Hepatitis C: A Comprehensive Overview of Its Historical Development, Viral Nature, Disease Mechanism, And Associated Complications

Mehvish Fayaz[1], Pankaj Mehta[2]
[1]*Department of Biotechnology, Chandigarh University, Mohali, Punjab, India (140413)*
[2]*Assistant Professor Department of Biotechnology, Chandigarh University, Mohali, Punjab, India (140413)*

***Abstract*—Infection of Hepatitis C is a liver ailment that is caused by the hepatitis C virus (HCV). HCV have been identified as a worldwide health complication due to which the development in liver cirrhosis and hepatocarcinoma. As a result of the worldwide effect on people, there is a growing number of new treatment and treatment agents for HCV. Therefore, today HCV is considered a worldwide burden. Advances in the development of treatment and clinical results depend upon the genome of HCV as well as biodiversity, pathogenesis, diet plan factors, socio-economic and ecological factors. Infection of Chronic hepatitis C is mostly undiagnosed however it may cause liver damage before it is diagnosed. The excessive load of HCV and the considerable health effects which are related to chronic infections that makes HCV a crucial public health concern. Advancement in the treatment of HCV had produced possibilities to reduce HCV-related illnesses and deaths. These therapies are secure, allowed, and extremely effectual; although, the advantage cannot be achieved without a consequential rise in the number of people being examined for HCV so that all infected people can monitor their diagnosis and be connected to proper medical treatment. In this review paper, we mainly discuss its history, genetics of HCV, clinical outcomes, mode of transmission, diagnosis and treatment.**

***Index Terms*—Hepatitis C, Virology, Pathogenesis, Therapeutic invention.**

I. INTRODUCTION

Within the US, infection of Hepatitis C virus is the main cause of hepatic related death, liver cirrhosis and liver cancer [1,2]. Around 170 million individuals worldwide have been affected with the hepatitis C virus (HCV). Subsequently it was discovered in 1989, however it has not till 1992 the blood was tested for HCV disease; Consequently, before 1992, the infected blood components have been a major cause of disease [3,4]. The range of acute HCV cases has dropped by above 80 percent [5]. Presently, the infection of HCV is firstly attained via transcutaneous blood exposed, usually via injecting drug injections. Previously, the treatment of HCV was used regularly due to its complications and limited use; but since 2011 and eventually increased since 2013, protected, endurable, and therapeutic techniques have dramatically changed the medical and community health structure associated with the prevention, control, and medical care of hepatitis C virus [3]. In spite of hopeful progress, major challenges remain to reduce HCV-related illnesses and deaths. Although, hepatitis C virus remains a vital health concern due to which 60–80 percent of infected people are infected with a long-term infection [6]. Main pathways to transmit drug **use** through injections, blood exchange, haemodialysis (kidney dialysis), organ transplant and abstinence. There are six main genetic variants (1-6) of hepatitis C virus had been recognized, and they have different local distribution. The Genotype species 1, 2 and 3 are still widely spread with genotype 1 considering 40-80% of all cases. Within the Middle East and Egypt genotype 4 is determined. While in South Africa genotype 5 is found and, in South East Asia genotype 6 is discovered.

II. HEPATITIS C

The viral infection which is caused by a virus that is hepatitis C affects the liver and causes inflammation or swelling. It can cause either acute or chronic

hepatitis or both that ranges from mild to serious illness, long term disease includes Scarring of liver and hepatocellular cancer. Diagnosis for the major stage of hepatitis occurred previously after discharge of infection with another familiar hepatitis viruses at that time and was originally named as non-A, non-B (NANB) hepatitis [7]. Therefore, it has now been described and termed as hepatitis C. The infection of hepatitis C infection is diagnosed through a blood transfuse, blood components, haemodialysis, intravenous drug abuse, random cuts and injections for health care workers. Around 90% of post-transfusion is a form of hepatitis C.Upto 5% specialists of donors and around 1-2% of blood donors were carriers for HCV. The incubation period of hepatitis C is 20-90 days. Therapeutically HBV is less serious than acute HCV, Although HCV has highest progression rate in long-term hepatitis than HBV. The significant features of HCV are persistent of infection and chronic hepatitis disease. The different last outcomes of HCV infection are occurrence of liver cirrhosis after 5-10 years and progression to liver cancer. Presently, hepatitis C virus infection is regarded as the most significant cause of chronic hepatic infection globally than hepatitis B virus.

