AIM OF THE WORK

To determine the patients that had achieved a S. V. R, and the common side effects encountered during the course of treatment and cases that had stopped treatment and why.

REVIEW OF LITERATURE

Hepatitis C virus

Hepatitis C virus (**HCV**) is a small (55–65 nm in size), enveloped, positive-sense single-stranded RNA virus of the family *Flaviviridae*. Hepatitis C virus is the cause of hepatitis C in humans ***(Kapoor et al., 2011; Burbelo et al., 2012; Quan et al., 2013 and Kapoor et al., 2013)*****.**

Structure

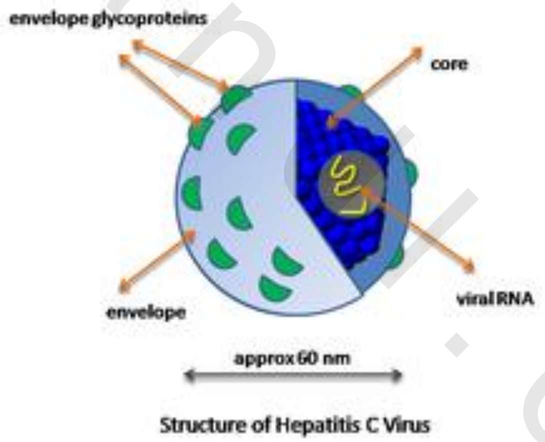

Fig 1: Simplified diagram of the structure of the Hepatitis C virus particle

The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope ***(Op De Beeck and Dubuisson, 2003)*.**

Genome

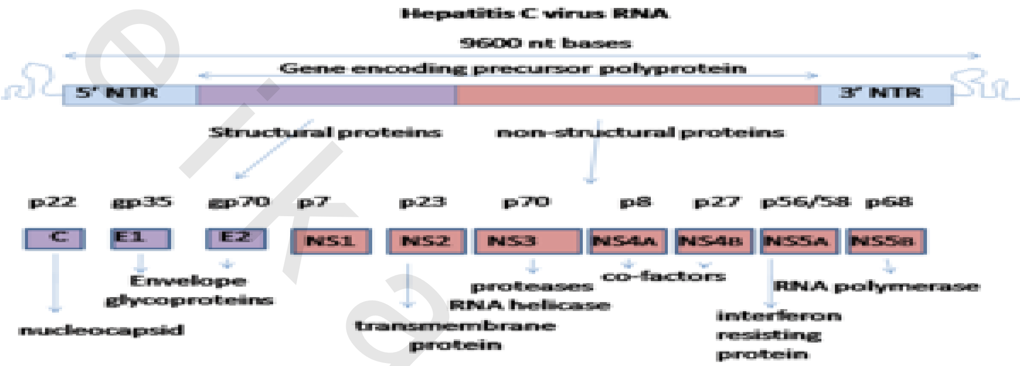

Fig 2: Genome organisation of Hepatitis C virus

Hepatitis C virus has a positive sense single-stranded RNA genome. The genome consists of a single open reading frame that is 9600 nucleotide bases long ***(Kato, 2000)*.** This single open reading frame is translated to produce a single protein product, which is then further processed to produce smaller active proteins.

At the 5' and 3' ends of the RNA are the UTR, that are not translated into proteins but are important to translation and replication of the viral RNA. The 5' UTR has a ribosome binding site ***(Jubin, 2001)*.** (IRES — Internal ribosome entry site) that starts the translation of a very long protein containing about 3,000 amino acids. The core domain of the hepatitis C virus (HCV) IRES contains a four-way helical junction that is integrated within a predicted pseudoknot ***(Berry et al., 2011)***. The conformation of this core domain constrains the open reading frame's orientation for positioning on the 40S ribosomal subunit. The large pre-protein is later cut by cellular and viral proteases into the 10 smaller proteins that allow viral replication within the host cell, or assemble into the mature viral particles ***(Dubuisson, 2007)***.

Structural proteins made by the hepatitis C virus include Core protein, E1 and E2; nonstructural proteins include NS2, NS3, NS4A, NS4B, NS5A, and NS5B.

Molecular biology

The proteins of this virus are arranged along the genome in the following order: N terminal-core-envelope (E1)–E2–p7-nonstructural protein 2 (NS2)–NS3–NS4A–NS4B–NS5A–NS5B–C terminal. The mature nonstructural proteins (NS2 to NS5B) generation relies on the activity of viral proteinases ***(De Francesco, 1999)***. The NS2/NS3 junction is cleaved by a metal dependent autocatalytic proteinase encoded within NS2 and the N-terminus of NS3. The remaining cleavages downstream from this site are catalysed by a serine proteinase also contained within the N-terminal region of NS3.

The core protein has 191 amino acids and can be divided into three domains on the basis of hydrophobicity: domain 1 (residues 1–117) contains mainly basic residues with two short hydrophobic regions; domain 2 (resides 118–174) is less basic and more hydrophobic and its C-terminus is at the end of p21; domain 3 (residues 175–191) is highly hydrophobic and acts as a signal sequence for E1 envelope protein.

Both envelope proteins (E1 and E2) are highly glycosylated and important in cell entry. E1 serves as the fusogenic subunit and E2 acts as the receptor binding protein. E1 has 4–5 N-linked glycans and E2 has 11 N-glycosylation sites.

The p7 protein is dispensable for viral genome replication but plays a critical role in virus morphogenesis. This protein is a 63 amino acid membrane spanning protein which locates itself in the endoplasmic reticulum. Cleavage of p7 is mediated by the endoplasmic reticulum's signal peptidases. Two transmembrane domains of p7 are connected by a cytoplasmic loop and are oriented towards the endoplasmic reticulum's lumen. NS2 protein is a transmembrane protein with protease activity.

NS3 is a protein whose N-terminal has serine protease activity and whose C-terminal has NTPase/helicase activity. It is located within the endoplasmic reticulum and forms a heterodimeric complex with NS4A—a 54 amino acid membrane protein that acts as a cofactor of the proteinase.

NS4B is a small hydrophobic integral membrane protein with 4 transmembrane domains. It is located within the endoplasmic reticulum and plays an important role for recruitment of other viral proteins. It induces morphological changes to the endoplasmic reticulum forming a structure termed the membranous web.

NS5A is a hydrophilic phosphoprotein which plays an important role in viral replication, modulation of cell signaling pathways and the interferon response. It is known to bind to endoplasmic reticulum anchored human VAP proteins ***(Gupta et al., 2012)*****.**

The NS5B protein is the viral RNA dependent RNA polymerase. NS5B has the key function of replicating the HCV's viral RNA by using the viral positive RNA strand as its template and catalyzes the polymerization of ribonucleoside triphosphates (rNTP) during RNA replication ***(Moradpour et al., 2007 and Rigat et al., 2010).*** Several crystal structures of NS5B polymerase in several crystalline forms have been determined based on the same consensus sequence BK (HCV-BK, genotype 1) ***(Biswal et al., 2005).*** The structure can be represented by a right hand shape with fingers, palm, and thumb. The encircled active site, unique to NS5B, is contained within the palm structure of the protein. Recent studies on NS5B protein genotype 1b strain J4's (HC-J4) structure indicate a presence of an active site where possible control of nucleotide binding occurs and initiation of de-novo RNA synthesis. De-novo adds necessary primers for initiation of RNA replication (***O'Farrell et al., 2003).*** Current research attempts to bind structures to this active site to alter its functionality in order to prevent further viral RNA replication ***(Biswal et al., 2006).***

An 11th has also been described ***(Walewski et al., 2001 and Baghbani-arani et al., 2012).*** This protein is encoded by a +1 frameshift in the capsid gene. It appears to be antigenic but its function is unknown.

Replication

Replication of HCV involves several steps. The virus replicates mainly in the hepatocytes of the liver, where it is estimated that daily each infected cell produces approximately fifty virions (virus particles) with a calculated total of one trillion virions generated. The virus may also replicate in peripheral blood mononuclear cells, potentially accounting for the high levels of immunological disorders found in chronically infected HCV patients. HCV has a wide variety of genotypes and mutates rapidly due to a high error rate on the part of the virus' RNA-dependent RNA polymerase. The mutation rate produces so many variants of the virus it is considered a quasispecies rather than a conventional virus species ***(Bartenschlager and Lohmann, 2000).*** Entry into host cells occur through complex interactions between virions and cell-surface molecules CD81, LDL receptor, SR-BI, DC-SIGN, Claudin-1, and Occludin ***(Zeisel et al., 2009 and Kohaar et al., 2010).***

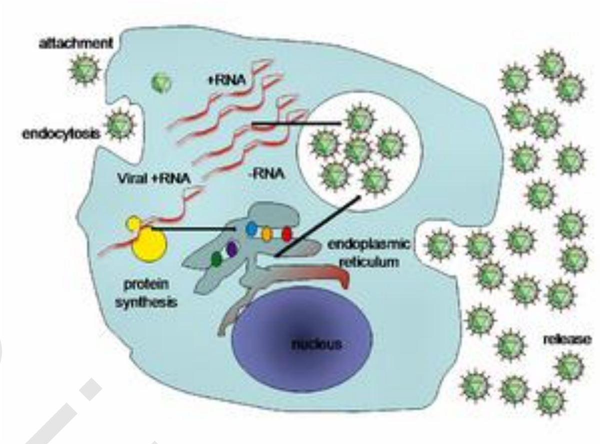

Fig 3: A simplified diagram of the HCV replication cycle

Once inside the hepatocyte, HCV takes over portions of the intracellular machinery to replicate ***(Lindenbach and Rice, 2005).*** The HCV genome is translated to produce a single protein of around 3011 amino acids. The polyprotein is then proteolytically processed by viral and cellular proteases to produce three structural (virion-associated) and seven nonstructural (NS) proteins. Alternatively, a frameshift may occur in the Core region to produce an Alternate Reading Frame Protein (ARFP) ***(Branch et al., 2005).*** HCV encodes two proteases, the NS2 cysteine autoprotease and the NS3-4A serine protease. The NS proteins then recruit the viral genome into an RNA replication complex, which is associated with rearranged cytoplasmic membranes. RNA replication takes places via the viral RNA-dependent RNA polymerase NS5B, which produces a negative strand RNA intermediate. The negative strand RNA then serves as a template for the production of new positive strand viral genomes. Nascent genomes can then be translated, further replicated or packaged within new virus particles. New virus particles are thought to bud into the secretory pathway and are released at the cell surface.

The virus replicates on intracellular lipid membranes (***Dubuisson et al., 2002).*** The endoplasmic reticulum in particular are deformed into uniquely shaped membrane structures termed 'membranous webs'. These structures can be induced by sole expression of the viral protein NS4B ***(Egger et al., 2002).*** The core protein associates with lipid droplets and utilises microtubules and dyneins to alter their location to a perinuclear distribution ***(Boulant et al., 2008).***

Release from the hepatocyte may involve the very low density lipoprotein secretory pathway ***(Syed et al., 2010).***

Genotypes

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into seven genotypes (1–7) with several subtypes within each genotype (represented by lower-cased letters) ***(Simmonds et al., 1993 and Nakano et al., 2011).*** Subtypes are further broken down into quasispecies based on their genetic diversity. Genotypes differ by 30–35% of the nucleotide sites over the complete genome ***(Ohno et al., 2007).*** The difference in genomic composition of subtypes of a genotype is usually 20–25%. Subtypes 1a and 1b are found worldwide and cause 60% of all cases.

Clinical importance

Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6) ***(Simmonds et al., 2005)***. Duration of standard interferon-based therapy for genotypes 1 and 4 is 48 weeks, whereas treatment for genotypes 2 and 3 is completed in 24 weeks. Sustained virological responses occur in 70% of genotype 1 cases, ~90% of genotypes 2 and 3, ~65% of genotype 4 and ~80% of genotype 6 ***(Yu and Chuang, 2009).***

Infection with one genotype does not confer immunity against others, and concurrent infection with two strains is possible. In most of these cases, one of the strains removes the other from the host in a short time. This finding opens the door to replace strains non-responsive to medication with others easier to treat ***(Laskus et al., 2001)*.**

Vaccination

Unlike hepatitis A and B, there is currently no vaccine to prevent hepatitis C infection ***(Yu and Chiang, 2010).***

Hepatitis C Disease

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV) ***(Ryan and Ray, 2004)*.** The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer, or life-threatening esophageal and gastric varices ***(Ryan and Ray, 2004).***

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment, and transfusions. An estimated 150–200 million people worldwide are infected with hepatitis C ***(Gravitz, 2011; World Health Organization (WHO), 2011 and (Mohd Hanafiah et al., 2013).*** The existence of hepatitis C (originally identifiable only as a type of non-A non-B hepatitis) was suggested in the 1970s and proven in 1989 ***(Houghton, 2009).*** Hepatitis C infects only humans and chimpanzees ***(Shors, 2011).***

The virus persists in the liver in about 85% of those infected. This chronic infection can be treated with medication: the standard therapy is a combination of peginterferon and ribavirin, with either boceprevir or telaprevir added in some cases. Overall, 50–80% of people treated are cured. Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading reason for liver transplantation, though the virus usually recurs after transplantation (***Rosen, 2011).*** No vaccine against hepatitis C is available.

