatively severe. The side effects that occur in each individual are different, some patients treated with Peg-INF have experienced mild to severe side effects. Evaluation The side effects of Peg-INF on chronic hepatitis B and / or C have not been widely reported. Thus, I will conduct research on the side effects of Peg-INF therapy in chronic hepatitis B and / or C patients by combining two or more research results that can be combined to obtain new quantitative data. The purpose of this study was to determine the side effects of Peg-INF treatment in chronic hepatitis B and C patients. This research uses the Systematic Review method. With the keyword "*Efek Samping* Pegylated Interferon"; "Pegylated Interferon successful treatment"; Pegylated Interferon Hepatitis in Asia". As a result total of 19 journal articles were obtained and the side effects of Peg-INF were hematological, systemic, psychiatric, autoimmune and hearing function side effects.

Keywords: Hepatitis B; Hepatitis C; Side Effects; Pegylated Interferon.

---

* Corresponding author.

1. Introduction

Hepatitis B virus and hepatitis C virus are the main causes of chronic viral hepatitis. This disease is an infectious disease whose complications can be life-threatening for the patient. Chronic hepatitis B and C are very dangerous with a broad clinical spectrum ranging from chronic hepatitis, liver cirrhosis (SH) and hepatocellular carcinoma (HCC). Complications of chronic liver disease can be prevented by anti-viral treatment. At this time there are two treatment for hepatitis B virus, namely orally with Nucleoside Analog (NA) and injection with Pegylated Interferon (Peg-INF) with various side effects [26]. The use of Peg-INF injection has a therapeutic effect as an immunomodulator and anti-virus. However, Peg-INF has more severe side effects than NA, so it is necessary to closely monitor the side effects of Peg-INF treatment.The goal of HBV and HCV treatment is to slow or treat complications of liver disease in patients. HBV and/or HCV therapy can be given by oral NA or by injection with Peg-INF. But until now there is no more effective therapy for the treatment of hepatitis b virus. One of the permitted treatments for patients with hepatitis b is Peg-INF, the use of Peg-INF can be combined with lamivudine. There are three types of interferon, alpha-interferon (INF-a), beta-interferon (INF-b), and gamma-interferon (INF-g). INF works by preventing viral penetration, synthesizing messenger RNA (m-RNA), translating viral proteins and spreading viruses [26].The epidemiology of HBV and HCV is constantly evolving due to increased safety in blood donation, improved health care conditions, increased use of intravenous drugs, and immigration from endemic areas to Europe. Vaccination programs reduce the incidence of HBV in Europe and the United States (US) but that does not mean the burden of HBV is reduced, because the number of people who are HBsAg positive will continue to increase. Meanwhile, the incidence of HCV infection has decreased since the early 1990s. HCV is a curable disease although absorption of treatment remains low, the reasons are various including economic problems, fear of side effects that arise especially with peg interferon therapy [32].

2. Materials and Methods

2.1 Study Design

This research is a Systematic Review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses method or called PRISMA, this method is carried out systematically by following the correct stages or research protocol.

2.2 Data Collection

This method is carried out systematically by following the correct stages or research protocol. This research was conducted from July 2019 to December 2020. The source of the data taken from this research is journal articles that have been published online. This research was conducted on the internet through the Pubmed and Google Scholar databases. In this study, contact with patients or manual tracing was not carried out. The total number of articles identified through the database is 24,782 articles. The 24,782 articles obtained will be filtered based on abstract reviews. The aim is to see whether the article is in accordance with the research variables. A total of 19 articles were included based on abstract review. The exclusion process was carried out on articles that were not related to the problem under study and also the year of publication was more than 10 years.