III. HISTORY OF HEPATITIS C VIRUS

The infection of HCV can be an acute or chronic hepatitis. Acute hepatitis generally has no symptoms that hardly give rise to liver failure or fulminant hepatic failure. The acute Symptomatic HCV have mild clinical manifestation with <25% of people having jaundice. Around 60–80% of individual with mild infection develops serious infection [8]. The automatic rate of virus clearance in people with serious infection is extremely low. About one- fifth (20–30%) of individuals with chronic infection develops Scarring of liver over the duration of 10–30 years [9]. There are many factors that can determine the speed of disease. Some of the most common symptoms are HCV diagnosis in the age group (> 40-55 years), male sex, co HIV infection, high body weight, the presence of fatty liver disease and alcohol consumption. People suffering from liver cirrhosis can decompensate problems. Reduced liver cirrhosis prompts hypertension, that leads to ascites, autoimmune bacterial peritonitis, throat varices, neurological problems like portosystemic encephalopathy and comatosenses, and hepatorenal disease that give rise to kidney failure. Chronic infections related to extra-hepatic diseases including cryoglobulinemic disease, acquired hepatic porphyria, arthritis, mesangiocapillary glomerulonephritis (MCGN), Sicca syndrome, Raynaud's disease, immune thrombocytopenia and non-Hodgkin lymphoma [10]. Anually 1-4% people having liver cirrhosis, develops liver cancer. Chronic infection related deaths are often the consequences of problems of liver cancer and decompensated scarring of liver [11]. The Survival chances decrease quickly as the deterioration begins. The patients with compensated liver cirrhosis having 5-year survival rate is as much as 90% compared to 50% for those with advanced liver cirrhosis [12].

IV. VIROLOGY OF HCV

HCV is a linear single-stranded RNA virus, having positive polarity, enclosed in the middle and encircled by an envelope, bearing glycoprotein spikes. It is classified as a different type of genus- hepacivirus belonging to the family flaviviridae[13].HCV is circular in shape, contains hepatotropic RNA virus which causes mild and serious hepatitis in human.[14] It is 30-60nm in diameter.It exhibits significant epigenetic and genomic diversity. There are six main types of genotypes and multiple subtypes had been recognized, which indicates mutation rate is high. These genotypes and subgenotypes are based on genetic differences that encode one of its two envelopes' glycoproteins. This genetic diversity occurs in "hypervariable" region of glycoprotein envelope. As a result of this diversity, there is some autologous or analogous post infection in hepatitis C infection.HCV hasn't been cultivated in culture in spite of that it has been cloned in bacteria-Escherichia coli [15]. The main causative agent of hepatitis C was HCV, which was recognized in 1989[16]. The HCV gene contains about 3000 amino acids of proteins which consists structural and non-structural proteins [17,18]. The HCV of genomic sequencing exhibit 5` terminal end, C region (Capsid-Isohedral) and envelope regions which are enveloped having projections are E1 and E2 in the exon. Hepatitis C virus comprises 9.6-kb RNA genome with a 5′ UTR (untranslated region) which acts as the insertion of inner ribosome, a one ORF (open reading frame)

coding a polyprotein of round about 3000 amino acids and to 3′ untranslated region. This protein(polypeptide) is broken down after translation into host cell proteinase (proteases) to produce three structural proteins called E1, E2, core, p7 and viral proteinase, producing 6 non-structural proteins called as NS2, NS3, NS4a, NS4b, N4a and NS5B[19,20,21].In comparison to direct-stranded RNA viruses, replication takes place in the form of RNA between negative-strand and is processed by NS proteins, forming a polymerase related to cytoplasm membrane complex[22] (Fig 1).