Egypt has the highest HCV antibody prevalence in the world ***(Alter, 2007).*** The start of the epidemic is attributed to insufficiently sterilised intravenous injections during the mass anti-schistosomiasis treatment campaigns in rural areas during the 1970s ***(Frank et al., 2000)***. Spread of HCV has therefore been studied mainly in rural areas. An early survey documented HCV clustering among households of individuals with history of parenteral treatment for schistosomiasis (***Rao et al., 2002)***. More recently, in cohort studies of rural areas of Egypt, having an anti-HCV-positive family member was the strongest predictor for incident HCV infection, after adjustment for iatrogenic and community exposures ***(Mohamed et al., 2005)***. Also, a mathematical model estimated that within HCV-infected couples, 6% would have acquired their infection from their partners ***(Magder et al., 2005)*****.**

Hepatitis C virus genotype 4 (HCV-4) is the most common variant of the hepatitis C virus in the Middle East and Africa, particularly Egypt. which is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation in the country.

Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has simply not been the subject of widespread research; therefore, the features of this genotype and management strategies for patients infected with this genotype are not as well developed as for genotypes 1, 2, and 3 ***(Nguyen and Keeffe, 2005; Egyptian Ministry of Health, 2007 and Abdel-Aziz F et al., 2000)***.

Signs and symptoms

Acute infection

Hepatitis C infection causes acute symptoms in 15% of cases ***(Maheshwari et al., 2008).*** Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss ***(Wilkins et al., 2010).*** and rarely does acute liver failure result ***(Bailey, 2010)***. Most cases of acute infection are not associated with jaundice ***(Davis GL, 2011).*** The infection resolves spontaneously in 10–50% of cases, which occurs more frequently in individuals who are young and female ***(Davis GL, 2011)***

Chronic infection

About 80% of those exposed to the virus develop a chronic infection ***(Nelson et al., 2011).*** This is defined as the presence of detectable viral replication for at least six months. Most experience minimal or no symptoms during the initial few decades of the infection ***(Davis GL, 2011).*** Chronic hepatitis C can be associated with fatigue ***(Ray and Thomas, 2009)*** and mild cognitive problems ***(Forton et al., 2005).*** Chronic infection after several years may cause cirrhosis or liver cancer (***Rosen, 2011).*** The liver enzymes are normal in 7–53% ***(Nicot,***

2004). Late relapses after apparent cure have been reported, but these can be difficult to distinguish from reinfection ***(Nicot, 2004).***

Fatty changes to the liver occur in about half of those infected and are usually present before cirrhosis develops ***(El-Zayadi, 2008 and Paradis and Bedossa, 2008).*** Usually (80% of the time) this change affects less than a third of the liver ***(Jamall et al., 2008).*** Worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma ***(Alter, 2007).*** About 10–30% of those infected develop cirrhosis over 30 years (***Rosen, 2011 and Wilkins et al., 2010)***. Cirrhosis is more common in those also infected with hepatitis B, schistosoma, or HIV, in alcoholics and in those of male gender (***Wilkins et al., 2010).*** In those with hepatitis C, excess alcohol increases the risk of developing cirrhosis 100-fold ***(Mueller et al., 2009).*** Those who develop cirrhosis have a 20-fold greater risk of hepatocellular carcinoma. This transformation occurs at a rate of 1–3% per year (***Rosen, 2011 and Wilkins et al., 2010)*** Being infected with hepatits B in additional to hepatitis C increases this risk further ***(Fattovich et al., 2004).***

Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and hepatic encephalopathy ***(Ozaras and Tahan, 2009)*****.** Ascites occurs at some stage in more than half of those who have a chronic infection ***(Zaltron et al., 2012)*****.**

Extrahepatic complications

The most common problem due to hepatitis C but not involving the liver is mixed cryoglobulinemia (usually the type II form) — an inflammation of small and medium-sized blood vessels (***Dammacco and Sansonno, 2013 and Iannuzzella et al., 2010)*****.** Hepatitis C is also associated with Sjögren's syndrome (an autoimmune disorder); thrombocytopenia; lichen planus; porphyria cutanea tarda; necrolytic acral erythema; insulin resistance; diabetes mellitus; diabetic nephropathy; autoimmune thyroiditis and B-cell lymphoproliferative disorders ***(Zignego et al., 2007 and Ko et al., 2012)*****.** Thrombocytopenia is estimated to occur in 0.16% to 45.4% of people with chronic hepatitis C ***(Louie et al., 2011)*****.** 20–30% of people infected have rheumatoid factor — a type of antibody ***(Dammacco et al., 2000)*****.** Possible associations include Hyde's prurigo nodularis ***(Lee and Shumack, 2005)*****.** and membranoproliferative glomerulonephritis ***(Raya and Thomas, 2009).*** Cardiomyopathy with associated arrhythmias has also been reported ***(Matsumori, 2006).*** A variety of central nervous system disorders have been reported ***(Monaco et al., 2012).***

Occult infection

Persons who have been infected with hepatitis C may appear to clear the virus but remain infected ***(Sugden et al., 2012).*** The virus is not detectable with conventional testing but can be found with ultra-sensitive tests ***(Carreño, 2006).*** The original method of detection was by demonstrating the viral genome within liver biopsies, but newer methods include an antibody test for the virus' core protein and the detection of the viral genome after first concentrating the viral particles by ultracentrifugation ***(Carreño García et al., 2011).*** A form of infection with persistently moderately elevated serum liver enzymes but without antibodies to hepatitis C has also been reported ***(Pham et al., 2010).*** This form is known as cryptogenic occult infection.

Several clinical pictures have been associated with this type of infection ***(Carreño et al., 2012).*** It may be found in people with anti-hepatitis-C antibodies but with normal serum levels of liver enzymes; in antibody-negative people with ongoing elevated liver enzymes of unknown cause; in healthy populations without evidence of liver disease; and in groups at risk for HCV infection including those on haemodialysis or family members of people with occult HCV. The clinical relevance of this form of infection is under investigation ***(Carreño et al., 2008).*** The consequences of occult infection appear to be less severe than with chronic infection but can vary from minimal to hepatocellular carcinoma ***(Carreño García et al., 2011).***

The rate of occult infection in those apparently cured is controversial but appears to be low ***(Nicot, 2004).*** 40% of those with hepatitis but with both negative hepatitis C serology and the absence of detectable viral genome in the serum have hepatitis C virus in the liver on biopsy ***(Scott and Gretch, 2007).*** How commonly this occurs in children is unknown ***(Robinson, 2008).***

Transmission

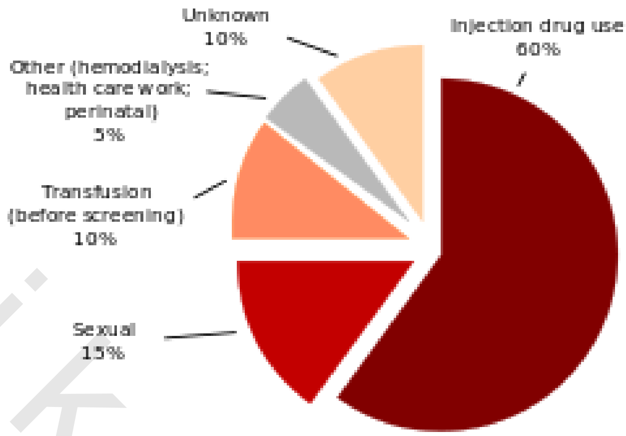

Fig 4: Hepatitis C infection in the United States by source

The primary route of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe medical procedures ***(Maheshwari and Thuluvath, 2010)*.** The cause of transmission remains unknown in 20% of cases;***(Pondé, 2011)*.** however, many of these are believed to be accounted for by IDU ***(Davis GL, 2011)*.**

Intravenous drug use

Intravenous drug use is a major risk factor for hepatitis C in many parts of the world ***(Xia et al., 2008)*.** Of 77 countries reviewed, 25 (including the United States) were found to have prevalences of hepatitis C in the intravenous drug user population of between 60% and 80% ***(Nelson et al., 2011 and (Xia et al., 2008).*** Occurrence of hepatitis C among prison inmates in the United States is 10 to 20 times that of the occurrence observed in the general population; this has been attributed to high-risk behavior in prisons such as IDU and tattooing with nonsterile equipment ***(Imperial, 2010 and Vescio et al., 2008).***

Healthcare exposure

Blood transfusion, transfusion of blood products, or organ transplants without HCV screening carry significant risks of infection ***(Wilkins et al., 2010).*** The United States instituted universal screening in 1992 ***(Marx, 2010)*** and Canada instituted universal screening in 1990 ***(Day et al., 2009).*** This decreased the risk from one in 200 units ***(Marx, 2010)*** to between one in 10,000 to one in 10,000,000 per unit of blood (***Davis GL, 2011 and Pondé, 2011).***

Those who have experienced a needle stick injury from someone who was HCV positive have about a 1.8% chance of subsequently contracting the disease themselves ***(Wilkins et al., 2010).*** The risk is greater if the needle in question is hollow and the puncture wound is deep (***Alter, 2007).*** There is a risk from mucosal exposures to blood; but this risk is low, and there is no risk if blood exposure occurs on intact skin (***Alter, 2007*)**.

Hospital equipment has also been documented as a method of transmission of hepatitis C, including reuse of needles and syringes; multiple-use medication vials; infusion bags; and improperly sterilized surgical equipment, among others (***Alter, 2007*)**. Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world ***(Al Bawaaba News. (2010)*.**

Sexual intercourse

Sexual practices that involve higher levels of trauma to the anogenital mucosa, such as anal penetrative sex, or that occur when there is a concurrent sexually transmitted infection, including HIV or genital ulceration, do present a risk ***(Tohme and Holmberg, 2010)*.** The United States Department of Veterans Affairs recommends condom use to prevent hepatitis C transmission in those with multiple partners, but not those in monogamous relationships ***(US. Department of Veterans Affairs. (2006)*.**

Body modification

Tattooing is associated with two to threefold increased risk of hepatitis C. This can be due to either improperly sterilized equipment or contamination of the dyes being used. The risk also appears to be greater for larger tattoos ***(Jafari et al., 2010)*****.** It is rare for tattoos in a licensed facility to be directly associated with HCV infection ***(Centers for Disease Control and Prevention (CDC), 2012)*****.**

Shared personal items

Personal-care items such as razors, toothbrushes, and manicuring or pedicuring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV ***(Lock et al., 2006 and Centers for Disease Control and Prevention (CDC), 2012)***. Appropriate caution should be taken regarding any medical condition that results in bleeding, such as cuts and sores ***(Centers for Disease Control and Prevention (CDC), 2012).*** HCV is not spread through casual contact, such as hugging, kissing, or sharing eating or cooking utensils ***(Centers for Disease Control and Prevention (CDC), 2012).*** Neither is it transmitted through food or water ***(Wong and Lee, 2006)*****.**

Vertical transmission

Vertical transmission of hepatitis C from an infected mother to her child occurs in less than 10% of pregnancies ***(Lam et al., 2010).*** There are no measures that alter this risk ***(Lam et al., 2010).*** It is not clear when during pregnancy transmission occurs, but it may occur both during gestation and at delivery (***Pondé, 2011).*** There is no evidence that breast-feeding spreads HCV; however, to be cautious, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding ***(Mast, 2004)*** or her viral loads are high (***Pondé, 2011)*.**

Diagnosis

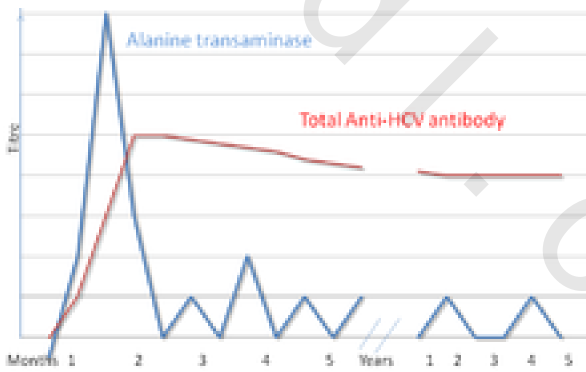

Fig 5: Serologic profile of Hepatitis C infection

There are a number of diagnostic tests for hepatitis C, including HCV antibody enzyme immunoassay or ELISA, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR) ***(Wilkins et al., 2010).*** HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected ***(Ozaras and Tahan, 2009).***

Chronic hepatitis C is defined as infection with the hepatitis C virus persisting for more than six months based on the presence of its RNA ***(Davis GL, 2011)*** Chronic infections are typically asymptomatic during the first few decades ***(Davis GL, 2011),*** and thus are most commonly discovered following the investigation of elevated liver enzyme levels or during a routine screening of high-risk individuals. Testing is not able to distinguish between acute and chronic infections (***Alter, 2007*)**. Diagnosis in the infant is difficult as maternal antibodies may persist for up to 18 months 9 **(*Robinson, 2008*).**

