

Antiviral Therapy for Hepatitis C Prophylaxis in Percutaneous Exposure and Acute Hepatitis C

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ABSTRACT

Incidence of percutaneous exposure to hepatitis C virus (HCV) is still quite high, particularly in medical staffs. Though not all will cause infection, but if acute HCV infection occurs, it usually develops into chronic hepatitis which finally causes cirrhosis and hepatocellular carcinoma. Untill now, there is no standard method either in regiments, administration time, or duration of administration to prevent HCV infection after exposure occurs, as well as the use of antiviral therapy in acute HCV. HCV therapy target is viral eradication, thus the therapy response is defined using virological parameter than clinical parameter.

Different from hepatitis B virus (HBV), immunoglobulin administration after exposure to HCV is not recommended as it is not proven to prevent transmission, similarly with pegylated interferon (PEG-IFN) or interferon (IFN) administration. In addition, several studies concluded that risk of HCV transmission after percutaneous exposure is low, therefore regular strict monitoring (monthly in the first 16 weeks after exposure) to clinical and laboratory results (HCV-RNA, alanine aminotransferase) is more required, so that detection and early treatment to acute HCV can be performed, considering that several studies showed that early monotherapy using IFN/PEG-IFN in acute HCV could reach quite high sustained virological response (SVR).

Keywords: hepatitis C, post exposure prophylaxis, acute infection treatment

ABSTRAK

Insiden paparan perkutaneus terhadap hepatitis C virus (HCV) masih cukup tinggi, terutama di kalangan petugas medis. Walaupun tidak semua akan menyebabkan infeksi, namun apabila terjadi infeksi HCV akut, maka seringkali dapat berkembang menjadi hepatitis kronik yang akhirnya dapat menimbulkan sirosis dan karsinoma hepatoseluler. Hingga saat ini belum ada metode baku baik dalam hal regimen, waktu pemberian, maupun lama pemberian untuk pencegahan infeksi HCV setelah terjadinya paparan. Begitu pula dengan terapi antivirus pada HCV akut. Target terapi HCV adalah eradikasi virus, sehingga respon terapi lebih didefinisikan dengan parameter virulogik daripada parameter klinis.

Berbeda dengan hepatitis B virus (HBV), pemberian imunoglobulin paska paparan terhadap HCV bukan merupakan rekomendasi karena tidak terbukti mencegah transmisi, begitupula dengan pemberian pegylated interferon (PEG-IFN) ataupun interferon (IFN). Selain itu dari beberapa studi juga disimpulkan bahwa risiko transmisi HCV setelah paparan perkutaneus adalah rendah, sehingga pemantauan berkala yang ketat (setiap bulan dalam 16 minggu pertama setelah paparan) terhadap klinis dan hasil laboratorium (HCV-RNA, alanin amino transferase) lebih diperlukan agar deteksi dan terapi dini terhadap HCV akut dapat dilakukan, mengingat beberapa studi menunjukkan bahwa monoterapi dini menggunakan IFN/PEG-IFN pada HCV akut dapat mencapai respon virulogi menetap yang cukup tinggi.

Kata kunci: hepatitis C, profilaksis paska paparan, terapi infeksi akut

INTRODUCTION

Incidence of percutaneous exposure, such as through syringe-needle or open wound, is a potential cause of communicable infectious disease transmission through blood in health care workers. Based on data from disease control and prevention (CDC) USA (2000), at least 600,000 health workers in United States experienced percutaneous exposure every year. This happens due to mistakes in syringe-needle insertion technique, closing used syringe-needles, and way to dispose syringe-needles or mistakes in the use of protective equipments, such as not using gloves or using gloves with inappropriate size. Agustian et al, conducted a study to estimate the transmission risk of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infection among medical staffs in Indonesia. Study results revealed that the estimation of infection in year 2005 due to percutaneous exposure was 1,445 people for HBV, 399 people for HCV, and 18 people for HIV.¹

Acute HCV infection often developed into chronic hepatitis which may finally cause cirrhosis and hepatocellular carcinoma, therefore the progressivity prevention effort of this disease become very important. Till date, there is no standard method either in regiments, administration time, or even administration duration to prevent HCV infection after being exposed; similarly with the use of antiviral therapy in acute HCV. Few studies recommended early therapy in acute condition to achieve sustained virological response (SVR). However, the right time to initiate therapy is still controversial because in 15-30%, acute hepatitis C could heal spontaneously (self-limited). Several predictor factors in spontaneous HCV clearance have been studied, but generally the study was not performed with big sample size and good prospective study design.² This review will elaborate the benefit and risk of antiviral therapy for HCV prophylaxis after percutaneous exposure and antiviral therapy for acute hepatitis C.