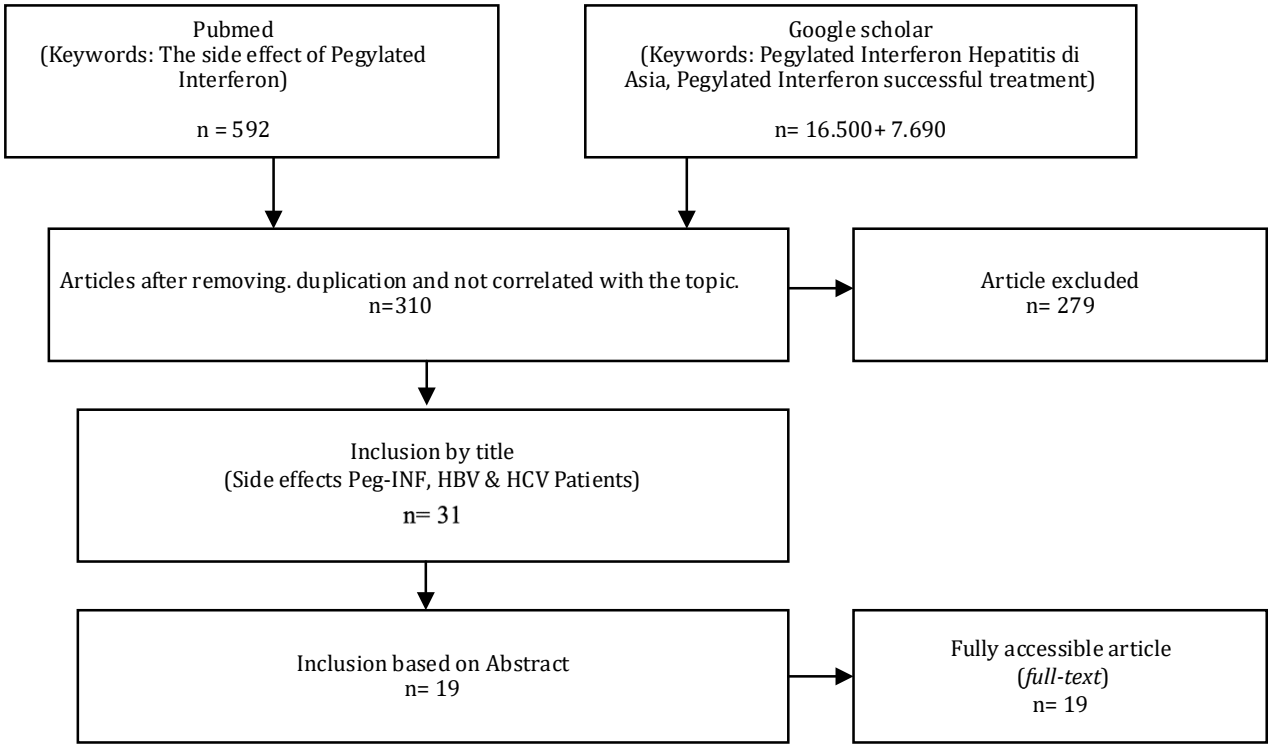

Figure 1: Flow Diagram of Study Selection

3. Results

As listed in Table 1, the total number of patients in each studies, the countries, where the studies were conducted, the reference year and the side effects. All the selected studies were conducted between 2010 and 2020.