Serology

Hepatitis C testing typically begins with blood testing to detect the presence of antibodies to the HCV, using an enzyme immunoassay ***(Wilkins et al., 2010)*** If this test is positive, a confirmatory test is then performed to verify the immunoassay and to determine the viral load ***(Wilkins et al., 2010).*** A recombinant immunoblot assay is used to verify the immunoassay and the viral load is determined by a HCV RNA polymerase chain reaction ***(Wilkins et al., 2010).*** If there are no RNA and the immunoblot is positive, it means that the person tested had a previous infection but cleared it either with treatment or spontaneously; if the immunoblot is negative, it means that the immunoassay was wrong ***(Wilkins et al., 2010).*** It takes about 6–8 weeks following infection before the immunoassay will test positive ***(Raya and Thomas, 2009).*** A number of tests are available as point of care testing which means that results are available within 30 minutes ***(Shivkumar et al., 2012)*****.**

Liver enzymes are variable during the initial part of the infection ***(Davis GL, 2011)*** and on average begin to rise at seven weeks after infection. The elevation of liver enzymes does not closely follow disease severity ***(Raya and Thomas, 2009).***

Biopsy

Liver biopsies are used to determine the degree of liver damage present; however, there are risks from the procedure. The typical changes seen are lymphocytes within the parenchyma, lymphoid follicles in portal triad, and changes to the bile ducts. There are a number of blood tests available that try to determine the degree of hepatic fibrosis and alleviate the need for biopsy ***(Abdel-Aziz et al., 2000).***

Screening

It is believed that only 5–50% of those infected in the United States and Canada are aware of their status ***(Jafari al., 2010).*** Testing is recommended in those at high risk, which includes injection drug users, those who have received blood transfusions before 1992 ***(Moyer et al., 2013)***, those who have been in jail, those on long term hemodialysis ***(Moyer and U.S. Preventive Services Task, Force, 2013)*** and those with tattoos ***(Jafari al., 2010).*** Screening is also recommended in those with elevated liver enzymes, as this is frequently the only sign of chronic hepatitis ***(Senadhi, 2011).*** Routine screening is not currently recommended in the United States ***(Wilkins et al., 2010).*** In 2012, the U.S. Centers for Disease Control and Prevention (CDC) added a recommendation for a single screening test for those born between 1945 and 1965***(Smith et al., 2012).***

Prevention

No vaccine protects against contracting hepatitis C ***(Halliday et al., 2011).*** A combination of harm reduction strategies, such as the provision of new needles and syringes and treatment of substance use, decrease the risk of hepatitis C in intravenous drug users by about 75% ***(Hagan et al., 2011).*** The screening of blood donors is important at a national level, as is adhering to universal precautions within healthcare facilities ***(Raya and Thomas, 2009).***

Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40–80% of these clear with pegylated interferon/ribavirin treatment ***(Torresi et al., 2011 and Ilyas and Vierling, 2011).*** In rare cases, infection can clear without treatment ***(Davis GL, 2011).*** Those with chronic hepatitis C are advised to avoid alcohol and medications toxic to the liver, and to be vaccinated for hepatitis A and hepatitis B. Ultrasound surveillance for hepatocellular carcinoma is recommended in those with accompanying cirrhosis ***(Wilkins et al., 2010).***

Medications

In general, treatment is recommended for those with proven HCV infection and signs of liver inflammation. As of 2010, treatments consist of a combination of pegylated interferon alpha and the antiviral drug ribavirin for a period of

24 or 48 weeks, depending on HCV genotype ***(Matsumori, 2006)***. This produces cure rates of between 70 and 80% for genotype 2 and 3, respectively, and 45 to 70% for other genotypes ***(Liang and Ghany, 2013)***.

Combining either boceprevir or telaprevir with ribavirin and peginterferon alfa improves antiviral response for hepatitis C genotype 1 ***(Foote et al., 2011; Smith et al., 2011 and Ghany et al., 2011)***. Adverse effects with treatment are common, with half of people getting flu like symptoms and a third experiencing emotional problems ***(Wilkins et al., 2010).*** Treatment during the first six months is more effective than once hepatitis C has become chronic ***(Ozaras and Tahan, 2009).*** If someone develops a new infection and it has not cleared after eight to twelve weeks, 24 weeks of pegylated interferon is recommended ***(Ozaras and Tahan, 2009).***

Sofosbuvir with ribavirin and interferon appears to be around 90% effective in those with genotype 1, 4, 5, or 6 disease ***(De Clercq, 2013)***. Sofosbuvir with just ribavirin appears to be 70 to 95% effective in type 2 and 3 disease ***(Liang and Ghany, 2013 and De Clercq, 2013).*** This benefit is somewhat offset by a greater rate of adverse effects ***(Liang and Ghany, 2013).*** Treatments that contain ledipasvir and sofosbuvir for genotype 1 has success rates of around 93 to 99% but is very expensive ***(Hoofnagle and Sherker, 2014).*** In genotype 6 infection, pegylated interferon and ribavirin is effective in 60 to 90% of cases ***(Bunchorntavakul et al., 2013).*** There is some tentative data for simeprevir use in type 6 disease as well ***(Bunchorntavakul et al., 2013).***

Prognosis

The responses to treatment is measured by sustained viral response and vary by HCV C genotype. A sustained response occurs in about 40–50% in people with HCV genotype 1 given 48 weeks of treatment ***(Rosen, 2011).*** A sustained response is seen in 70–80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment ***(Rosen, 2011).*** A sustained response occurs about 65% in those with genotype 4 after 48 weeks of treatment. The evidence for treatment in genotype 6 disease is sparse and what evidence there is supports 48 weeks of treatment at the same doses used for genotype 1 disease ***(Fung et al., 2008).*** Successful treatment decreases the future risk of hepatocellular carcinoma by 75% ***(Morgan et al., 2013).***

Epidemiology

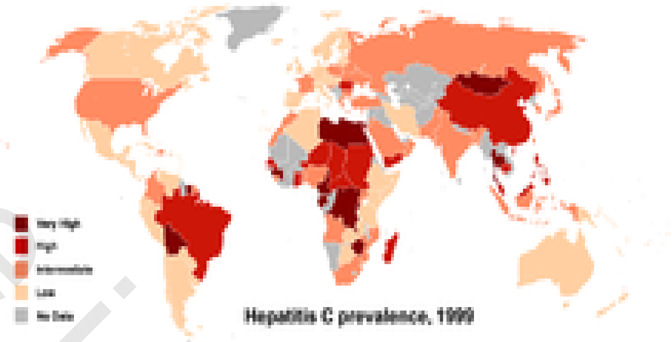

Fig 6: Prevalence of hepatitis C worldwide in 1999

It is estimated that 150–200 million people, or ~3% of the world's population, are living with chronic hepatitis C ***(Gravitz, 2011; World Health Organization (WHO), 2011 and Mohd Hanafiah et al., 2013).*** About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases ***(World Health Organization (WHO), 2011).*** During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection ***(Lozano, 2012).*** Rates have increased substantially in the 20th century due to a combination of intravenous drug abuse and reused but poorly sterilized medical equipment (***Alter, 2007).***

Rates are high (>3.5% population infected) in Central and East Asia, North Africa and the Middle East, they are intermediate (1.5%-3.5%) in South and Southeast Asia, sub-Saharan Africa, Andean, Central and Southern Latin America, Caribbean, Oceania, Australasia and Central, Eastern and Western Europe; and they are low (<1.5%) in Asia Pacific, Tropical Latin America and North America ***(Mohd Hanafiah et al., 2013).***

Among those chronically infected, the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10–15% for men and ~1–5% for women. The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1–4% per year ***(Yu and Chuang, 2009).*** Rates of new infections have decreased in the Western world since the 1990s due to improved screening of blood before transfusion ***(Ozaras and Tahan, 2009).***

In the United States, about 2% of people have hepatitis C ***(Wilkins et al., 2010),*** with the number of new cases per year stabilized at 17,000 since 2007 ***(Centers for Disease Control and Prevention (CDC), 2013).*** The number of deaths from hepatitis C has increased to 15,800 in 2008 ***(Centers for Disease Control and Prevention (CDC), 2012)*** and by 2007 had overtaken HIV/AIDS as a cause of death in the USA ***(Centers for Disease Control and Prevention (CDC), 2012)***

This mortality rate is expected to increase, as those infected by transfusion before HCV testing become apparent ***(Blatt and Tong, 2004)***. In Europe the percentage of people with chronic infections has been estimated to be between 0.13 and 3.26% ***(Blachier et al., 2013)***.

The total number of people with this infection is higher in some countries in Africa and Asia ***(Holmberg et al., 2012)***. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%) ***(World Health Organization (WHO).*** It is believed that the high prevalence in Egypt is linked to a now-discontinued mass-treatment campaign for schistosomiasis, using improperly sterilized glass syringes (***Alter, 2007)***.

The Interferon / Ribavirin regimen for treatment of chronic HCV infection

Drugs used in this regimen

Interferon

Interferons (IFNs) are proteins made and released by host cells in response to the presence of pathogens such as viruses, bacteria, parasites or tumor cells. They allow for communication between cells to trigger the protective defenses of the immune system that eradicate pathogens or tumors.

IFNs belong to the large class of glycoproteins known as cytokines. Interferons are named after their ability to "interfere" with viral replication within host cells. IFNs have other functions: they activate immune cells, such as natural killer cells and macrophages; they increase recognition of infection or tumor cells by up-regulating antigen presentation to T lymphocytes; and they increase the ability of uninfected host cells to resist new infection by virus. Certain symptoms, such as aching muscles and fever, are related to the production of IFNs during infection.

About ten distinct IFNs have been identified in mammals; seven of these have been described for humans. They are typically divided among three IFN classes: Type I IFN, Type II IFN, and Type III IFN. IFNs belonging to all IFN classes are very important for fighting viral infections.

Types of interferon

Based on the type of receptor through which they signal, human interferons have been classified into three major types.

- Interferon type I: All type I IFNs bind to a specific cell surface receptor complex known as the IFN-α receptor (IFNAR) that consists of IFNAR1 and IFNAR2 chains ***(de Weerd et al., 2007)*****.** The type I interferons present in humans are IFN-α, IFN-β, IFN-ε, IFN-κ and IFN-ω ***(Liu, 2005)*****.**
- Interferon type II: Binds to IFNGR that consists of IFNGR1 and IFNGR2 chains. In humans this is IFN-γ.
- Interferon type III: Signal through a receptor complex consisting of IL10R2 (also called CRF2-4) and IFNLR1 (also called CRF2-12). Acceptance of this classification is less universal than that of type I and type II, and unlike the other two, it is not currently included in Medical Subject Headings ***(Vilcek, 2003)*****.**

Function

All interferons share several common effects; they are antiviral agents and can fight tumors.

As an infected cell dies from a cytolytic virus, viral particles are released that can infect nearby cells. However, the infected cell can warn neighboring cells of a viral presence by releasing interferon. The neighboring cells, in response to interferon, produce large amounts of an enzyme known as protein kinase R (PKR). This enzyme phosphorylates a protein known as eIF-2 in response to new viral infections; the phosphorylated eIF-2 forms an inactive complex with another protein, called eIF2B, to reduce protein synthesis within the cell. Another cellular enzyme, RNAse L—also induced following PKR activation—destroys RNA within the cells to further reduce protein synthesis of both viral and host genes. Inhibited protein synthesis destroys both the virus and infected host cells. In addition, interferons induce production of hundreds of other proteins—known collectively as interferon-stimulated genes (ISGs)—that have roles in combating viruses ***(Vilcek , 2003 and de Veer et al., 2001)*.** They also limit viral spread by increasing p53 activity, which kills virus-infected cells by promoting apoptosis ***(Takaoka et al., 2003 and Moiseeva et al., 2006)*.** The effect of IFN on p53 is also linked to its protective role against certain cancers ***(Takaoka et al., 2003)***.

Another function of interferons is to upregulate major histocompatibility complex molecules, MHC I and MHC II, and increase immunoproteasome activity. Higher MHC I expression increases presentation of viral peptides to cytotoxic T cells, while the immunoproteasome processes viral peptides for loading onto the MHC I molecule, thereby increasing the recognition and killing of infected cells. Higher MHC II expression increases presentation of viral peptides to helper T cells; these cells release cytokines (such as more interferons and interleukins, among others) that signal to and co-ordinate the activity of other immune cells.

Interferons, such as interferon gamma, directly activate other immune cells, such as macrophages and natural killer cells.

Interferons can inflame the tongue and cause dysfunction in taste bud cells, restructuring or killing taste buds entirely ***(Wang et al., 2007)***.