NATURAL PROGRESSION OF HEPATITIS C

HCV infection may cause acute or chronic hepatitis. Acute hepatitis usually does not cause symptoms (asymptomatic). However, if it present with symptoms, they usually subside in few weeks. Acute HCV infection is generally defined as new viremia incidence which is marked with conversion of HCV-RNA negative to HCV-RNA positive. In the serum, HCV-RNA can be detected in

1-2 weeks after exposure. Anti-HCV seroconversion can be detected in 2-6 months (window period) or even could be more than six months in particular group, thus anti-HCV examination to diagnose acute HCV become inappropriate if compared to HCV-RNA test. Acute phase of HCV infection is erected in the first six months and in 20-50%, spontaneous resolution may occur, while in the other 50-80%, chronic HCV will develop. In chronic HCV, 20% will develop into cirrhosis, 6% into end-stage liver disease, while the other 14% into hepatocellular carcinoma.^{3,4}

TREATMENT SUCCESS CRITERIA

HCV therapy target is viral eradication, as an effort to prevent complication of the disease, such as necroinflammation, fibrosis, cirrhosis, hepatocellular carcinoma, and mortality. If HCV is eradicated, then necroinflammation process will not continue and cirrhosis progression will be ceased in non-cirrhosis patient, thus therapy response is more defined with virological parameter rather than clinical parameter. Virological response, is divided into several types based on achievement time to therapy target (Table 1).^{4,5} Short term therapy response can be measured biochemically (normalization of ALT serum), virologically (no detection of HCV-RNA serum), and histologically (improvement in inflammatory score and no worsening of fibrosis score).⁵

PROPHYLAXIS THERAPY AFTER PERCUTANEOUS EXPOSURE

Public health service USA in 2001 published guidelines on management of prophylaxis after occupation exposure to HBV, HCV, and HIV. In that guideline, it was explained that different from HBV, immunoglobulin administration after occupation exposure to HCV was not recommended. Results of several studies which evaluated the efficacy of immunoglobulin to HCV exposure were difficult to be interpreted because difference in diagnostic criteria or even study design.⁶ An experimental study using chimpanzees which were injected with high titer anti-HCV immunoglobulin in one hour after exposure to blood containing HCV, obtained that this was not proved to prevent transmission of HCV infection.⁷

Corey et al, performed a prospective study on prophylaxis after HCV exposure to 51 health care workers in Massachusetts, Boston, who experienced exposure to HCV patients' blood.⁸ Prophylaxis therapy was given to 44 subjects who were willing to receive

Table 1. Therapy response based on virological parameter^{4,5}

Virological response	Definition	Clinical benefits
Rapid virological response (RVR)	HCV RNA (-) in week 4 therapy using sensitive PCR-based quantitative assay	Can be used as a consideration to shorten therapy in genotype 2 & 3 and in genotype 1 with low viral load
Early virological response (EVR)	Partial EVR: HCV-RNA level reduction ≥ 2 log compared to baseline HCV-RNA level Complete EVR: HCV RNA (-) in week 12 therapy	Predicting SVR failure
End of treatment response (ETR)	HCV-RNA (-) in the end of therapy (24 or 48 weeks)	
Sustained virological response (SVR)	HCV-RNA (-) after 24 weeks of therapy cessation	Best predictors of long term therapy response
Breakthrough	Re-emergence of HCV-RNA in the serum when the therapy is ongoing	
Relapse	Re-emergence of HCV-RNA in the serum after therapy is ceased	
Non-responder	Failure to eradicate HCV-RNA in the serum after 24 weeks therapy	
Null-responder (NR)	Reduction of HCV-RNA level $< 2\log_{10}$ IU/mL from the baseline after 12 weeks therapy	
Partial-responder (PR)	Reduction of HCV-RNA level $> 2\log_{10}$ IU/mL from the baseline after 12 weeks baseline after therapy but HCV-RNA is still detected in week 12 and 24	