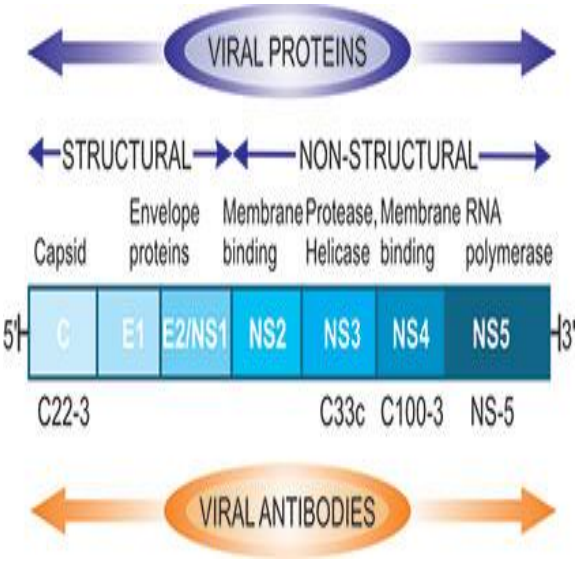

Fig1. Structure of HCV

The outcomes of viral proteins in serology interactions as well as in viral attributes of hepatitis C virus infection are as follows (Fig2):

1. The anti-HCV test of antibodies. The three generations of anti-hepatitis C virus Immunoglobulin G analysis are obtainable:

i) The antibodies of first generation are resistant to C100-3 regional proteins which appears for about 1 to 3 months post infection.

ii) The antibodies of Second generation are resistant to C200 and C33c regional proteins which emerge for about month prior to the first generation.

iii) The antibodies of third generation are resistant to C22-3 and NS-5 regional protein which are acquired too early.

2. HCV-RNA. The disease of hepatitis C virus, although is verified by HCV-RNA using a PCR procedure that can be observed within a couple of days after exposed to hepatitis C virus infection, even prematurely the occurrence of anti-hepatitis C virus and for constant period of hepatitis C virus disease [7] .

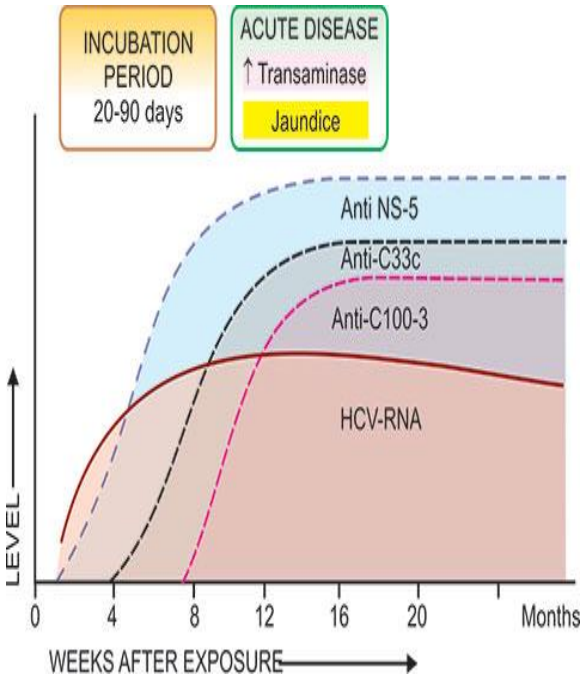

Fig2. Sequence of serology and virology attributes of hepatitis C virus infection

The numerous genotypes (GT) of species that are recognized as 1 2, 3, 4, 5, 6, and 7 indicates the spread of the virus globally [23]. The typical genotypes are GT 1–4. The 7 certified species include 67 subtypes, 20 subspecies and 21 subdivided species. The common infection appears that change with the genotype; others are connected with a greater chance of eliminating the malignant infection i.e. GT3 is probably to be more pronounced in comparison to GT1[24]. Actually, HCV is spread in infected people as a community of different, however strongly associated mutants named as “quasi species”. The time period for HCV is 6–8 weeks.HCV is risky than HBV, since it is called as a silent disease or “killer” because mostly it has no symptoms and undiagnosed at early stage which makes the early treatment of HCV infection complicated. In majority of cases HCV does not determine and henceforth produce various problems that can damage the liver completely. In the course of a natural infection, the immune system is generated that is why it avoids exposure. This infection has no lasting effects; it may vary from mild to severe and can cause fibrosis. The flow chart provided below in Figure 3 depicts the stages of liver

damage from major HCV demonstration to HCC.