Virus resistance to interferons

Many viruses have evolved mechanisms to resist interferon activity ***(Navratil et al., 2010).*** They circumvent the IFN response by blocking downstream signaling events that occur after the cytokine binds to its receptor, by preventing further IFN production, and by inhibiting the functions of proteins that are induced by IFN ***(Lin et al., 2004).*** Viruses that inhibit IFN signaling include Japanese Encephalitis Virus (JEV), dengue type 2 virus (DEN-2) and viruses of the herpesvirus family, such as human cytomegalovirus (HCMV) and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV8)

(Lin et al., 2004 and Sen, 2001)*.** Viral proteins proven to affect IFN signaling include EBV nuclear antigen 1 (EBNA1) and EBV nuclear antigen 2 (EBNA-2) from Epstein-Barr virus, the large T antigen of Polyomavirus, the E7 protein of Human papillomavirus (HPV), and the B18R protein of vaccinia virus ***(Sen, 2001 and Alcamí et al., 2000). Reducing IFN-α activity may prevent signaling via STAT1, STAT2, or IRF9 (as with JEV infection) or through the JAK-STAT pathway (as with DEN-2 infection) ***(Lin et al., 2004).*** Several poxviruses encode soluble IFN receptor homologs—like the B18R protein of the vaccinia virus—that bind to and prevent IFN interacting with its cellular receptor, impeding communication between this cytokine and its target cells (***Alcamí et al., 2000).*** Some viruses can encode proteins that bind to double-stranded RNA (dsRNA) to prevent the activity of RNA-dependent protein kinases; this is the mechanism reovirus adopts using its sigma 3 (σ3) protein, and vaccinia virus employs using the gene product of its E3L gene, p25 ***(Minks et al., 1979; Miller and Samuel, 1992 and Chang et al., 1992)*.** The ability of interferon to induce protein production from interferon stimulated genes (ISGs) can also be affected. Production of protein kinase R, for example, can be disrupted in cells infected with JEV ***(Lin et al., 2004).*** Some viruses escape the anti-viral activities of interferons by gene (and thus protein) mutation. The H5N1 influenza virus, also known as bird flu, has resistance to interferon and other anti-viral cytokines that is attributed to a single amino acid change in its Non-Structural Protein 1 (NS1), although the precise mechanism of how this confers immunity is unclear ***(Seo et al., 2002)*****.**

Side effects of interferons

Nearly all patients receiving interferon experience side effects, which can be serious. Fatigue and flu-like symptoms are common, and the drug can also cause psychiatric symptoms (including depression or psychosis), weight loss, seizures, peripheral neuropathy, and bone marrow suppression ***(Pawlotsky et al., 2007)***.

Ribavirin

Ribavirin is a guanosine (ribonucleic) analog used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor ***(Carter and Saunders, 2007).*** Its brand names include Copegus, Rebetol, Ribasphere, Vilona, and Virazole, and it is an anti-viral drug used off-label for severe RSV infection (individually), (notably for persistent ***(Carter and Saunders, 2007)*****.** hepatitis C infection (can be used in conjunction with peginterferon alfa-2b or peginterferon alfa-2a), and some other viral infections. Ribavirin is a prodrug, which when metabolized resembles purine RNA nucleotides. In this form it interferes with RNA metabolism required for viral replication. How it exactly affects viral replication is unknown; many mechanisms have been proposed for this but none of these has been proven to date. Multiple mechanisms may be responsible for its actions.

It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system ***(World Health Organization (WHO), 2013)***.

Medical uses

Ribavirin is used primarily to treat hepatitis C and viral hemorrhagic fevers (which is an orphan indication in most countries) ***(Hepatitis B/Hepatitis C Agents and RSV Agents, 2014).*** In this former indication the oral (capsule or tablet) form of ribavirin is used in combination with pegylated interferon alfa ***(Paeshuyse et al., 2011; Flori et al., 2013; Druyts et al., 2013 and Zeuzem and Poordad, 2010)***. Including in people coinfected with hepatitis B, HIV and in the pediatric population (***Druyts et al., 2013; Zeuzem and Poordad, 2010;***

Liu et al., 2012 and Basso et al., 2013). Statins may improve this combination's efficacy in treating hepatitis C ***(Zhu et al., 2013).***

Adverse effects

List of adverse effects of ribavirin by frequency ***(Kato, 2000; Jubin, 2001 and Berry et al., 2011).***

Very common (>10% frequency)

- Viral pharyngitis
- Anemia
- Neutropenia
- Appetite loss
- Weight loss
- Depression
- Anxiety
- Emotional lability
- Insomnia
- Headache
- Dizziness
- Dry mouth
- Concentration impaired
- Shortness of breath
- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Hair loss
- Dry skin
- Itchiness
- Rash
- Joint aches and pains
- Muscle aches and pains
- Musculoskeletal pain
- Fatigue

Uncommon (0.1-1% frequency)

- Hypersensitivity
- Diabetes mellitus
- Hypertriglyceridemia
- Neuropathy
- Heart attack
- Mouth pain
- Pancreatitis
- Bone pain
- Facial edema
- Immediately life-threatening psychiatric disturbances, including suicide attempts and hallucinations

- Rigors
- Fever
- Influenza-like illness
- Muscle weakness
- Irritability

Mechanisms of action

RNA viruses

Ribavirin's carboxamide group can make the native nucleoside drug resemble adenosine or guanosine, depending on its rotation. For this reason, when ribavirin is incorporated into RNA, as a base analog of either adenine or guanine, it pairs equally well with either uracil or cytosine, inducing mutations in RNA-dependent replication in RNA viruses. Such hypermutation can be lethal to RNA viruses ***(Ortega-Prieto, et al., 2013 and Crotty et al., 2002)***.

The interferon ribavirin regimen:

The combination of pegylated interferon and ribavirin. This is a regimen that has evolved over the last 18 years. Recombinant interferon was first approved by the FDA for the treatment of non-A, non-B hepatitis in 1991 as monotherapy, but it was effective in a relatively small proportion of patients ***(Davis et al., 1989 and Poynard et al., 1996)***. Ribavirin was added to the regimen after it was noted that it reduced the chance of relapse when treatment was stopped ***(McHutchison et al., 1998)***. Pegylated interferons replaced the standard formulation in 2001 and offered the convenience of once a week dosing ***(Manns et al., 2001 and Fried et al., 2002)***. Improved outcomes have accompanied these changes (Fig.7).

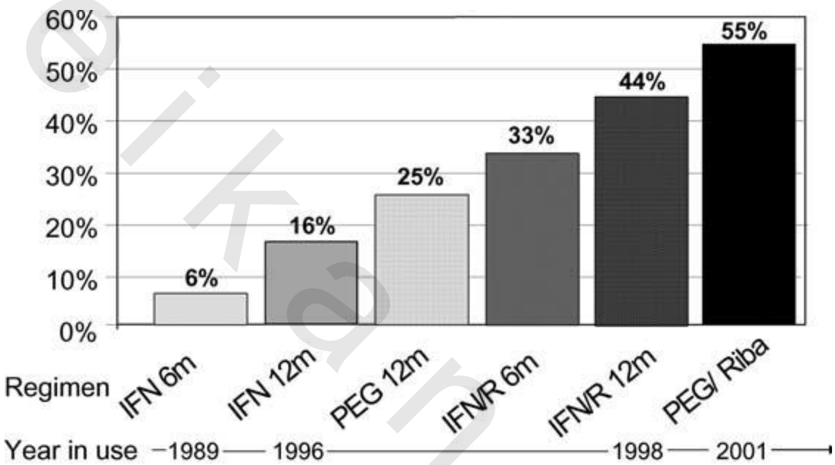

Fig 7. Outcomes of treatment regimens for chronic hepatitis C.

Agents used:

Interferons are naturally occurring glycoproteins that are produced in vivo by cells, particularly leukocytes, in response to viral infection.

Commercially available interferons today are recombinantly produced.

Interferons inhibit the replication of many viruses, including hepatitis viruses, through a variety of mechanisms, including direct antiviral (inhibition of virus attachment and uncoating, induction of intracellular proteins and ribonucleases) and by amplification of specific (cytotoxic T-lymphocyte) and nonspecific (natural killer cell) immune responses ***(Peters etg al., 1986)***. In the late 1980 s, interferons were among the first agents studied for treatment of what was then called chronic non-A, non-B hepatitis ***(Davis et al., 1989)***. Although IFN suppresses the level of HCV replication, the exact mechanisms of action in HCV infection are not known. Nonetheless, it is generally believed that clearance of the HCV is at least in part mediated by IFN-related enhancement of the host immune response to the virus.

Initially, standard recombinant interferons were used for treatment of chronic HCV infection. These had a limited half-life that required dosing three times per week. Long-acting pegylated interferons replaced standard interferons after their approval by FDA in 2001. Pegylation involves the attachment of a large inactive molecule (polyethylene glycol; PEG) to the interferon molecule in order to reduce its renal clearance.

This process results in some variable loss of activity of the native protein that is dependent on the size and site of attachment of the PEG molecule but is also associated with a tenfold increase in drug half-life and a corresponding decrease in clearance ***(Wang et al., 2000; Glue et al., 2000 and Pedder, 2003)***. The PEG molecule is cleaved after binding of the complex to the interferon receptor and cleared. The longer half-life allows large doses of the drug to be administered less frequently (once weekly instead of three times per week), increases host exposure to interferon, and doubles the response seen with standard interferon preparations ***(Heathcote et al., 2000; Zeuzem et al., 2000 and Lindsay et al., 2001)***. Pegylated interferons are more effective than standard interferon and there is a clear dose response with increasing doses of the PEG-interferons ***(Davis et al., 1989; Manns et al., 2001; Fried et al., 2002 and Modi et al., 2000).***

Ribavirin (1-_-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) is a synthetic nucleoside analogue which structurally resembles guanosine and has in vitro activity against many viruses, including flaviviridae which closely resemble HCV ***(Patterson, 1990; Crumpacker, 1984 and Vo et al., 2003)***. The mechanism of action in HCV infection is not clear, but the predominant current opinion is that ribavirin induces lethal mutations in the viral genome, a mechanism known as viral error catastrophe ***(Patterson, 1990; Crumpacker, 1984 and Vo et al., 2003)***. Early studies of ribavirin alone found that serum ALT levels fell to within the normal range in 40% of treated patients, but virus levels did not significantly change ***(Reichard et al., 1991; Di Bisceglie et al., 1992 and Bodenheimer et al., 1997)***. However, when combined with interferon, the combination both improves response during treatment and reduces subsequent relapse. Thus, there is a dramatic improvement in the sustained virologic response rate ***(McHutchison et al., 1998; Poynard et al., 1998; Reichard et al., 1998 and Zeuzem et al., 1998)***. The results of two similarly designed large randomized controlled trials comparing combination therapy to interferon monotherapy showed sustained viral-negative responses in 41 and 33% of subjects treated with 12 or 6 months of combination therapy, respectively, compared to 16 and 6% in those treated with interferon alone for 12 or 6 months ***(McHutchison and Poynard, 1999).*** Furthermore, the combination of pegylated interferon with ribavirin (the current standard of care) showed an even higher viral response rate ***(Manns, 2001 and Fried et al., 2002).*** PEG-interferon alfa-2b 1.5 g/kg once weekly plus 800 mg daily ribavirin led to a sustained virologic response rate of 54%, even though the dose of ribavirin in this study was suboptimal ***(Manns, 2001).*** Sustained response was 42% in patients infected with genotype 1 and 82% in those with genotype 2 or 3. Similarly, PEG-interferon alfa-2a 180 _g once weekly plus 1000–1200 mg of ribavirin per day resulted in a sustained virologic response rate of 56% ***(Fried et al., 2002).*** Sustained response was 46% in patients infected with genotype 1 and 76% in those with genotype 2 or 3.

Optimizing Treatment Regimens:

The sensitivity of different HCV genotypes to interferon-based therapies varies considerably and this determines both the drug doses and the treatment duration required (Table 1). Thus, the determination of the virus genotype before treatment remains the initial critical step in evaluating a patient with chronic hepatitis C. Patients infected with genotype 1 should receive 1 year of one of the two available pegylated interferons (PEG-IFN) plus ribavirin. The two pegylated interferons are, for all intents and purposes, bioequivalent. Although the approved dose of ribavirin is 1000–1200 mg/day for those with weight less than or greater than 75 kg, respectively ***(Hadziyannis et al., 2004),*** an extended weight-based dose ranging from 800 to 1400 mg/day is commonly used (Table 1)

(Jacobson et al., 2007). It is not known whether such dosing improves response or is appropriate for other genotypes. Recently, some investigators have suggested that “rapid viral response” (RVR; undetectable HCV RNA after 4 weeks of treatment) in patients with genotype 1 identifies a small subgroup (about 20% of treated patients) who may be treated for only 24 weeks and still achieve an SVR rate of 73–91% ***(Jensen et al., 2005)***. Others have found a lower SVR rate with 24 weeks of treatment, so this needs to be confirmed before becoming standard practice ***(Zeuzem et al., 2006)***.

Patients with genotype 2 or 3 respond as well with doses of 800 mg/day and just 6 months of treatment as they do with higher doses and a longer duration ***(Hadziyannis et al., 2004)***. Recently, studies have suggested that some patients with genotype 2 or 3 infection who respond rapidly to treatment (RVR) can be treated for as little as 12–16 weeks with excellent outcomes if weight-based dosing of ribavirin is utilized ***(von Wagner et al., 2005; Mangia et al., 2005 and Dalgard O, et al., 2004)***.

Shortening the course of treatment is not recommended regardless of the early viral response if a standard dose (800 mg per day) of ribavirin has been used ***(Shiffman et al., 2007)***.

Patients who are infected with genotype 4 have viral response rates similar to or perhaps slightly better than genotype 1 and, like genotype 1, some achieve good responses with only 24 weeks of therapy ***(El-Zayadi et al., 2005)***. Genotypes 5 and 6 have SVR rates approaching those achieved with genotypes 2 and 3, although they require a full year of therapy ***(Legrand-Abravanel et al., 2004 and Yuen and Lai, 2006)***.