Table 1: Characteristics of the study

Author	Year	N	Design	Side Effects	Of Country
Cetin Karaca and his colleagues	2013	32	Case control study	Leukopenia, thrombocytopenia,fatigue	Turkey
Chen Hua Liu and his colleagues	2017	102	Randomized controlled trial	Flu like symptom, fatigue, headache, insomnia, irritability, depression, anorexia, diarrhea, constipation, cough, anemia, neutropenia, thrombocytopenia	Taiwan
Dong Jin Suh and his colleagues	2013	86	Case control study	Alopecia, neutropenia, fatigue, headache, pruritus, influenza like illness, upper respiratory tract, pain, myalgia, asthenia,diarrhea, dyspepsia, pyrexia,pharyngolaryngeal,dizziness, insomnia, urticaria	Korea
Eleanor L Ramos	2010	24	Cohort study	Fatigue, nausea, myalgia, insomnia,chill, pyrexia	Seattle
Francis E. Lotrich	2013	NA	Text and opinion	Fatigue, pancytophenia, anemia, hypothiroidism	Pittsburgh
Gulden E K and his colleagues	2010	54	Case control study	Otalgia, tinnitus,vertigo, imballance	Turkey
Haris Papafragkakis and his colleagues	2012	-	Text and opinion	Depression	Los Angeles
Kabacam g and his colleagues	2012	58	Randomize controlled trial	Fever, fatigue, headache, arthralgia, Hair loss, abdominal pain, muscle pain, sleep disorder, bleeding, thrombocytopenia,neutropenia	Turkey
Kan Kikuchi and his colleagues	2014	56	Experimental studies	Anemia, haemorrhage, thrombocytopenia, loss of appetite, low visual aculty, retonophaty, pneumonia, cholecystitis, angina, mood changes	Japan
Kelly F and his colleagues	2016	1059	Cross sectional studies	Anemia, neutropenia, thrombocytopenia	Sao Paulo
Maryam A and his colleagues	2011	163	Cohort study	Depression, anxiety,stress	Australia
Michel B and his colleagues	2017	12	Non randomised experimental studies	Thrombocytopenia, neutropenia, anemia, upper abdominal pain, nausea, pyrexia, chills, headache, pruiritis, urticaria, hyperaemia, hypotension	Canada
Muhammad A H and his colleagues	2016	200	Case series	Thyroid dysfunction	Pakistan
Mohamed M.H dan Amr M.E	2013	49	Case series	Tinnitus, vertigo, sensory neural hearing loss	Cairo
Nikolina B J and his colleagues	2016	16	Cross sectional studies	Arthralgia, flue like, pancytopenia, motion sickness, rectorrhagia, thrombocytopenia, anemia, endocarditis, myalgia, cough	Croatia
Sanjaya K. Satapathy and his colleagues	2010	103	Randomized controlled trial	Neutropenia, thrombocytopenia, anemia, headache, fatigue, myalgia, nausea, fever, insomnia, depression,irritability	New York
S.S Tan and his colleagues	2010	252	Randomize controlled trial	Anemia, fever, body ache, lethargy, loss of appetite, chills,nausea	Malaysia
Teresa Santantonio and his colleagues	2014	130	Randomized controlled trial	Pyrexia, arthralgia, headache, nausea, hematology	Italy
Zehui Y and his colleagues	2012	592	Case series	Thyroid dysfunction, thyroiditis	China