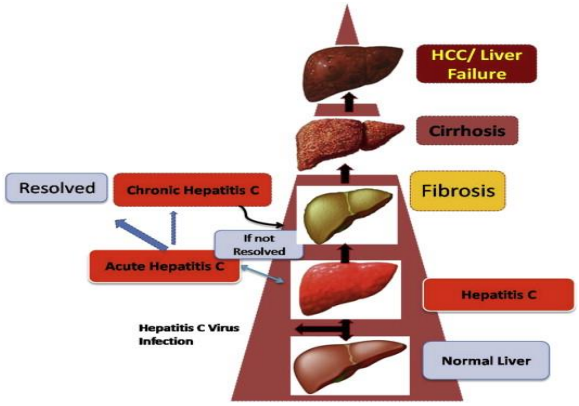

Fig3. Stages of liver damage

This complex type can be determined in about 20% of cases whereas other 80% of cases are transformed into chronic medical manifestation. In the incurable condition it produces three distinct stages namely acute, moderate and chronic. If not treated early, the result of all these is scarring of liver gives rise to liver cancer. The mechanism of infection where the liver is damaged and infected due to a healthy liver led to scarring of liver or liver cancer is shown in Figure 4.

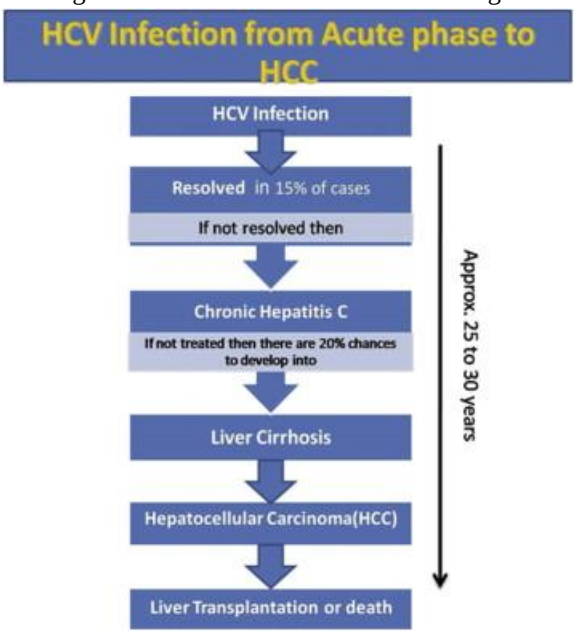

Fig4. HCV infection from acute phase to HCC

Pathogenesis

The infection of hepatitis C virus causes liver damage through a cell-mediated immune process.

1. It can be feasible when host lymphoid tissues are infected with HCV.
2. CD4 + helper T cells activate HCV which in turn stimulates CD8 + T cell through cytokines which are expressed by CD4 + helper T cells.
3. The Regenerated CD8 + T cell, in order to, produce cytokines that fights with viruses against different HCV antigens.
4. Additional help for the T-cell mediated process derive from the monitoring that the cell-mediated immune response is strong enough in people with HCV infection recover better than those with chronic HCV.
5. There is a specific role for some human leukocyte antigen (HLA) alleles and innate immunity in providing a variant response by various hosts for hepatitis C virus disease.
6. Natural killer cells (NK) appear to be effective in preventing hepatitis C virus infection.
7. As part of patients, there is a link between hepatitis C virus of viral antigens and to the anti-liver-kidney microsomal antibody (anti-LKM) that describes the connection of autoimmune chronic active hepatitis and HCV infection.