Patient Selection, Drug Administration,and Monitoring Therapy:

All HCV-infected patients should be counseled about routes of virus transmission, the natural history of the infection, the detrimental effects of alcohol and cannabis use on the course of disease, treatment options, possible treatment risks especially including the risk of teratogenicity of ribavirin, and outcomes regardless of what intervention, if any, is ultimately decided upon. If treatment is not considered, the importance of long-term follow-up must be emphasized.

Table 1: Doses and Duration of Antiviral Drugs According to Viral Genotype

Genotype	Interferon Dose (per week)	Ribavirin Dose (mg/day)	Duration (weeks)	SVR (%)
1	180µg PEG alfa-2a or 1.5µg/kg PEG alfa-2b	800–1400mg/day weight-based	48	41–42%
2	180µg PEG alfa-2a or 1.5µg/kg PEG alfa-2b	800 mg/day	24	66–75%
3	180µg PEG alfa-2a or 1.5µg/kg PEG alfa-2b	800mg/day	24	66-75%
4.5.6	180µg PEG alfa-2a or 1.5µg/kg PEG alfa-2b	1000-1200mg/day	48	55-64%

- Weight-based dosing of ribavirin is 800 mg daily in a divided dose for weight less than 65 kg, 1000 mg for weight 65–84 kg, 1200 mg for weight 85–104 kg, and 1400 mg for weight of 105 kg or more.
- Ribavirin dose should be weight-based if shorter duration of therapy is anticipated in patients with rapid viral response.

Rationale treatment management decisions are based on a clear understanding of the epidemiology and natural history of chronic hepatitis as well as the factors that influence the response to treatment.

The potential benefits in terms of freedom from risk of progression, longevity, and quality of life must be weighed against the current effectiveness, cost, tolerability of therapy, other comorbid conditions that the patient might have, financial impact, and desire for therapy. The balance of these factors defines the treatment threshold for a particular patient.

If the physician and patient agree to proceed with treatment, assessment of the status of the disease (as determined by liver biopsy) and infection (as determined by viral genotype and HCV RNA level) should be made. This allows a more accurate estimate of prognosis and chance of response to available treatment. It also allows the physician to use these patient characteristics that may independently influence treatment response to personalize the treatment strategy to achieve the optimal response (see above). Although most hepatologists use only viral genotype and histology to choose the best treatment duration, others have recommended a more complex "a la carte" method that also incorporatesgender, age, and viral level into Equation ***(Poynard et al., 2000)***. Retrospective analysis suggests that such algorithms might improve sustained viral response rates to 50–83%. However, the wisdom of complicated algorithms that would, in effect, treat a higher proportion of infected cases with a longer and more costly regimen is controversial and has not been confirmed prospectively.

Baseline assessment of liver tests, complete blood counts, and HCV RNA level are important in order to later determine treatment response and drug-related toxicity. The patient should be instructed in injection techniques. Treatment tolerance is improved if the patient is educated about the potential side effects of therapy and what they might expect. Some easy measures such as evening dosing, exercise, adequate hydration, and use of acetaminophen at the time of each interferon dose will reduce anxiety, side effects, and non-compliance. Physician extenders such as nurses, pharmacists, and commercial pharmacy support services are extremely helpful in this respect. Reinstitution of antidepressants should be considered in patients with active depression or a significant past history of depression. Monitoring response and potential drug toxicity is essential. Symptoms related to treatment rarely necessitate dose adjustments.

However, hematologic alterations, particularly anemia, can be significant and clinically important during the first few weeks and may require dose adjustments (Table 2). Therefore, blood counts including hemoglobin, white count, differential, and platelet count should be repeated 2 and 4 weeks after starting therapy. Transient interferon dose reduction is indicated only for a neutrophil count less than 750 per mL or platelets to less than 50,000 per mL. Ribavirin should be reduced if the hemoglobin falls to less than 10 g/dL. The amount of dose reduction required to reverse cytopenia has not been established and this has led to differences in the recommendations for the two interferon preparations (Table 2). Although the labeling of the drugs calls for reducing doses by approximately half, this is usually not necessary. Temporary dose modifications are common in patients treated with combination therapy.

In fact, in large controlled trials dose modifications were required at least transiently in 34 and 42%, respectively ***(Manns, 2001 and Fried et al., 2002).*** Ribavirin causes a hemolytic anemia that is accompanied by a vigorous reticulocytosis.

Although this usually serves to maintain stable levels of hemoglobin after the first few weeks of treatment, about 8–13% of patients will require reduction of the ribavirin dose for anemia, usually during the first 4 weeks of treatment ***(Maddrey, 1999)***. Ribavirin-induced anemia is dose dependent and therefore anemia usually stabilizes or improves with dose reduction. Occasionally transfusion or support with erythropoietin is necessary, though it generally takes 4–8 weeks before the hemoglobin increases after erythropoietin is started ***(Afdhal et al., 2004)***. About 15–20% of patients treated with pegylated interferon require dose reductions for neutropenia ***(Manns, 2001 and Fried et al., 2002)***. Growth factor support is rarely required for neutropenia.

Significant thrombocytopenia necessitating dose reduction is uncommon since the anemia caused by ribavirin induces a reactive thrombocytosis.

Thus, platelet counts tend to remain relatively stable throughout combination therapy, even when the pre-treatment count is low. Interferon should be permanently stopped only if symptoms are incapacitating, the absolute neutrophil count is less than 500 per mL, or the platelet count is less than 25,000 per mL. Discontinuation of therapy for cytopenia is uncommon if patients have been monitored and dose adjusted appropriately. It is extremely important that treatment not be stopped prematurely or for decreases in blood counts that do not meet the criteria stated above. Inappropriate dose reduction and discontinuation significantly reduces the likelihood of a treatment response. Early discontinuation of treatment can reduce the likelihood of a sustained treatment response by 80% ***(McHutchison et al., 2002)***.

The safety and tolerability of combination therapy have been reviewed in detail elsewhere and will only be highlighted here. These reviews are highly recommended for physicians who have not used these drugs before. Overall, interferon-based therapies are reasonably well tolerated. Most patients experience flu-like side effects including fatigue, fever, headache, myalgia, and arthralgia ***(Maddrey, 1999 and Fattovich 1996)***. These are most severe during the first few weeks of therapy and often abate to a large degree as treatment is continued. Gastrointestinal symptoms including nausea, vomiting, or diarrhea occur in about a third of patients but are rarely severe. Psychiatric symptoms such as depression, impaired concentration, irritability, and insomnia occur in about a third of cases, but are also common in untreated patients with chronic hepatitis C. Dermatologic signs and symptoms occur in about a quarter of patients. Injection site erythema is most common and occurs more frequently with pegylated interferons. A faint morbilliform rash can be seen from the ribavirin.

As described above, ribavirin causes a predictable dose-related hemolysis. Thus, the drug should be used with great caution or avoided completely if there is pre-existing anemia, a hemolytic disorder, coronary artery disease, or hypoxia. Since ribavirin is renally excreted, it can cause profound hemolysis in patients with renal failure and should generally be avoided. Careful consideration should be given to the potential effects of an acute anemia in each patient in whom combination treatment is considered. The mean fall in hemoglobin is 2–3 gm/dL ***(McHutchison et al., 1998; Manns et al., 2001; Fried MW, et***

al., 2002 and Poynard et al., 1998). The decline occurs gradually during the first 4 weeks of treatment and the hemoglobin level usually remains relatively stable thereafter.

Finally, ribavirin has embryotoxic and teratogenic effects in animals and should be avoided in patients of child-bearing potential unless adequate contraception is assured.

Severe adverse events, including severe psychiatric symptoms, suicide attempts, and profound cytopenia are extremely uncommon being reported in fewer than 1 in 1000 treated cases ***(Fattovich 1996)***. Development of immune-mediated disorders such as thyroid disease, diabetes, dermatologic conditions, neuropathy, and other autoimmune-like signs was seen in about 1% in a large retrospective series ***(Fattovich 1996)***. Development of autoantibodies is not necessarily associated with autoimmune disease.

Autoantibodies are common in patients with HCV infection and may be more common during interferon treatment (***El-Zayadi et al., 2005 and MacFarlane et al., 1994)***.

Table 2: Modification of Doses of Antiviral Drugs (from Product Labeling Except Where Noted)

Laboratory Values	*Dose Reduction*		
	Pegylated IFN alfa-2a	*Pegylated IFN alfa-2b*	*Ribavirin*
ANC >750/mm3	No change	No change	No change
ANC <750/mm3		Reduce by 50%	
ANC <500/mm3	Reduce to 135 µg Discontinue until ANC values return to more than 1000/mm3.		No change
Platelet<80,000/mm3	No change	Reduce by 50%	No change
Platelet<50,000/mm3	Reduce to 90 µg	Discontinue permanently	No change
Platelet<25,000/mm3	Discontinue permanently		
Hemoglobin: <10 gm/dL if no cardiac disease	• No change	• No change	❖
Hemoglobin>2 gm/dL fall if history of stable cardiac disease	• No change	• No change	❖
Hemoglobin <8.5 gm	Stop	Stop	Stop
Moderate side effects (symptoms)	Decrease dose to 135 µg (in some cases reduction to 90 µg may be needed).	Decrease dose by 50%	No recommendation
Severe side effects (symptoms)	Discontinue permanently	Discontinue permanently	Stop

- Authors' note: Interferon suppresses bone marrow function and modest dose reductions may allow the hemoglobin to stabilize and/or recover if ribavirin reduction alone is insufficient. Also consider iron deficiency of ribavirin reduction does not stabilize the hemoglobin level.

❖ Recommendation with Copegus (Roche) is to reduce dose to 600 mg/day. Recommendation with Rebetol (Schering) is to reduce in 200 mg/day increments until hemoglobin is stable.

Assessing Treatment Response:

Treatment responses are defined by changes in the HCV RNA level during and after treatment (Table 3). HCV RNA should be measured with a sensitive quantitative assay such as real-time PCR.

Serum ALT is not part of the definition of response since its level does not always reflect on treatment response. Ribavirin may cause the ALT to normalize in the absence of a virologic response and ALT may occasionally be elevated despite a virologic response, especially in those receiving pegylated products ***(Manns, 2001; Fried et al., 2002 and Bodenheimer et al., 1997)***.

Early virologic response (EVR) is defined as a fall in the HCV RNA level by at least 2 logs (99%) within the first 12 weeks of treatment.

EVR is based on the concept that the slope of the second phase decline in HCV RNA levels during treatment correlates with the likelihood of eventual virus clearance ***(Rocco et al., 2001)***[221]. Thus, EVR is used to assess responsiveness to treatment during the first weeks of therapy. Genotype 1-infected patients who fail to achieve an EVR have less than a

1% chance of reaching an SVR with continued therapy ***(Davis et al., 2003)***. **This** justifies discontinuation of therapy after 12 weeks in the 20% or so of patients without EVR. Patients with genotype 2 or 3 almost always reach an EVR, so it is not usually helpful to assess HCV RNA levels during treatment in them.

Measurement of HCV RNA at the end of therapy is helpful in identifying those who have cleared virus (ETR) and require subsequent screening to confirm a durable response. About 15% of patients with ETR will relapse during the first few months after treatment is stopped. Sustained viral response (SVR) is confirmed by the absence of detectable HCV RNA by a sensitive molecular test 6 months after completing therapy. Occasionally studies will report “SVR-3 months” since almost all relapses occur within 12 weeks of stopping treatment. SVR is the major goal of treatment and is durable. It implies viral eradication and is associated with histologic improvement, regression of inflammation and fibrosis, and in patients with cirrhosis, a marked reduction in risk for hepatocellular carcinoma and elimination of the risk of decompensation ***(Marcellin et al., 1997; Poynard et al., 2000 and Bruno et al., 2007)***.

The implications of rapid viral response (RVR) are described above, but this is a new concept and requires confirmation before influencing treatment duration in most patients. RVR identifies those patients who are most sensitive to antiviral treatment and might tolerate dose reductions or early treatment discontinuation. Importantly, failure to reach an RVR does not connote treatment failure and it is not a reason to stop treatment.

Table 3: Treatment Milestones and Endpoints *(Rocco et al., 2001and Davis et al., 2003)*.

Milestone	***Week of Treatment***	***Definition***	***Implication***
Rapid viral response (RVR)	4	HCV RNA undetectable by rtPCR or TMA	Higher chance of SVR may respond as well if treatment needs to be shortened
Early virologic response (EVR)	12	HCV RNA decreased by > 2 logs from baseline or HCV RNA undetectable	Failure to achieve EVR associated with <1% chance of SVR and treatment can usually be stopped
End-of-treatment response (ETR)	End-of-treatment	HCV RNA undetectable by rtPCR or TMA	On treatment response. Observe for SVR or relapse
Sustained virologic response (SVR)	24 weeks after treatment	HCV RNA undetectable by rtPCR or TMA	Eradication of virus (cure)

- rtPCR = real-time polymerase chain reaction such as TaqMan; TMA = transcription mediated amplification .