pegylated interferon (PEG-IFN) α -2b 1 μ g/kg body weight, subcutaneously, weekly for four weeks, since seven days after exposure. Four weeks duration was chosen because based on the available study, it was estimated that this duration was the fastest duration which gave out good efficacy, besides preventing the presence of side effects to interferon. Ribavirin was not given due to the numbers of reproductive age female participated in this study. Study results showed that none experienced HCV viremia or HCV antibody seroconversion at the end of therapy or in week 4 after therapy. Similarly, in the group who did not receive prophylaxis therapy, in the same period of time, HCV viremia or HCV antibody seroconversion was not found. In the group who received therapy, side effects were reported, such as flulike symptoms 41 (93%) subjects, headache 31 (70%) subjects, irritation on injection site 26 (59%) subjects, and mood depression in 3 (6.81%) subjects.⁸

Nukaya et al, conducted a survey to subjects who experienced exposure to blood (through syringe needles, surgical knife, or blood splashes) in Social Insurance Chukyo, Tokyo between 1993-2003, which was aimed to evaluate the benefit of recombinant IFN- α 2b 10 MU single administration intramuscularly to prevent transmission.⁹ This study concluded that prophylaxis benefit with that regiment was unclear, therefore there was no importance to administer IFN prophylaxis therapy. Continuous observation particularly in high risk cases was highly recommended, thus the therapy could be administered as soon as possible if acute hepatitis was revealed.⁹

Chung et al, performed a study to 684 health care workers who experienced occupation exposure (syringe-needles or surgical knife) to patients with anti-HCV positive. From 684 subjects, 279 (41%) were given IFN therapy directly after exposure or in 1-12 days after exposure. Administration duration was around 1-3 days. In three months of observation, one incidence of acute HCV was found in each group; therapy group (1/279; 0.4%) and non-therapy group (1/405; 0.2%). Therefore, it was concluded that HCV transmission risk after exposure to syringe-needles was low, and prophylaxis therapy with IFN in short duration was not needed.¹⁰

OTHER THERAPY OF ACUTE HEPATITIS

Kamal et al, conducted a study to 161 patients proven to suffer from acute HCV and 23% apparently experienced spontaneous resolution. In univariate analysis, age less than 30 years, onset of symptoms, and HCV-RNA less than 800,000 IU/mL were associated with spontaneous resolution, while in multivariate analysis only appearance of symptoms was a significant predictor of spontaneous resolution.¹¹

Until now, optimal strategy therapy for acute HCV is still a controversy, considering the possibility of spontaneous resolution and the absence of symptoms in most cases. But actually there are several factors which are quite rational to be considered in therapy administration, such as the high incidence of acute infection which developed into chronic and the absence of definite predictors on acute infection prognosis. Compared to acute HCV, chronic HCV is related with

bad prognosis, need of intensive therapy with PEG-IFN and ribavirin, long therapy duration, and decrease of therapy success rate. Conversely, intervention in acute phase is associated with the success of viral eradication, use of monotherapy regimens which have better tolerability, low price, more comfortable, and shorter duration of treatment.³

THErapy SELECTION

Acute HCV Monotherapy with IFN- α

Several studies on IFN- α 2b monotherapy for acute HCV gave out SVR between 53-100%. However, due to difference in inclusion criteria, sample size which is usually small, patients heterogeneity, absence of control, different type and dosage of interferon, difference in definition of therapy response, and inadequate observation time to eliminate long term relapse, made us difficult to interpret those study results (Table 2).¹²⁻¹⁵

Acute HCV Monotherapy with Pegylated Interferon- α

Several clinical trials on benefit and safety usage of PEG-IFN α as acute HCV therapy have been performed (Table 3). Transmission model in most cases in these studies was use of intravenous drugs, exposure to syringe-needles, medical procedures, or sexual contact with person known to suffer from hepatitis C.^{11,16-19} After therapy using PEG-IFN α -2b monotherapy for 12-24 weeks, thus the average range of SVR was 71-95%, depends on the population, HCV genotype, therapy onset, and adherence to therapy.³

Time to Initiate Therapy

Based on the literature, the best time to start acute HCV therapy has not been known precisely. Several clinical trials started therapy in different times, varying between 1-24 months after onset of symptoms, first detection of HCV-PCR, or when seroconversion occurred.