4. Discussion

4.1 Hematology Side Effects

The most common haematological side effects in patients treated with Peg-INF are anemia, neutropenia and thrombocytopenia. As listed in Figure 2, In a study conducted [6] side effects of neutropenia occurred at week 24 after being treated this case was similar to the study conducted [28] cases of neutropenia were very common in the 6th month after treatment, 65% of patients had neutropenia and 8% had severe neutropenia. An additional study of 25 patients described a decrease in mean neutrophils of 21% after the first dose of interferon [31] In general, according to research [16] Neutropenia symptoms appear 2 to 6 weeks after treatment with Peg-INF, but from the results of the data, the side effects of neutropenia occur after the patient is treated at 24 weeks. Side effects Thrombocytopenia can be seen at weeks 24 and 33 after the patient started therapy. But these results were different in a study [3] of 6 patients, there was 1 case of thrombocytopenia that occurred at week 12 after starting therapy. Wheres in the study [20] of 50 HCV patients treated with thrombocytopenia cases occurred in 4 patients (33.3%), this result was different in 48 HBV patients in the study conducted [11] as much as 63% the patient developed thrombocytopenia but this side effect did not lead to discontinuation of treatment. Dose reduction is recommended when the platelet count falls below 50,000/mL and discontinuation of therapy if the platelet count is below 25,000/mL. Discontinuation of therapy is sometimes followed by normalization of the platelet count in 4 to 8 weeks [16]. Meanwhile, in the red blood cell profile, a systematic review showed that the prevalence of anemia was lower than that of neutropenia and thrombocytopenia. Cases of anemia can be seen at week 24 of therapy, this side effect is similar to the study [8] 83% of patients had anemia at week 24 with Hb levels in anemia an average of 10.8 ± 0.8 g/dL. The side effect of anemia from the data obtained is indeed lower, a study [9] also showed the same results, as many as 23% of 48 HBV patients had anemia. Hematological side effects in patients receiving Peg-INF therapy can be compensated for in several ways. Patients who experienced side effects of neutropenia and thrombocytopenia in a study conducted by [4] contained 7 patients, and in the study of [8] there were 24 patients, who were given a modified dose of Peg-INF to overcome these side effects. Patients can also be given Supportive Growth Factor to reduce neutropenia. In a cohort study, it was explained that anemia was a common side effect in patients taking combination therapy compared to monotherapy [21] blood transfusions were given to patients taking combination therapy with ribavirin because the results of this study were 100% transfused. compared with patients receiving monotherapy. In the study of [29], Erythropoetin can be given to patients who are anemic, although erythropoetin is not present in many centers.

Table 2: Hematology Side Effects

Author	Year	N	Design study	Hematology Side effects
Chen Hua Liu and his colleagues	2017	102	Randomized controlled trial	anemia, neutropenia, thrombocytopenia
Kabacam g and his colleagues	2012	58	Randomize controlled trial	bleeding, thrombocytopenia, neutropenia
Kan Kikuchi and his colleagues	2014	56	Experimental studies	Anemia, haemorrhage, thrombocytopenia,
Kelly F and his colleagues	2016	1059	Cross sectional studies	Anemia, neutropenia, thrombocytopenia
Nikolina B J and his colleagues	2016	16	Cross sectional studies	thrombocytopenia, anemia,
Cetin Karaca and his colleagues	2013	32	Case control study	Leukopenia, thrombocytopenia
Dong Jin Suh and his colleagues	2013	86	Case control study	Alopecia, neutropenia,
Sanjaya K. Satapathy and his colleagues	2010	103	Randomized controlled trial	Neutropenia, thrombocytopenia, anemia
S.S Tan and his colleagues	2010	252	Randomize controlled trial	Anemia
Teresa Santantonio and his colleagues	2014	130	Randomized controlled trial	hematology

4.2 Systemic Side Effects

Systemic side effects that are very common in the data obtained are fatigue, flue like symptoms, headache, insomnia, anorexia, diarrhea, cough, hair loss, nausea, myalgia, fever, arthralgia, abdominal pain, muscle aches and others. this can occur within minutes or days in patients treated with Peg-INF. When compared to studies conducted [1]. fatigue occurred as much as 56%, this side effect was the highest case in patients.

Table 3: Systemic Side Effect

Author	Year	N	Design study	Systemic side effects
Chen Hua Liu and his colleagues	2017	102	Randomized controlled trial	Flu like symptom, fatigue, headache, anorexia, diarrhea, constipation, cough,
Eleanor L Ramos	2010	24	Cohort study	Fatigue, nausea, myalgia, insomnia, chill, pyrexia
g and his colleagues	2012	58	Randomize controlled trial	Fever, fatigue, headache, arthralgia, Hair loss, abdominal pain, muscle pain, sleep disorder,
Kan Kikuchi and his colleagues	2014	56	Experimental studies	loss of appetite, low visual aculty, retinophaty, pneumonia, cholecystitis, angina, mood changes
Michel B and his colleagues	2017	12	Non randomised experimental studies	Upper abdominal pain, nausea, pyrexia, chills, headache, pruiritis, urticaria, hyperaemia, hypotension
Nikolina B J and his colleagues	2016	16	Cross sectional studies	Arthralgia, flue like, motion sickness, rectorrhagia, endocarditis, myalgia, cough