Genotype 4 Outcomes:

Pegylated interferon markedly improved the rates of SVR in chronic HCV-4 ***(Alfaleh et al., 2004)***. The use of PEG-IFN-α2a (180 µg/week) or PEG-IFN-α2b (1.5 µg/kg/week) plus ribavirin (1000-1200 mg/day) was reported to result in SVR rates of 65%-69% in chronic HCV-4 patients in Egypt, Saudi Arabia, Qatar, and Kuwait ***(Kamal et al., 2007 and Shobokshi et al., 2003).***

Impact of Liver Disease on Treatment Outcome in Genotype 4:

Fibrosis, cirrhosis, and steatosis have been identified as significant factors in determining treatment outcomes for patients with chronic hepatitis C. In general, advanced liver disease is associated with poorer outcomes; however, PEG-IFN treatment is recognized to slow or even reverse the extent of liver disease in many patients ***(Fontana et al., 2004)***.

Early studies using conventional IFN-α plus ribavirin showed that SVR rates were lower among genotype 4patients with cirrhosis than in patients with normal liver function. In patients without cirrhosis, SVR rates were 8% in patients receiving IFN- α monotherapy and 42% in those receiving IFN-α combined with ribavirin. Conversely, among genotype 4 patients with cirrhosis, no patients receiving IFN- α monotherapy attained SVR, and only 14% of combination therapy recipients attained SVR ***(Zylberberg et al., 2000 and Koshy et al., 2000)***. Two studies ***(Hasan et al., 2004 and Kamal et al., 2005).*** reported that treatment outcomes were improved in genotype 4 patients with mild liver disease compared with those patients who had more advanced liver disease. Hepatic steatosis is an important variable for fibrosis progression and therapeutic response to IFN-based therapies.

Steatosis is present in 40%-73% of patients with chronic HCV-4 ***(Tsochatzis et al., 2007; Zayadi et al., 2007; Zein et al., 1996 and El Zayadi et al., 2005)***. In a recent study ***(El Zayadi et al., 2005)***, among a subgroup of patients analyzed for pretreatment steatosis, a greater proportion of patients without steatosis attained SVR than those with steatosis. A similar trend of SVR rates was observed among patients with or without steatosis after treatment. This strong association of steatosis with reduced SVR rates persisted even after adjustment for factors that influence treatment response, such as viral load, fibrosis, age, sex, pretreatment and posttreatment body mass index, glucose, and triglyceride values.

In patients receiving PEG-IFN- α plus ribavirin (1000-1200 mg/day) for 48 weeks, SVR rates were significantly higher among those with no or mild fibrosis (F0 (no fibrosis) to F2 (portal fibrosis with rare septa) ***(Zein , 1996)*** than in those with severe fibrosis or cirrhosis [F3 (numerous septa without cirrhosis) to F4 (cirrhosis)] ***(Fontana, 2004)***. fig.8

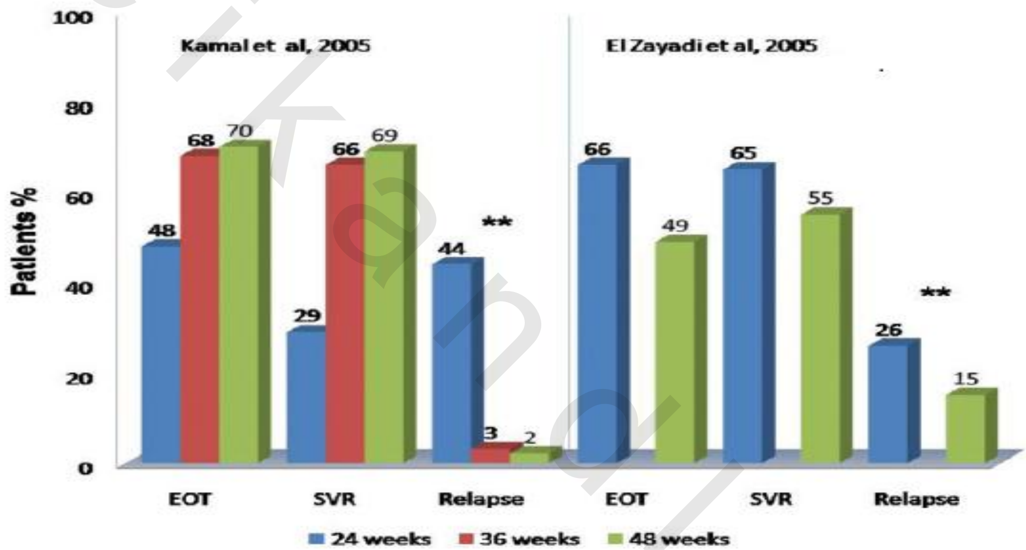

Figure.8. Virologic outcomes in patients with chronic HCV-4 receiving PEG-IFN- α plus ribavirin for 24, 36, or 48 weeks ***(Kamal , 2005 and El Zayadi et al., 2005)***

Cost Effectiveness of Chronic HCV-4 Treatment.

Cost-effectiveness analyses based xon clinical trial data in primarily genotype 1 patients have endorsed the tailored use of the combination therapy of PEG-IFN- α plus ribavirin.

These studies have shown that this combination therapy is a more cost-effective option than conventional IFN- α plus ribavirin and that administration of ribavirin according to patient body weight increases the efficiency of this approach ***(Buti et al., 2003)***. Furthermore, tailoring treatment according to week 4 and week 12 viral responses ***(El Zayadi et al., 2005 and Zeuzem et al., 2006)*** also promotes amore efficient use of this combination therapy by stopping treatment in patients with a high likelihood of treatment failure and shortening regimens in patients who show early viral responses that are predictive of favorable treatment outcomes.

No cost effectiveness studies have been conducted in genotype 4 patients, particularly in countries with high prevalence such as Egypt. These types of analyses are now urgently required for genotype 4 patients. In particular, economic analyses that are relevant to the health care delivery systems currently used in the regions of the world where genotype 4 predominates. In countries in which genotype 4 HCV is most commonly found, cost represents a considerable hurdle to patients seeking health care. Many patients are required to fund their own treatment, and failure to complete treatment regimens because of financial constraints is common. Zayadi et al.91 attempted to treat patients for 24 or 48 weeks according to financial affordability rather than pretreatment or treatment predictors. These investigators aimed to make therapy available to a larger number of patients, but nonresponse and relapse rates were high.

This dilemma has no easy solution, but financial constraints do not mean less effective treatments to patients in developing countries. Every effort should be made to make the most effective treatments affordable and available to infected persons to maximize the individual's opportunity for treatment success. Funding of therapeutic options should be considered alongside other measures aimed at limiting the spread of the infection, such as education programs, needle share programs for intravenous drug users, and use of safer needle devices and needleless systems in health care units ***(Kamal and Nasser, 2008)***.

The new anti viral drugs

Treatment for chronic hepatitis C virus (HCV) infection is evolving rapidly. The approval in 2013 of two new direct-acting antivirals—sofosbuvir (a polymerase inhibitor) and simeprevir (a second-generation protease inhibitor)—opens the door for an all-oral regimen, potentially avoiding interferon and its harsh side effects. Other direct-acting antivirals are under development.

In clinical trials of treatment for chronic HCV infection, regimens that included a direct-acting antiviral agent were more effective than ones that did not.

Sofosbuvir is approved in an oral dose of 400 mg once daily in combination with ribavirin for patients infected with HCV genotype 2 or 3, and in combination with ribavirin and interferon in patients infected with HCV genotype 1 or 4. It is also recommended in combination with ribavirin in HCV-infected patients with hepatocellular carcinoma who are awaiting liver transplantation.

Simeprevir is approved in an oral dose of 150 mg once daily in combination with ribavirin and interferon for patients with HCV genotype 1.

The new drugs are expensive, a potential barrier for many patients. As more direct-acting antiviral agents become available, their cost will likely decrease.

Combinations of direct-acting antiviral agents of different classes may prove even more effective and could eliminate the need for interferon entirely.

In late 2013, the US Food and Drug Administration (FDA) approved sofosbuvir and simeprevir, the newest direct-acting antiviral agents for treating chronic hepatitis C virus (HCV) infection. Multiple clinical trials have demonstrated dramatically improved treatment outcomes with these agents, opening the door to all-oral regimens or interferon-free regimens as the future standard of care for HCV.

Goal of treating HCV: a sustained virologic response

The aim of HCV treatment is to achieve a sustained virologic response, defined as having no detectable viral RNA after completion of antiviral therapy. This is associated with substantially better clinical outcomes, lower rates of liver-related morbidity and all-cause mortality, and stabilization of or even improvement in liver histology. This end point has traditionally been assessed at 6 months after the end of therapy, but recent data suggest the rates at 12 weeks are essentially equivalent.

Table 4: Summarizes the patterns of virologic response in treating HCV infection *(Singal et al., 2010 and Camma et al., 2004)*

Patterns of virologic response in treating hepatitis C virus (HCV) infection

Rapid virologic response
Undetectable HCV RNA at week 4 of treatment

Extended rapid virologic response
Undetectable HCV RNA at week 4 through week 12 of treatment

Sustained virologic response
Undetectable HCV RNA after treatment completion (currently commonly defined as 12 weeks after treatment completion)

Virologic relapse
Undetectable HCV RNA during treatment or at the end of treatment, but subsequent detection of HCV RNA following treatment cessation

Virologic breakthrough
Reappearance of HCV RNA while still on treatment in a patient who had a suppressed viral level earlier in the course of treatment

Partial response
At least a 2-$\log_{10}$ reduction in HCV RNA, but inability to fully remove the virus from the blood

No response
A reduction of less than 2 $\log_{10}$ from baseline HCV RNA during treatment

Interferon plus ribavirin: The standard of care for many years

HCV treatment has evolved over the past 20 years. Before 2011, the standard of care was a combination of interferon alfa-polyethylene glycol (peg-interferon), given as a weekly injection, and oral ribavirin. Neither drug has specific antiviral activity, and when they are used together they result in a sustained virologic response in fewer than 50% of patients with HCV genotype 1 and, at best, in 70% to 80% of patients with other genotypes ***(Paeshuyse et al., 2001)***.

An important bit of information to know when using interferon is the patient's*IL28B* genotype. This refers to a single-nucleotide polymorphism (C or T) on chromosome 19q13 (rs12979860) upstream of the *IL28B* gene encoding for interferon lambda-3. It is strongly associated with responsiveness to interferon: patients with the *IL28B* CC genotype have a much better chance of a sustained virologic response with interferon than do patients with CT or TT.

Boceprevir and telaprevir: First-generation protease inhibitors

In May 2011, the FDA approved the NS3/4A protease inhibitors boceprevir and telaprevir for treating HCV genotype 1, marking the beginning of the era of direct-acting antiviral agents ***(Ghany et al., 2001)***. When these drugs are used in combination with peg-interferon alfa and ribavirin, up to 75%

of patients with HCV genotype 1 who have had no previous treatment achieve a sustained virologic response.

But despite greatly improving the response rate, these first-generation protease inhibitors have substantial limitations. Twenty-five percent of patients with HCV genotype 1 who have received no previous treatment and 71% of patients who did not respond to previous treatment will not achieve a sustained virologic response with these agents ***(Soriano et al., 2012)***. Further, they are effective only against HCV genotype 1, being highly specific for the amino acid target sequence of the NS3 region.

Also, they must be used in combination with interferon alfa and ribavirin because the virus needs to mutate only a little—a few amino-acid substitutions—to gain resistance to them ***(Asselah and Marcellin, 2013)***. Therefore, patients are still exposed to interferon and ribavirin, with their toxicity. In addition, dysgeusia is seen with boceprevir, rash with telaprevir, and anemia with both ***(Manns et al., 2013 and Jacobson et al., 2011)***.

Finally, serious drug-drug interactions prompted the FDA to impose warnings for the use of these agents with other medications that interact with CYP3A4, the principal enzyme responsible for their metabolism.

The need to improve the rate of sustained virologic response, shorten the duration of treatment, avoid serious side effects, improve efficacy in treating patients infected with genotypes other than 1, and, importantly, eliminate the need for interferon alfa and its serious adverse effects have driven the development of new direct-acting antiviral agents, including the two newly FDA-approved drugs, sofosbuvir and simeprevir.

Table 5: DAAs and HTAs in clinical development at the beginning of 2014 *(Robert et al., 2014)*

Agent class	Generation	Compound	Manufacturer	Phase of clinical development
NS3-4A protease inhibitors	First-wave, first-generation	Telaprevir	Vertex, Janssen, Mitsubishi	Approved
		Boceprevir	Merck	Approved
	Second-wave, first-generation	Simeprevir	Janssen	Approved
		Faldaprevir	Boehringer-Ingelheim	III
		Asunaprevir	Bristol-Myers Squibb	III
		ABT-450/r	Abbvie	III
		Danoprevir/r	Roche	II
		Sovaprevir	Achillion	II[a]
		Vedroprevir	Gilead	II
		IDX320	Idenix	II
		Vaniprevir	Merck	III (Japan)
	Second-generation	MK-5172	Merck	III
		ACH-2684	Achillion	II
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir	Gilead	Approved
		VX-135	Vertex	II[b]
	Nucleoside analogue	Mericitabine	Roche	II
Non-nucleoside inhibitors of the HCV RdRp	Thumb domain I inhibitors	BMS-791325	Bristol-Myers Squibb	III
		TMC647055	Janssen	II
	Thumb domain II inhibitors	Lomibuvir	Vertex	II
		GS-9669	Gilead	II
	Palm domain I inhibitors	Dasabuvir	Abbvie	III
		ABT-072	Abbvie	II
		Setrobuvir	Roche	II
NS5A inhibitors	First-generation	Daclatasvir	Bristol-Myers Squibb	III
		Ledipasvir	Gilead	III
		Ombitasvir	Abbvie	III
		PPI-668	Presidio	II
		PPI-461	Presidio	II
		ACH-2928	Achillion	II
		GSK2336805	GlaxoSmithKline	II
		BMS824393	Bristol-Myers Squibb	II
		Samatasvir	Idenix	II
	Second-generation	MK-8742	Merck	II
		ACH-3102	Achillion	II
		GS-5816	Gilead	II
Cyclophilin inhibitors	First-generation	Alisporivir	Novartis	II[c]
		SCY-635	Scynexis	II
Antagonist of miRNA-122	First-generation	Miravirsen	Santaris	II

Sofosbuvir: a polymerase inhibitor

Sofosbuvir is a uridine nucleotide analogue that selectively inhibits the HCV NS5B RNA-dependent RNA polymerase. It targets the highly conserved nucleotide-binding pocket of this enzyme and functions as a chain terminator ***(Rodriguez-Torres et al., 2013)***. While the protease inhibitors are genotype-dependent, inhibition of the highly conserved viral polymerase has an impact that spans genotypes.