Kamal et al, conducted a study to 168 acute HCV patients. In 129 patients known to not experience spontaneous healing in week 8, randomization was performed to obtain PEG-IFN α -2b monotherapy (1.5 μ g/kg/week) which was started at week 8, 12, or 20 with 12 weeks of administration duration. Study results showed that in the group, in which therapy was initiated at week 8 (43 subjects), week 12 (43 subjects), and in week 20 (43 subjects), the SVR achievements were 95%, 92%, and 76%, respectively. Overall, SVR achievement was better in those infected with genotype

2, 3 and 4 compared to genotype 1. However, among those infected with HCV genotype 1 and had high viral load, earlier therapy initiation resulted in better SVR achievement.¹⁷ Delwaide et al, performed a prospective study to assess the benefits of early therapy using IFN- α 2b in acute HCV. Study results showed that early therapy since onset of symptoms was the most relevant predictor in SVR achievement (Table 4).¹⁵

Combination of IFN α or PEG-IFN α and Ribavirin

Prospective study carried out by Kamal et al, exhibited the absence of significant difference between PEG-IFN α monotherapy and combination therapy of PEG-IFN- α and ribavirin as acute HCV monotherapy in terms of SVR. This study performed observation to 54 acute HCV patients, who were divided into 3 groups, which are group who received PEG-IFN α plus ribavirin (n = 20), monotherapy PEG-IFN group (n = 20), and group who did not receive therapy (n = 14). After 24 weeks therapy, it was obtained that there was no significant difference in SVR achievement (p = 0.27) in group receiving combination of PEG-IFN plus ribavirin (SVR 85%) and PEG-IFN monotherapy group (SVR 80%), while in the group who did not receive therapy, 5 people was known to experience spontaneous healing.²⁰

Kamal et al, conducted a prospective study on specific response of T CD4+ cell to HCV and cytokines production to various types of HCV proteins in the peripheral blood of 42 patients who received IFN α -2a, PEG-IFN α -2a monotherapy, or combination of PEG-IFN α -2a and ribavirin and its correlation to the success of therapy. Study results showed that SVR was significantly higher in the PEG-IFN group (42% in monotherapy PEG-IFN α -2a and 57% in combination PEG-IFN α -2a plus ribavirin) compared to IFN α -2a group (14%). In the success of PEG-IFN α -2a monotherapy or even in combination with ribavirin, in achieving SVR it was thought to be related with the high ability of PEG-IFN in inducing and maintaining response of T CD4+ specific cells to HCV.²¹

Rocca et al, performed a cohort study to 16 patients to evaluate transmission model and efficacy of antiviral therapy in acute HCV patients.²² Study results showed that among 13 patients receiving acute HCV therapy, 12 patients who completed therapy have average SVR and biochemical response for more than 15 months after the therapy was ceased (about 4-36 months). Therapy duration, types of interferon, and combination with ribavirin did not give significant difference to therapy response. Thus, it could be concluded that early