4.3 Psyciatric Side Effects

Based on systematic review data, the most common side effect of Peg-INF therapy is depression. At week 24 the average patient showed symptoms of depression. This result is different from the study [35] which showed that depressive symptoms appeared earlier at week 12 after Peg-INF therapy. More than 20% have symptoms of major depression and about 30% have symptoms of mild depression. When compared with a study from [36] patients who experienced side effects of depression also occurred at week 12, the results obtained were 13 patients out of 39 patients (33%) experienced depression. In patients who experience depressive symptoms, the dose of PEG-IFN can be adjusted. In a study conducted [27] in patients with mild to moderate depression, the dose of Peg-IFN was reduced by half and monitored by psychiatrist. If depressive symptoms increase to a severe condition, Peg-IFN therapy is discontinued and consultation with a psychiatrist is carried out. Administration of a prophylactic SSRI (paroxetine) 2 weeks before IFN therapy in patients who have a history of at least 1 depression in their life is significantly associated with a significant reduction in side effects of major depression and discontinuation of treatment [15]. However, the choice of antidepressant medication requires adjustment, as depression may improve or worsen with treatment options.

Table 4: Psyciatric Side Effects

Author	**Year**	**N**	**Design study**	**Psychiatric side effects**
Chen Hua Liu and his colleagues	2017	102	Randomized controlled trial	insomnia, irritability, depression, anorexia,
Kan Kikuchi and his colleagues	2014	56	Experimental studies	mood changes
Maryam A and his colleagues	2011	163	Cohort study	Depression, anxiety, stress
Haris Papafragkakis and his colleagues	2012	-	Text and opinion	Depression
Sanjaya K. Satapathy and his colleagues	2010	103	Randomized controlled trial	insomnia, depression, irritability
Francis E. Lotrich	2013	NA	Text and opinion	depression

4.4 Autoimmune Side Effect

Research that discusses autoimmune side effects, one of which is thyroid disorders or hypothyroidism in patients treated with Peg-INF. In this study thyroid dysfunction was very common and symptoms appeared at week 24, these results were similar in a study conducted [2] thyroid dysfunction occurred in 30 (12%) of 254 HCV patients, 20 patients had hypothyroidism and 10 had hypothyroidism. patients developed hyperthyroidism, with 9 out of 30 patients developing thyroid symptoms. The above results are also related to the study group [7] as many as 24 patients (17.14%) who initially did not show the characteristics of an autoimmune process, an increase in anti-thyroid antibodies was found during Peg-INF therapy. After 6 months of treatment hyperthyroidism occurred in 11 patients, while 6 of them had hyperthyroidism. Another study from (Watanabe, and his colleagues 1994) 9 of 106 patients with normal thyroid function before Peg-INF treatment had impaired thyroid function. Six of them developed hyperthyroidism after 16 to 30 weeks of therapy and hypothyroidism was revealed after 8 to 23 weeks.

Table 5: Autoimmune Side Effects

Author	Year	N	Design Study	Autoimmune Side Effects
Muhammad A Hameed and his colleagues	2016	200	Case series	Thyroid dysfunction
Zehui Yen and his colleagues	2012	592	Case series	Thyroid dysfunction, thyroiditis

4.5 Hearing Function Side Effects

Side effects of hearing loss due to Peg-INF have been rarely reported in studies. The average duration of treatment is 48 weeks, the mechanism that occurs in hearing loss during Peg-INF treatments is autoimmune, microvascular and autotoxic directly from Peg-INF.