Sofosbuvir dosage and indications

Sofosbuvir is approved in an oral dose of 400 mg once daily in combination with ribavirin for patients infected with HCV genotype 2 or 3 and in combination with ribavirin and interferon alfa in patients infected with HCV genotype 1 or 4 (**Table 5**). It could be considered for HCV genotype 1 in combination with ribavirin alone for 24 weeks in patients who are ineligible for interferon.

Table 6: Approved regimens of sofosbuvir ***(Singal et al., 2010 and Camma et al., 2004)***

Approved regimens of sofosbuvir

HCV genotype	Regimen	Duration
1 or 4	Sofosbuvir 400 mg once daily, peg-interferon alfa 180 µg once weekly, and ribavirin 1,000 mg (if < 75 kg) or 1,200 mg (if ≥ 75 kg) daily in two divided doses	12 weeks
2	Sofosbuvir with ribavirin	12 weeks
3	Sofosbuvir with ribavirin	24 weeks

Sofosbuvir is also recommended in combination with ribavirin in HCV-infected patients with hepatocellular carcinoma who are awaiting liver transplantation, for up to 48 weeks or until they receive a transplant, to prevent posttransplant reinfection with HCV.

Sofosbuvir is expensive

A course of therapy is expected to cost about $84,000, which is significantly more than the cost of previous triple therapy (peg-interferon, ribavirin, and either boceprevir or telaprevir) ***(Soriano et al., 2013)***. This high cost will undoubtedly lead to less widespread use in developing countries, and potentially even in the United States. As newer direct-acting antiviral agents become available, the price will likely come down, enhancing access to these drugs.

Simeprevir: a second-generation protease inhibitor

Telaprevir and boceprevir are NS3/A4 protease inhibitors that belong to the alfa-ketoamid derivative class. Simeprevir belongs to the macrocyclic class and has a different way of binding to the target enzyme ***(You and Pockros, 2013)***. Like sofosbuvir, simeprevir was recently approved by the FDA for the treatment of HCV genotype 1.

The therapeutic efficacy of simeprevir has been tested in several clinical trials (**table 7**), including QUEST-1 ***(Jacobson et al., 2013)*** and QUEST-2 ***(Manns et al., 2013)*** (in previously untreated patients), PROMISE ***(Lawitz et al 2013)*** (in prior relapsers), and ASPIRE ***(Zeuzem et al., 2013)*** (in prior partial and null responders). Results from these trials showed high overall rates of sustained virologic response with triple therapy (ie, simeprevir combined with peg-interferon and ribavirin). It was generally well tolerated, and most adverse events reported during 12 weeks of treatment were of mild to moderate severity.

Table 7: Clinical trials of simeprevir in HCV genotype 1

Clinical trials of simeprevir in HCV genotype 1

Trial name	Phase	Population	Treatment groups and duration	Rate of sustained virologic response
QUEST-1[24] and QUEST-2[25]	3	Previously untreated	Simeprevir 150 mg daily + peg-interferon and ribavirin for 12 weeks and, if extended rapid virologic response achieved: peg-interferon and ribavirin for another 12 weeks (total 24 weeks) If not: peg-interferon and ribavirin for another 36 weeks (total 48 weeks)	Overall 80% Genotype 1a 75% Genotype 1b 85%
			Placebo + peg-interferon and ribavirin for 48 weeks	Overall 50% Genotype 1a 47% Genotype 1b 53%
PROMISE[26]	3	Relapsed after prior interferon-based therapy	Simeprevir 150 mg daily + peg-interferon and ribavirin for 12 weeks and (if extended rapid virologic response achieved): peg-interferon and ribavirin for another 12 weeks (total 24 weeks) If not: peg-interferon and ribavirin for another 36 weeks (total 48 weeks)	Overall 79% Genotype 1a 70% Genotype 1b 86%
			Placebo + peg-interferon and ribavirin for 48 weeks	Overall 37% Genotype 1a 28% Genotype 1b 43%
ASPIRE[27]	2	Failed prior therapy with peg-interferon and ribavirin	Simeprevir 100 mg or 150 mg daily for 12, 24, or 48 weeks + peg-interferon and ribavirin for 48 weeks	Overall at 24 weeks 61%–80% In prior relapsers 77%–89% In prior partial responders 48%–86% In prior null responders 38%–59%
			Placebo + peg-interferon and ribavirin for 48 weeks	23%

Simeprevir vs other direct-acting antiviral drugs

Advantages of simeprevir over the earlier protease inhibitors include once-daily dosing, a lower rate of adverse events (the most common being fatigue, headache, rash, photosensitivity, and pruritus), a lower likelihood of discontinuation because of adverse events, and fewer drug-drug interactions (since it is a weak inhibitor of the CYP3A4 enzyme).

Simeprevir was FDA-approved for HCV genotype 1 and in combination with interferon alfa and ribavirin. Compared with sofosbuvir, the treatment duration with simeprevir regimens is longer overall (interferon alfa and ribavirin are given for 12 weeks in sofosbuvir-based regimens vs 24 to 48 weeks with simeprevir). As with sofosbuvir, the estimated cost of simeprevir is high, about $66,000 for a 12-week course.

Simeprevir dosage and indications

Simeprevir was approved at an oral dose of 150 mg once daily in combination with ribavirin and interferon alfa in patients with HCV genotype 1 (**table 8**).

Table 8: Approved regimens of simeprevir for HCV genotype 1

Approved regimens of simeprevir for HCV genotype 1

Patient group	Regimen	Duration
Previously untreated and prior relapsers	Simeprevir 150 mg once daily, peg-interferon alfa 180 μg once weekly, and ribavirin 1,000 mg (if < 75 kg) or 1,200 mg (if ≥ 75 kg) daily in two divided doses for 12 weeks, then peg-interferon alfa and ribavirin alone for an additional 12 weeks	24 weeks
Prior partial responders and nonresponders	Simeprevir with peg-interferon alfa and ribavirin for 12 weeks, then peg-interferon alfa and ribavirin alone for an additional 36 weeks	48 weeks

The approved regimens for simeprevir are fixed in total duration based on the patient's treatment history. Specifically, all patients receive the drug in combination with peg-interferon and ribavirin for 12 weeks. Then, previously untreated patients and prior relapsers continue to receive peg-interferon and ribavirin alone for another 12 weeks, and patients infected with HCV genotype 1a should be screened for the NS3 Q80K polymorphism at baseline, as it has been associated with substantially reduced response to simeprevir.

Preliminary data also indicate efficacy in patients infected with HCV genotype 4 ***(Robert et al., 2014)***.

Sofosbuvir and simeprevir in combination

The COSMOS trial. ***(Jacobson et al., 2013)*** Given their differences in mechanism of action, sofosbuvir and simeprevir are being tested in combination. The COSMOS trial is an ongoing phase 2 randomized open-label study investigating the efficacy and safety of simeprevir and sofosbuvir in combination with and without ribavirin in patients with HCV genotype 1, including nonresponders and those with cirrhosis. Early results are promising, with very high rates of sustained virologic response with the sofosbuvir-simeprevir combination (93% to 100%) and indicate that the addition of ribavirin might not be needed to achieve sustained virologic response in this patient population.

The future

The emergence of all-oral regimens for HCV treatment with increasingly sophisticated agents such as sofosbuvir and simeprevir will dramatically alter the management of HCV patients. In view of the improvement in sustained virologic response rates with these treatments, and since most HCV-infected persons have no symptoms, the US Centers for Disease Control and Prevention ***(Smith et al., 2012)*** recently recommended one-time testing of the cohort in which the prevalence of HCV infection is highest: all persons born between 1945 and 1965. This undoubtedly will increase the detection of this infection—and the number of new patients expecting treatment.

Future drugs promise further improvements (**table 9**) ***(Sulkowski et al., 2013; Pawlotsky, 2013; Yu et al., 2013; Aghemo and De Francesco, 2013; Liang and Ghany, 2013 and Flisiak et al., 2013)***. Advances in knowledge of the HCV molecular structure have led to the development of numerous direct-acting antiviral agents with very specific viral targets. A second wave of protease inhibitors and of nucleoside and nonnucleoside polymerase inhibitors will soon be available. Inhibitors of NS5A (a protein important in the assembly of the viral replication complex) such as daclatasvir and ledipasvir, are currently in phase 3 clinical trials. Other viral proteins involved in assembly of the virus, including the core protein and p7, are being explored as drug targets. In addition, inhibiting host targets such as cyclophilin A and miR122 has gained traction recently, with specific agents currently in phase 2 and 3 clinical trials.

Table 9: Direct-acting antiviral drugs for hepatitis C virus infection in clinical development

Direct-acting antiviral drugs for hepatitis C virus infection in clinical development

INHIBITORS OF VIRAL TARGETS

NS3 protease inhibitors
Danoprevir, faldaprevir, asunaprevir, sovaprevir, vaniprevir, GS-9451, GS-9256, ABT-450, MK-5172, BILN-2061, ACH-2684

NS4B inhibitors
Clemizole, silibinin

NS5A inhibitors
Daclatasvir, ledipasvir, ABT-267, GSK-2336805, ACH-2928, BMS824393, IDX719, PPI-461, PPI-668, ACH-3102, MK-8742

NS5B nucleoside inhibitors
Mericitabine, ALS-2200

NS5B Non-nucleoside inhibitors
Tegobuvir, filibuvir, lomibuvir, setrobuvir, MK-3281, GS-9669, BI-207127, TMC-647055, BMS-791325

INHIBITORS OF HOST TARGETS

Cyclophilin A inhibitors
Cyclosporin A, alisporivir, NIM811, SCY-635

MiR122 inhibitors
Miravirsen

Entry inhibitors
ITX5061

Factors that previously were major determinants of response to treatment, such as *IL28B* genotype, viral load, race, age, extent of fibrosis, and genotype 1 subtypes, will become much less important with the introduction of highly potent direct-acting antiviral agents.

Many all-oral combinations are being evaluated in clinical trials. For example, the open-label, phase 2 **LONESTAR** trial tested the utility of combining sofosbuvir and ledipasvir (an NS5A inhibitor) with and without ribavirin for 8 or 12 weeks in previously untreated patients with HCV genotype 1, and for 12 weeks in patients with HCV genotype 1 who did not achieve a sustained virologic response after receiving a protease inhibitor-based regimen (half of whom had compensated cirrhosis) ***(Lawitz et al, 2013)***. Sustained virologic response rates were very high (95% to 100%) in both previously treated and previously untreated patients, including those with cirrhosis. Similar rates were achieved by the 8-week and 12-week groups in noncirrhotic patients who had not been previously treated for HCV. The typical hematologic abnormalities associated with interferon were not observed except for mild anemia in patients who received ribavirin. These results suggest that the combination of sofosbuvir and ledipasvir could offer a very effective, short, all-oral treatment for patients with HCV genotype 1, including those with cirrhosis, who up to now have been difficult to treat.

Table 10: Therapeutic options likely to be available in 2014-2015 *(Robert et al., 2014)*

HCV Therapeutic Options Likely to Be Available in 2014–2015

HCV genotype 1	Simeprevir + pegylated IFNα + ribavirin	24–48 weeks
	Sofosbuvir + pegylated IFNα + ribavirin	12 weeks
	Faldaprevir + pegylated IFNα + ribavirin	24–48 weeks
	Daclatasvir + pegylated IFNα + ribavirin	24 weeks
	Asunaprevir + daclatasvir + pegylated IFNα + ribavirin	24 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation
	ABT-450/r + ombitasvir + dasabuvir ± ribavirin	12 weeks
	Sofosbuvir + simeprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + faldaprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12–24 weeks
	Sofosbuvir + ledipasvir fixed dose combination ± ribavirin	8–12 weeks
HCV genotype 2	Sofosbuvir + ribavirin	12–16 weeks
HCV genotype 3	Sofosbuvir + pegylated IFNα + ribavirin (off-label in the United States)	12 weeks
	Sofosbuvir + ribavirin	24 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12 weeks
HCV genotype 4	Sofosbuvir + pegylated IFNα + ribavirin	12 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation
	Simeprevir + pegylated IFNα + ribavirin (off-label?)	24–48 weeks
	Sofosbuvir + simeprevir ± ribavirin (off label?)	12 weeks
	Sofosbuvir + daclatasvir ± ribavirin (off label?)	12–24 weeks
	Sofosbuvir + ledipasvir fixed dose combination ± ribavirin	8–12 weeks
HCV genotypes 5 and 6	Sofosbuvir + pegylated IFNα + ribavirin (off-label in the United States)	12 weeks
	Sofosbuvir + ribavirin (IFN-intolerant/ineligible, pretransplant)	24 weeks, up to transplantation

NOTE. Off-label use was dependent on local interpretation of the label.
/r, ritonavir-boosted.