Table 2. Summary of studies on acute HCV monotherapy using IFN- α ¹²⁻¹⁵

Study type	Cohort	Transmission	HCV genotype (%)	Spontaneous clearance (%)	Regiment	Initial therapy timing	Therapy duration (week)	SVR n (%)
Non Random								
Vogel et al n = 24	Whites, most of symptomatic	IDU Medical procedure Unknown	1(42) 2/3 (21) Mixed/ unknown(37)	NA	IFN α -2b 10 MU/day	NA	Till normal value of ALT 18-43 day	20/22 (91)
Jaekel et al n = 44	Whites, most of symptomatic	Syringe-needle/medical procedure (48%) IDU (20%) Sexual contact (23%) Unknown (9%)	1(61) 2/3 (27) 4 (0) NA (12)	NA	Induction of IFN α -2b 5 MU/day for 4 weeks followed by IFN α -2b 5MU 3 times/week	Immediate (average 89 days after infection)	20 week	42/43 (98)
Delwalle et al n = 28	Whites symptomatic (78.5%)	NA	1 (12) 2/3 (5) 4 (1) NA (10)	19%	IFN α -2b 5MU/day	Average 110 \pm 44 days	8 week	21/28 (75)
Random								
Nomura et al n = 30	Asians Most of symptomatic (59%)	Syringe-needle (30%) IDU (10%) Sexual contact (13%) Unknown (43%)	1 (87) 2/3 (13)	NA	Early intervention: IFN α (human lymphoblastoid IFN) 6 MU/day IM Further intervention: IFN α (human lymphoblastoid IFN) 6 MU/day IM	8 weeks since onset/symptom presence after 1 year of observation	4 week	13/15 (87) 8/15 (53)

 IDU: intravenous drug user; IFN α -2b: interferon α -2b; HCV: hepatitis C virus; SVR: sustained virological response; ALT: alanine aminotransferase; NA: not applicable

Table 3. Summary of studies on PEG-IFN therapy in acute HCV patients^{11,15-19}

Type of study	Cohort	Transmission	HCV genotype (%)	Spontaneous clearance n/N (%)	Regiment	Initial therapy timing	Therapy duration (week)	SVR n/N (%)
Non-random								
Wiegand et al n = 89	Symptomatic (60%) HIV co-infection (4%)	Medical procedure & syringe-needle (30%) IVDU (22%) Sexual contact (22%) Etc (8%)	1 (66) 2/3 (22) 4 (1) Unidentified (1)	NA	PEG-IFN α -2b 1.5 μ g/kg	76 days after infection	24	63/89 (71%)
De Rosa et al n = 19	Most of asymptomatic (74%)	IVDU (74%) Sexual contact (16%) Syringe-needle (10%)	1 (58) 2/3 (42)	NA	PEG-IFN α -2b 1.06-1.66 μ g/kg/week	Average 33.6 days (range 0-116 days)	12	14/19 (74)
Random								
Kamal et al n = 168	Symptomatic & asymptomatic	Occupation exposure, medical procedure	1b (40) 2/3 (8) 4 (58)	31/141 (22)	PEG-IFN α -2b 1.5 μ g/kg	8	12	41/43 (95) 40/43 (93) 33/43 (77)
Kamal et al n = 173	Symptomatic & asymptomatic	Occupation exposure, medical procedure	Most of 4a and 1b	29/131 (22)	PEG-IFN α -2b 1.5 μ g/kg/week	12	8 12 24	23/34 (68) 28/34 (82) 31/34 (91)
Unknown design								
De Rosa et al n = 23	Symptomatic & asymptomatic	IVDU (100%)	1 (58) 2/3 (42)	NA	PEG-IFN α -2b 1.33 μ g/kg/week	12	12	17/23 (74)

PEG-IFN: pegylated interferon; HCV: hepatitis C virus; IVDU: intravenous drug user; SVR: sustained virological response; NA: not applicable

intervention with IFN α was effective in preventing the progression of acute HCV infection to chronic in most patients without concerning about the therapy duration, types of interferon, or even combination with ribavirin.²²

Wiegand et al, carried out a study which was aimed to analyze the benefit of early therapy in acute HCV with PEG-IFN α -2b. As many as 89 individuals with acute HCV infection received PEG-IFN- α 2b therapy for 24 weeks. Median of therapy initiation was 76 days after infection (14-150 days). From 65 (73%) patients who had good adherence (received 80% interferon dose and fulfilled 80% determined therapy duration), SVR achievement was 94%. From all analyzed variables (age, viral load, HCV genotype, bilirubin level, ALT level), only ALT level more than 500 U/L before therapy was the factor associated with therapy success ($p < 0.025$). From this study, it was concluded that early therapy with PEG-IFN α -2b in acute HCV infection patients with high adherence would result in high SVR.¹⁶

Kamal et al, made a recommendation on when to initiate therapy in acute HCV as follows in Figure 1.³