Table 5: Hearing Function Side Effect

Author	Year	N	Design Study	Hearing Function Side Effects
Gulden E Karlidag and his colleagues	2010	54	Case control study	Otalgia, tinnitus, vertigo, imballance
Mohamed M.H dan Amr M.E	2013	49	Case series	Tinnitus, vertigo, sensory neural hearing loss

5. Conclusion

There are 19 research studies that are included in a systematic review by design. Randomized controlled trial, cohort study, case control study, experimental studies, cross sectional studies, non randomized experimental studies, case series. Of the 19 articles, the data taken were included in this study. The research was conducted from July 2019 to December 2020. This research was conducted on the Internet through the pubmed and google scholar databases. The common side effects of Peg-INF is hematology, systemic psychiatric, autoimmune and hearing functions. The results of the data obtained from each country are different but on average get the same side effects after taking this hepatitis treatment.

References

[1]. Ashley M, Onyema M. “Pegylated interferon alpha 2A for the treatment of hepatitis C virus infection” Expert opinion on drug metabolism and toxicology, 14(2); 219-227. 2018.

[2]. Asnis GM, De La Garza R. “Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches” J Clinic Gastroenterol, 40 (4): 322-335.2006.

[3]. Bruchfeld A, Lindahl K, Reichard O, Carlsson T, Schvarcz R. “Pegylated interferon and ribavirin in haemodialysis patients” Nephrology Dialysis Transplantion, 21(5): 1444-1445. 2006.

[4]. Cetin K, Ozlem M S, Bulent B, Asli C O, Suut G, Esra A, Sami E, Filiz A, Kadir D, Fatih B, Sabahattin K. “Efficacy of pegylated interferon- alpha treatment for 24 months in chronic delta hepatitis and predictors of respons” International Medical Press, 18: 561-566. 2013.

[5]. Calvaruso V, Mazza M, Almasio P L. "Pegylated-interferon-α2ain clinical practice: how to manage patients suffering from side effects". Expert Opinion on Drug Safety, 10(3):429–435.2011.

[6]. Chen H L, Chung F H, Chun J L, Chia Y D, Cheng C L, Jee-Fu H, Peir H H, Hung B S., Meng K S, Shih I C, Jou W L, Sheng S Y, Tung H S, Hung C Y, Pei J C, Ding S c, Wan L C, Ming L Y, Jia H K. "Pegylated Interferon Alpha 2A or without low dose ribavirin for treatment- naïve patients with hepatitis c virus genotype 1 receiving hemodialysis". Annal of internal medicine, Vol 159: 729-738.2017

[7]. Dosouky, Ibtesam., Elhawari, Soha., Emara, Mohamed., Hamed, Emad. "Types and Predictors of Interferon/Ribavirin Induced Cardiac Complications in The Egyptian Patients With Chronic Hepatitis C Virus". Faculty of Medicine Zagazig University Egypt. Vol 20: 643-653. 2014.

[8]. Dong J S, Han C L, Kwan S B, Mong C, Young O K, Won Y T, Chae Y C, Kwang C K, Young S L. "Efficay and safety of pegylated interferon -alpha 2A in patients with lamivudine – resitant HBeAg-positive chronic hepatitis B". Antiviral Therapi. 18: 765-773. 2013.

[9]. Dan A A, Martin L M, Crone C, Ong J P, Farmer D W, Wise T, Younossi Z M. "Depression anemia and health related quality of life in chronic hepatitis C". Journal of hepatology, 44(3): 491-498. 2006

[10]. Eleanor L M. "Preclinical and Clinical Development of Pegylated Interferon". Journal of Interferon & Cytokine Research, 30 (8): 591-598. 2010

[11]. Elif D Kartal, Saygin N A, Ilhan O, Gaye U. "Adverse effects of high – dose interferon -alpha 2A treatment for chronic hepatitis B". Advances in therapy. 24: 963. 2007.

[12]. Francis E Lotrich. "Psychiatric Clearance for Patients Started on Interferon Alpha Based Therapies". Am J Psychiatry, 170:6. 2013.