V. MODE OF TRANSMISSION

Blood transfusion is a major form of hepatitis C virus transmission. The unreliable injection use include: reused or contaminated needles and syringes that is the medical management and the use of recreational drug injection are very significant for the spread of HCV infection globally [25]. The main source for cause of hepatitis C virus disease is intravenous course. The people who are at risk of developing hepatitis C are intravenous injection users (90%), as well as blood transmission, blood components like hemophilia and during surgery while 0.4–3% infection occurs through sexual contact or close contact considerably lower than hepatitis B virus infection. About 3-5% of infections occur from infected mother having HCV to newborns (prenatal via placenta, during delivery in birth canal, post-natal). The spread of contagious infection from mother to child is mostly because of direct transmission and there are no or less chances of breastfeeding therefore the virus becomes inactive in the baby's digestive tract [26,27]. Direct transmission is possible in approximately 6% of babies which are born from infected HCV mothers and transference can be two times as expected to develop in babies born from HCV / HIV-positive mothers or from HCV

uninfected mothers having heavy burden of virus. There is a 5% chance of HCV transmission via stick needle injury. In the breast milk and saliva, hepatitis C virus was detected but not recorded as transmitted by breast milk [28]. Stick needle open wounds in the workplace can be damaged by hepatitis C or by HCV transmission that may occur via another source that may be contagious such as contacting sports or by sharing things and different activities like slamming that may be associated to exposure of blood. Sexually transmitted infections are often ineffective; but rising number of incidences sexually transmitted infections had been notified in between HIV-positive men having sex with men [MSM] [29]. Eventually, the transmission of hepatitis C virus was also reported in the use of non-injected drugs and in the setup of uncontrolled tattoos. By inappropriate contraceptive methods, HCV can transmit from person to person through tattoo dyeing, ink bottle and ear piercing etc. Brushes, blades scissors or frequent visits to hairdressers can be a mode of transmission for spreading HCV infection to a healthy person by distributing the things with people who are infected [30].

VI. SYMPTOMS

The chronic hepatitis C virus of HCV is also called as Long–term infection. It is typically a "silent killer" -mainly subclinical and its infection remains for many years, till the liver damages by the virus is sufficient for cause of signs and symptoms of hepatic infection [31]. All chronic hepatitis C virus infections begin in the short-term (acute) phase. Severe hepatitis C is generally undetected as it hardly causes symptoms. If symptoms and signs are present, it includes jaundice, as well as fatigue, nausea, fever (pyrexia) and muscle ache (myalgia). Serious symptoms may appear 1-3 months after exposed to the virus and lasts for about 2-3 weeks.

The Short –term infection with HCV is called as acute hepatitis C infection. It does not turn into chronic infection every time. Few people detach HCV from their bodies after a critical phase, the result of which is called as spontaneous virus clearance. In a study where people are diagnosed with highly contagious HCV, autoimmune viral load varies from 15% to 25%. It also responds properly to course of antiviral medication.

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Signs and symptoms of HCV:

- Bleeding disorder
- Ecchymosis easily
- Tiredness
- Anorexia
- Yellow color of the skin, mucus membrane and eyes (jaundice)
- Rhabdomyolysis
- Pruritus
- Buildup of fluid in the abdomen (ascites)
- Edema
- Weight loss
- Mental confusion, sleepiness and Dysarthria (hepatic encephalopathy)
- Spider angiomas