Duration of Therapy

Optimal duration for acute HCV therapy is still undecided. Guidelines by American Association for the Study of Liver Diseases (AASLD) stated that based on the current available information and study

results, no definite recommendation about optimal duration required for acute HCV therapy could be made. However, it was stated that 12 weeks and 24 weeks duration could be considered.⁵

Several clinical trials which have been performed using conventional IFN or even PEG-IFN, applied different duration with variable results, and most studies did not perform long enough observation to eliminate the possibility of long term relapse. From four clinical trials, it was obtained that 12 weeks duration of therapy in acute HCV could give SVR 74-93%.^{11,17-19}

Study results of Kamal et al, revealed that from 102 acute HCV patients who received therapy for 8, 12, and 24 weeks, overall did not find significant difference between therapy duration and SVR achievement. However, if related with viral genotype, there was significant difference between therapy duration and SVR achievement in genotype-1 compared to other genotypes, in which 24 weeks therapy gave out better SVR achievement compared to 8 and 12 weeks therapy. Further analysis to those infected with genotype one obtained that 24 weeks therapy gave out much better SVR achievement in those who had high viral load or those who did not achieve RVR. Hence, from this study, it was concluded that therapy duration should be optimized based on genotype, viral load, and also RVR achievement (Figure 2).¹¹