[13]. Gulden E K, Turgut K, Kutbetiin D, Erol K. "The Effects of Pegylated Interferon/ Lamivudin Therapy on Auditory Function in Patients with Hepatitis B". Auris Nasus Larynx International Journal of ORL &HNS, Vol 38: 312-318. 2011.

[14]. Gökhan K, George N D, Yìlmaz Ç, Kalliopi Z, Thomas b, Andreas E, Stefan Z, Fehmi T, Kendal Y A, Mithat B, Hans P D, Hakan B, Michael M, Heiner W, Cihan Y. "Pegylated Interferon Based Treatment in Patients With Advanced Liver Disease due to Chronic Delta Hepatitis". Turk Journal Gastroenterol, 23(5): 560-568. 2012.

[15]. Haris P, Murali S R, Martin M, Sonu D, Paul M. "Deppresion and pegylated Interferon – Based Hepatitis C Treatment". International Journal of Interferon, Cytokin, and Mediator Research. Vol: 4, 25-23. 2012.

[16]. Hubert S, Michael C, Sammy S. "Management of hepatitis c antiviral therapy adverse effect". Current hepatology reports. 10: 33-40. 2011.

[17]. Janina K, Marta W S, Waldemar U, Jakub P, Anhelli S. "The influence of interferon alpha on the induction of autoimmune thyroiditis in patients treated for chronic viral hepatitis type C". Endokrynologia Polska, 62(6):517-22 . 2011.

[18]. Kelly F N D, Angelo A M, Christiane V T, Fernanda W O, Leandro C, Alberi A F, Christofali B, Paulo R L A. "Impact of the pegylated interferon and ribavirin therapy on the treatment related mortality of patients with cirrhosis due to hepatitis c virus". Revista do instituto de medicina tropical de sao Paulo, 58: 37. 2016.

[19]. Kan K, Takashi A, Kosaku N, Ikuto M, Ryoichi, Namiki I, Masanori A, Chikao Y, Fumi K, Naoki H, Yoahihiro T, Etsuro O, Kazuhiko H, Masaki N, Hiroshi K, Masanor K, Hiroyuki K, Norisato, Hideki, Misaki M, Michio I, Tadao A. "Multicenter study of pegylated interferon alpha-2A monotherapy for hepatitis C virus infected patients on hemodyalisis: Reach study". Therapeutic Apheresis and Dialysis, 18(6): 603-611. 2014.

[20]. Kokoglu O F, Ucmak H, Hosoglu S, Cetinkaya A, Kantarceken B, Buyukbese M A, Isik I O. "Efficacy and tolerability of pegylated interferon alpha-2a in hemodyalisis patients with chronic hepatitis C". Journal of gastroenterology and hepatology, 21 (3): 575-580. 2006.

[21]. Mario E, Jesus H, Maria D A, Fernando C, Carlos C, Fabrizio F. "Pegylated interferon alone or with ribavirin for chronic hepatitis c in haemodialysis population". Kidney blood Press Res, 40(3): 258-65. 2015.

[22]. Maryam A, Jason G, Gail V M, Kathy P, Barbara Y, Carolyn D, Andrew R L, Ingrid V B, John M K, Margaret H, Gregory J D, Paul S H. "Effect of pegylated interferon alpha-2a treatment on mental health during recent hepatitis c virus infection". Journal of gastroenterology and hepatology, 27: 957-965. 2012.

[23]. Michel B, Victor P, Valentin C, Lilia C, Pavline J, Jeffrey, A, Peter S, Frederic L G, Emmanuel G, Adalbert K H, Hadi K, Michael R, Andrew V. "Safety and efficacy of REP 2139 and pegylated interferon alpha-2A for treatment- naïve patients with chronic hepatitis b virus and hepatitis d virus co-infection (REP 301and REP 301-LTF): a non randomized, open label, phase 2 trial". Lancet Gastroenterol Hepatol, 2 (12): 877-889. 2017.