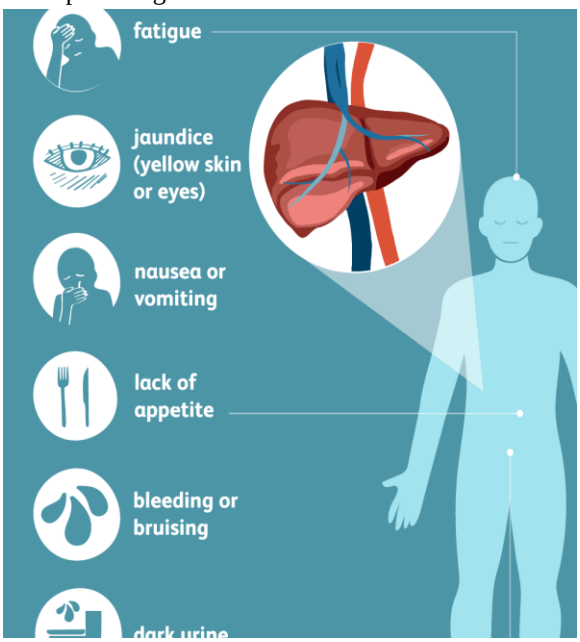

Fig5. Symptoms of HCV

A. Clinical features and diagnostic evaluation

Many patients having chronic hepatitis C virus have no symptoms or contains unspecific symptoms like tiredness or illness. A few of them may have joint pain and muscle pain. Patients having deteriorated liver disease may show peripheral indication of scarring of liver, including slane's disease, Nevus araneus, palmar fibromatosis, man boobs, parotidomegaly, temporary muscle atrophy, ascites, hepatosplenomegaly (enlargement of liver and spleen) or testicular atrophy (shrinking degenerated of testicles). Hepatitis C virus diagnosis is made with the presence of HCV RNA and anti-HCV antibody in the blood. Additional tests including genotype and measuring viral loads of HCV, mostly in the range of 0.2–5 million IU per ml. Science lab tests such as liver panel, pro time test (PT) and hepatitis B and HIV serology test should be carried out. Liver biopsy is mostly helpful for making a proper diagnosis which determines the stages of liver fibrosis and chronicity of swelling [32].

B. Risk Factors

- The risk factor of hepatitis C infection increases if:
- A health worker had been exposed to infected blood, which could take place if the infected needle penetrates the skin.
- Ever you have injected or inhaled illegal drugs
- Being HIV positive
- Getting a piercing or tattoo in a dirty place using unclean materials
- Prior to 1992, received a blood transmission or organ transplantation
- Prior to 1987, concentrated clotting factor is accepted
- Have received long-term hemodialysis treatment
- They were born from a woman with hepatitis C disease
- Born between 1945 and 1965, with the highest rates of hepatitis C infection among age groups.

VII. COMPLICATIONS

Hepatitis C infection persists for many years and can cause serious problems, are as under:

- Liver damage (Liver cirrhosis) - After years of HCV infection, liver cirrhosis can develop. Cirrhosis is the last stage of hepatic disease. In this disease, liver tissue have scars which gradually replaces healthy hepatic cells and this scarring remains permanently.The scars on the liver makes it harder for liver to function properly .
- Hepatic cancer - One of the most common kinds of liver cancer that is Hepatocellular carcinoma (HCC) or Hepatoma. Some people infected with hepatitis C infection can develop hepatic cancer.
- Fulminant hepatic failure – It is also called as liver failure. Improved liver cirrhosis can cause liver to stop working.

A. Treatment

Therapeutic invention for hepatitis C virus is based on the appearance of the disease (acute vs chronic), genotyping, lab test values, the presence of a combined infection (HIV, hepatitis B) and the associated disease. The primary goal of HCV treatment is to obtain a continuous virologic (SVR) response, which is described as the absence of HCV RNA for about 6 months in serum after stoppage of medication. The 48-week treatment costs range from $ 30,000 to $ 40,000 excluding physical checkup throughout continous treatment [33]. Therefore, each and every patient should be carefully monitored for treatment indications, associated diseases, treatment adherence and sincerely follow-up. Treatment for hepatitis C complications will concentrate on directing the underlying cause. Here in this case, it means that body gets rid of HCV infection. The treatments are available for long term hepatitis C infection. The doctor prescribes some of the medicines. According to the National Institutes of Health (NIH), these drugs can treat chronic hepatitis C from 80 -95% Reliable Source of individuals with this infection. In severe cases of liver damages fulminant hepatic failure, or liver cancer, doctor will recommend a liver transplantation. During a liver transplantation, doctor will remove the liver and insert a healthy one from a healthy donor. Liver cancer can also be cured by using some methods that are designed to destroy cancer cells. Some of the examples are radiotherapy and chemotherapy.