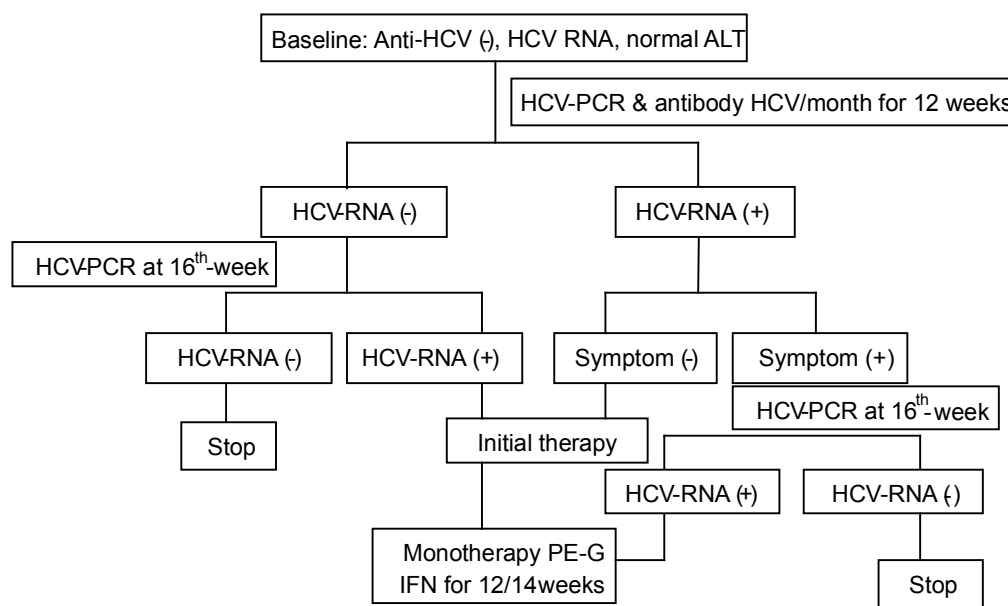


Figure 1. Recommended algorithm of acute HCV management³

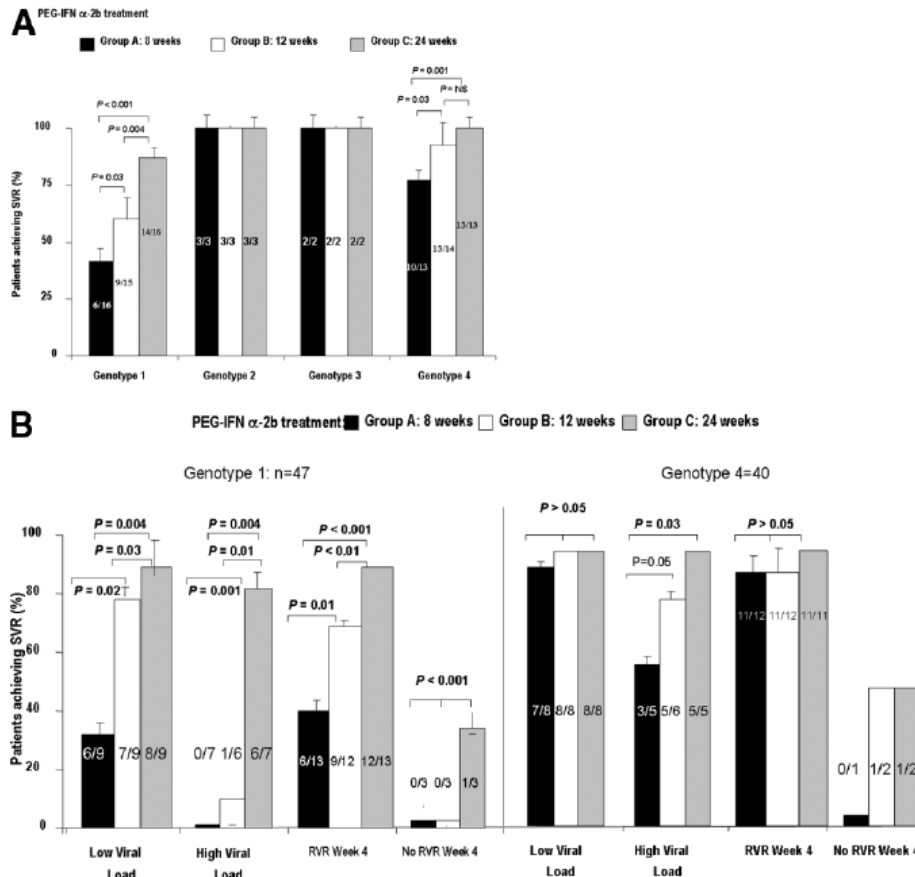


Figure 2. SVR achievement related to therapy duration associated with genotype, also viral load in genotype 1 and 4¹¹

Table 4. Summary of studies which describe good sustained virological response in 12 weeks therapy duration^{11,17-19}

Study type	Cohort	Transmission	HCV genotype (%)	Spontaneous clearance n/N (%)	Regiment	Initial therapy (week)	Therapy duration (week)	SVR n (%)
Non-random								
De Rosa et al n = 19	Most of asymptomatic (74%)	IVDU (74%) Sexual contact (16%) Syringe-needle (10%)	1 (58) 2/3 (42)	NA	PEG-IFN α -2b 1.06-1.66 μ g/ kg/ week	Average 33.6 days (range 0-116 days)	12	14/19 (74)
Random								
Kamal et al n = 168	Symptomatic & asymptomatic	Occupation exposure, medical procedure	1b (40) 2/3 (8) 4 (58)	31/141 (22)	PEG-IFN α -2b 1.5 μ g/ kg	8 12 20	12	41/43 (95) 40/43 (93) 33/43 (77)
Kamal et al n = 173	Symptomatic & asymptomatic	Occupation procedure, medical procedure	Most of 4a and 1b	29/131 (22)	PEG-IFN α -2b 1.5 μ g/ kg/week	12 12 24	8 12 24	23/34 (68) 28/34 (82) 31/34 (91)
Unknown design								
De Rosa et al n = 23	Symptomatic asymptomatic	IVDU (100%)	1 (58) 2/3 (42)	NA	PEG-IFN α -2b 1.33 μ g/kg/week	12	12	17/23 (74)

IVDU: intravenous drug user; PEG-IFN α : pegylated interferon- α ; NA: not applicable

CONCLUSION

Based on the study results mentioned above, it can be concluded that HCV transmission risk after percutaneous exposure is low, and prophylaxis therapy with immunoglobulin or IFN is not required. If exposure occurs, it is better to directly perform HCV-RNA, anti HCV, and ALT examinations as baseline data. Further, close regular monitoring (every month in the first 16 weeks after exposure) is performed to clinical and laboratory results (HCV-RNA, ALT) so therapy administration can be directly performed if acute HCV occur, considering that several studies showed that early monotherapy using IFN/PEG-IFN in this condition could reach quite high SVR. Regular monitoring can be ceased if after 16 weeks after exposure, HCV-RNA still gives out negative results.

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