[24]. Muhammad A M, Asif M, Muhammad A F, Ghias U N T, Israr U H T. "Hypothiroidsm in hepatitis c patients on pegylated interferon therapy". J ayub med coll Abottabad, 20(4): 706- 708. 2016.

[25]. Nikolina B J, Marijana G, Jasna S, Valentina C M, Bosilijka I, Sanjin R, Nilenka S, Rajko O, Irena H, Dragan L, Boris V, Petar K. "Pegylated interferon for treatment of chronic hepatitis c in hemodialysis patients in Croatia". Kidney Blood Pressure Research, 34: 53-57. 2011.

[26]. Nurdjanah, Siti. "Therapy for Chronic Viral Hepatitis". The Indonesiam Journal of Gastroenterology, Hepatology, and Digestive Endescopu, Vol 2(1). 2001.

[27]. Sanjaya K S, Chandra S L, Shawnette P, Shobhana C, Susan W. " Equally Poor Outcomes to Pegylated Interferon – based Therapy in African American and Hispanics with Chronic Hepatitis C Infection". J Clinic Gastroenterol, Vol. 44 No.2. 2010.

[28]. Serrano-Villar S, Quereda C, Moreno A, Pérez-Elías M J, Casado J L, Royuela A, Moreno, S. "Neutropenia During Therapy With Peginterferon and Ribavirin in HIV-Infected Subjects With Chronic Hepatitis C and The Risk of Infection". Clinical Infectious Diseases, 57 (3): 458-464. 2013.

[29]. Tan S S, Abu Hassan M R, Abdullah A, Ooi B P, Korompis T T, Merican M I. "Safety and Efficacy of an Escalating Dose Regimen of Pegylated Interferon alpha 2B in The Treatment of Haemodialysis Patients with Chrronic Hepatitis C". Journal of Viral Hepatitis, Vol 17, 410-418. 2010.

[30]. Teresa S, Massimo F, Evangelista S, Paulo T, Sergio B, Paolo F, Mario T, Giovanni D P, Nicoletta M, Eligio P, Gioacchino A. "Acute Hepatitis C: A 24 – Week Course of Pegylated Interferon Alpha 2b Versus a 12- Week Course of Pegylated Interferon Alpha -2B Alone or with Ribavirin". Official Journal of The American Association for The Study of Liver Disease, Vol. 59, No. 6. 2014.

[31]. Peck–Radosavljevic, M, Wichlas M, Homoncik–Kraml, M, Kreil, A, Hofer, H, Jessner, W, Ferenci, P. (2002). "Rapid suppression of hematopoiesis by standard or pegylated interferon-α". Gastroenterology, 123(1):141–151. 2002.

[32]. Pierre Deltenre. "Studies on the epidemiology of hepatitis B and C virus infections are still needed". J Hepatol, 62(6): 1225-7. 2015.

[33]. Watanabe U, Hashimoto E, Hisamitsu T, Obata H, Hayashi N. "The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C". Am J Gastroenterol, 89 (3): 399-403. 1994.

[34]. Zehui Y, Ke F, Yi F, Xiaohong W, Qing M, Guohong D, & Yuming W, Don J S, Han C L, Kwan S B, Mong C, Young O K, Won Y T, Chae Y C, Kwang C K, Young S L. 2013. "Efficacy and Safety of Pegylated Interferon alpha2A in Patients, with Lamivudine – Resistant HBeAG-Positive Chronic Hepatitis B". International Medical Press, 18:765-773. 2013.

[35]. Zorana P, Dragan D, Nadja P M, Olivera V, Miroslava J G. "Depressive symptoms in patients with hepatitis c treated with pegylated interferon alpha therapy: a 24 week prospective study". Psychiatria Danubina. 23(4): 370-377. 2011.

[36]. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, Hill J et al. "A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C". Mol psychiatry, 7:942-7. 2002.