B. Chronic hepatitis C

In adults, HCV infection causes in 40-60% of chroncity cases. It is specifically related to increasing form of chronic hepatitis that may develop into liver cirrhosis. In adults,

the treatment for chronic hepatitis C virus is advised for those have high levels of HCV RNA, high levels of transaminase, liver biopsy detection that indicate progressive liver disease and the absence of the serious conditions associated with illness or conflict as noted[34].Although, alanine aminotransferase (ALT) levels, are not always related to the severity of the disease and therefore, those with normal ALT levels, treatment should not be denied there.Treatment of hepatitis C has enhanced significantly over the years. The current advance treatment for chronic HCV is a combination of PEG-IFN (pegylated interferon) alfa-2b and tribavirin.In 1986, Interferon alfa was the first shown which is beneficial for chronic hepatitis C infection.About 5-15% of patients have acquired SVR after a study of 6 to 12-month of IFN-α. Total response rates were significantly increased with the addition of oral nucleoside analog tribavirin. IFN-α, by activating various antibodies, is active against several RNA viruses, which includes HCV. The process of action of tribavirin is not well defined. Although, it has no direct antiviral properties but appears to increase the antiviral effect of IFN-alfa in the treatment of hepatitis C virus, possibly through a combination of methods [35].

C. Acute hepatitis C

Accute HCV causes milder necrosis, with steatosis in hepatic cells, indicates presence of lymphoid which aggregates in the form of portal tract and degeneration in the epithelium of bile duct.Proper treatment for acute hepatitis C has not been developed yet. The Genotype and levels of HCV RNA doesn't appear to play a role in finding the outcomes of treatment outcomes [36]. Upto 50% of HCV infected persons spontaneously has viral clearance [37]. Therefore, treatment delays have been suggested for about 8–12 weeks after the beginning of acute hepatitis C. A recent study showed> 90% of SVR levels in people with severe HCV when pegylated interferon treatment was started in 12 weeks after the beginning of the disease. Both IFN and pegylated interferon With or without tribavirin both IFN and PEG-IFN has been used in a variety of researches with positive results. Research with IFN-alfa have been reported high SVR levels as 95%, treated for about 24 weeks. Likewise, study of PEG-IFN with or without combination of tribavirin have been reported 80-89% SVR levels,patients are treated for 24 weeks of treatment

D. Vaccine

Presently, the vaccine for hepatitis C infection is not available even though the HCV envelope antibody had been developed.No vaccine is available due to epigenetic variability of glycoprotein[13].

E. Prevention

Many hepatitis C problems originate from the liver, therefore keeping the liver healthy is very significant if you are suffering from hepatitis C infection [38]. There are a lot of things or ways that can prevent complications, which are as follows:

- Take HCV treatment.
- Avoid taking alcohol, even as it can cause liver cirrhosis.
- Be vaccinated for different types of viral hepatitis, like hepatitis A and hepatitis B.
- Take nutritious food, however consider reducing intake of salt, so that can put pressure on liver and worsen inflammation.
- Visit to the doctor before taking a new medicine or supplements, involving those which are readily available, as some depress the liver.
- Changing lifestyles and adopting healthy one including physical exercise, leaving smoking and maintain a healthy weight.

Fig6. Prevention of HCV

VIII. CONCLUSION

The heavy load of HCV and the important health effects related to chronic hepatitis C infection that makes HCV a very important public health concern. Advancement in the treatment of HCV had created new possibilities to reduce HCV-related illnesses and deaths. These therapies are secure or safe, approved, and extremely effectual; therefore, the advantages cannot be acquired without a remarkable rise in the number of individuals being tested for HCV so that all infected people can monitor their diagnosis and be connected to proper clinical care. Prevention and outrun attempt to concentrate on baby boom and Person Who Inject Drug (PWIDs) in certain will be important in reducing the spread, reducing the incidence, and attaining HCV eradication. Treatment for hepatitis C infection have been advanced significantly in levels of response over all genotypes. Although, further progression is needed to improve SVR levels in genotype 1 patients and recurrent and non-responsive recipients. Till the new agents mentioned above are strictly tested in medical trials, the recent combined treatment of PEG-IFN and ribavirin or tribavirin remains centrepiece for the treatment of hepatitis C infection for the upcoming 3-5 years.

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