Challenges remaining

The success of sofosbuvir and simeprevir paves the way for interferon-free regimens ***(Drenth, 2013)***. For a long time, the treatment of HCV infection required close monitoring of patients while managing the side effects of interferon, but the current and emerging direct-acting antiviral agents will soon change this practice. Given the synergistic effects of combination therapy—targeting the virus at multiple locations, decreasing the likelihood of drug resistance, and improving efficacy—combination regimens seem to be the optimal solution to the HCV epidemic. Lower risk of side effects and shorter treatment duration will definitely improve the acceptance of any new regimen. New agents that act against conserved viral targets, thereby yielding activity across multiple genotypes, will be advantageous as well.

Comparing the rates of sustained virologic response of the different currently approved HCV treatment regimens. (**Table 11**)

Table (11): Overall rates of sustained virologic response of approved HCV treatment regimens

Overall rates of sustained virologic response of approved HCV treatment regimens

Treatment regimen	Overall rate of sustained virologic response
Peg-interferon alfa and ribavirin (for 24 to 48 weeks depending on HCV genotype)	56%
Telaprevir or boceprevir with peg-interferon alfa and ribavirin (in HCV genotype 1 for 24 to 48 weeks)	75%
Sofosbuvir with peg-interferon alfa and ribavirin (in HCV genotype 1 for 12 weeks)	90%
Sofosbuvir with peg-interferon alfa and ribavirin (in HCV genotype 4 for 12 weeks)	96%
Sofosbuvir with ribavirin (in HCV genotype 2 for 12 weeks)	95%
Sofosbuvir with ribavirin (in HCV genotype 3 for 24 weeks)	85%
Simeprevir with peg-interferon alfa and ribavirin (in HCV genotype 1 for 24 to 48 weeks)	80%

Clinical challenges remain, including the management of special patient populations for whom data are still limited.

These include patients with cirrhosis, chronic kidney disease, renal failure, and concurrent infection with human immunodeficiency virus, and patients who have undergone solid organ transplantation. Clinical trials are under way to evaluate the treatment options for these patients, who will likely need to wait for the emergence of additional agents before dramatic improvement in sustained virologic response rates may be expected ***(Casey and Lee, 2013)***.

As the treatment of HCV becomes simpler, safer, and more effective, primary care physicians will increasingly be expected to manage it. Difficult-to-treat patients, including the special populations above, will require specialist management and individualized treatment regimens, at least until better therapies are available. The high projected cost of the new agents may limit access, at least initially. However, the dramatic improvement in sustained virologic response rates and all that that implies in terms of decreased risk of advanced liver disease and its complications will undoubtedly make these therapies cost-effective ***(Afdhal et al., 2013)***.

SUBJECTS AND METHODS

- This retrospective study was done at the out patients hepatology clinic of al mabarra hospital at kafer el Dawar city at el behira governorate where 100 Egyptian HCV+ve (genotype4) patients where followed up retro-spectivly during their course of treatment by peg interferon(Reiferon 1.2)and ribavirin(Ribavirin400) between may 2011and may 2012.
- Before starting therapy patients were subjected to the following to select cases that are candidate for interferon and ribavirin therapy and to exclude cases that are contra indicated for such therapy :
  - Complete history taking .
  - Complete physical examination
  - Pelvi-abdominal ultra-sound : to exclude cases with decompensated liver cirrhosis (ascites- portal hypertention)
  - Liver biopsy :to assess degree of liver inflammation and fibrosis grade and to exclude other causes of liver cirrhosis.

- Upper GIT endoscopy: to exclude cases with portal hypertension manifested as Gastric or esophogeal varices or portal hypertensive grastropathy .
- Funds examination : to exclude possible retinal pathology .
- ECG: to exclude possible cardiac abnormalities .
- Laboratory investigations as follow:
  - HCV Ab and HCV PCR: to confirm chronic HCV infection .
  - HBS Ag : to exclude HBV infection.
  - ANA (Anti nuclear antibody), TSH (thyroid stimulating hormore): to exclude autoimmune diseases.
  - Fasting blood sugar, glycated haemoglobin (FBS, HBAIC): to exclude undiagnosed diabetes mellitus.
  - CBC (Complete blood count) : to exclude possible haematological abnormalities
  - Kidney function tests: blood urea nitrogen (BUN), S.creatinine.
  - Liver function tests including: ALT, AST, ALKP, GGT, .S. albumin, S. billrubin (total ,direct), prothrombin time and activity to exclude decompensated liver disease and other liver pathology .

- In our study we followed the study cases retro spectively during their course of therapy to determines changes in the following parameters as follow:
  1. Complete history taking with special emphasis on possible side effects of therapy .
  2. Complete physical examination to determine possible physical signs of attributed to therapy .
  3. The following laboratory parameters were followed to determine possible changes as follow:
     - PCR HCV at (3-6-12-18) months of treatment .
     - ALT, AST, S.billrubin ,ALKP,TSH at (3-6-12-18) months of treatment .
     - CBC at 2weeks- 4weeks then every 8weeks till the end of the treatment.

Methodology:

HCV PCR Methodology:

1. Purpose:

1.1 Roche COBAS Ampliprep COBAS Taqman (CAP-CTM) is an *IVD* nucleic acid amplification test for the quantitation of Hepatitis C Virus (HCV) RNA genotypes 1 through 6 in human serum or plasma

1.2 Specimen preparation is automated using the COBAS AmpliPrep Instrument with automated amplification and detection using the COBAS TaqMan 48 Analyzer.

2. Principle of the procedure:

2.1. The COBAS AmpliPrep/COBAS TaqMan HCV Test is based on three major processes: (1) Automated specimen preparation; (2) Automated reverse transcription to generate complementary DNA (cDNA), and (3) Automated PCR amplification and detection of HCV target RNA and HCV Quantitation Standard (QS) Armored RNA.

2.2. The COBAS® TaqMan® HCV test, uses reverse transcription and PCR amplification primers that define a sequence within the highly conserved 5'-untranslated region of the HCV genome.

2.3. The Master Mix reagent contains primers and probes specific for both HCV RNA and HCV QS RNA. The detection of amplified DNA is performed using a target-specific and a QS-specific dual-labeled oligonucleotide probe that permit independent identification of HCV amplicon and HCV QS amplicon.

2.4. The quantitation of HCV viral RNA is performed using the HCV Quantitation Standard(QS) which is a non-infectious Armored RNA construct , it contains the HCV sequences with identical primer binding sites as the HCV RNA target and a unique probe binding region that allows HCV QS amplicon to be distinguished from HCV target amplicon. The HCV QS is incorporated into each individual sample and control at a known copy number and is carried through the sample preparation, reverse transcription, PCR amplification and detection steps along with the HCV target.

2.5. The COBAS® TaqMan® 48 Analyzer calculates the HCV RNA titer in the test samples by comparing the HCV signal to the HCV QS signal for each sample and control.

2.6. The HCV QS compensates for effects of inhibition and controls for the preparation and amplification processes to allow the accurate quantitation of HCV RNA in each sample.

3. Sample collection and storage:

- Serum or EDTA plasma are accepted
- Blood is collected in gel separation tubes or in lavender top EDTA tubes.

- Store whole blood at 2-25^{0}C for no longer than 6 hours from collection time.
- Separate serum or plasma from whole blood within 6 hours of collection by centrifugation for 20 minutes at room temperature.
- Separated serum or plasma can be stored at 4ºC for up to 72 hours and at -20 ºC for up to 6 weeks.
- Minimum volume required is 650 ul serum or plasma.
- Frozen samples must not be thawed more than twice.
- For each patient, additional serum aliquot will be stored at -20ºC for 2 weeks before being discarded.

CBC Methodology:

CBC is performed on a fully automated 5 parts differential cell counter (Advia, Siemens)

AST, ALT, Alkaline phosphatase methodology:

The 3 enzymes were performed using an enzymatic kinetic method, on the fully automated Cobas e6000 analyzer from Roche diagnostics

Bilirubin methodology:

It was performed using a fully automated colorimetric test on Cobas e6000 analyzer from Roche diagnostics

TSH methodology:

It was performed using an electrochemiluminescence technique, on the Cobas e6000 analyzer from Roche diagnostics.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM *SPSS software package version 20.0.* Qualitative data were described using number and percent. Quantitative data were described using Range (minimum and maximum), mean and standard deviation. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between two independent population were done using independent t-test while more than two population were analyzed F-test (ANOVA) to be used, also paired t-test is used to analyse two paired data. Significance of the obtained results was judged at the 5% level.

CASES OF THE STUDY

NO: 1 Non Responder age: 58y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
2.6 X 10^{6}	6.6 X 10^{5}	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
39 42	43 55	----	-----	-----	1.2 0.2	1.1 0.1	-----	-----	-----	68	66	-----	-----	-----	0.9	1.2	-----	-----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	17.3 186 4.6	14.6 144 4	14.6 135 3.6	14 108 2.9	-----	-----	-----	-----

Side effects: Flu like symptoms

NO: 2 Relapse age: 47y Male

PCR				
Basal	3m	6m	12m	18m
3.9×10^6	- ve	- ve	- ve	+ve 2.8×10^4

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
92 35	62 40	75 49	45 43	55 38	1 0.2	0.6 0.1	0.6 0.1	0.43 0.1	0.82 0.3	88	119	95	110	115	1.9	1.8	2.3	2.8	2.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	15.6	11.2	10.7	9.9	10	10.3	9.6	15.0
PLT	174	166	160	151	133	127	130	133
WBC	8.6	6.2	5.5	4.5	4.2	3.6	3.1	2.6

Side effects: Flu like symptoms
Fatigue

NO: 3 **Relapse** **age: 33y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.8 X 10^4	- ve	- ve	- ve	+ve 3.5 X 10^5

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
183 89	38 35	27 37	36 41	45 52	1.1 0.1	0.9 0.1	1 0.3	1 0.4	1.3 0.2	112	101	95	133	89	1.0	1.3	1.4	0.9	1.2

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	15.6	14.2	13.1	13.7	10.8	12.6	9.4	11.2
PLT	218	195	176	214	188	192	200	245
WBC	6.9	6.4	6.2	6.5	5.2	4.5	5.7	6.3

Side effects: Flu like symptoms
Fatigue

NO: 4 **S.V.R** **age: 48y** **Male**

PCR				
Basal	3m	6m	12m	18m
8.4×10^4	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
34 34	51 50	11 0.5	29 18	20 13	0.7 0.1	0.3 0.30	1.4 2.2	1.4 0.1	1.0 0.3	125	144	130	155	93	0.46	6.53	1.2	1.4	0.55

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	15.8	13.2	11.9	10.3	11.5	13.8	14.2	14.7
PLT	186	163	149	99	153	166	170	188
WBC	8.8	6.2	4.3	4.2	5.0	5.3	7.2	7.6

Side effects: **Flu like symptoms**
Fatigue

NO: 5 Relapse age: 55y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
1.6 X 10^6	4 X 10^3	-ve	-ve	+ ve 5.7 X 10^4

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
155 150	36 29	35 38	44 131	113 56	1.1 0.2	0.5 0.3	0.6 0.3	1.2 0.3	1.1 0.1	109	155	83	99	111	1.1	1.3	2.3	1.1	1.3

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	14.7 131 7.2	14.5 195 8.8	14.7 211 9.2	9 195 2.3	10.2 183 2.9	11.5 195 3.2	13.2 210 6.0	13.0 200 6.9

Side effects: Flu like symptoms

NO: 6 break throught at 24 age: 54y Male

PCR				
Basal	3m	6m	12m	18m
3.6×10^5	- ve	2.6×10^5	---------	-----------

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
154 73	96 45	138 55	------	------	0.5	0.8	0.7	-----	-----	79	88	81	-----	-----	1.3	2.8	1.4	-----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.2 794 4.9	13.2 173 4.2	12.5 154 3.5	11.1 153 4.1	13.2 153 3.4	--------	-----------	-----------

Side effects: Flu like symptoms

NO: 7 **relapse** **age: 47y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.1 X 10^6	- ve	- ve	- ve	+ ve 9.1 X 10^5

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
12 10	60 38	61 34	76 48	66 33	0.6 0.1	0.9 0.1	1.1 0.1	1.3 0.3	0.9 0.1	109	119	78	86	143	0.3	0.3	1.2	1.8	0.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.0 290 6	14.9 275 5.3	14.7 322 6.6	13.3 419 5.5	13.0 300 5.0	12.2 377 4.7	13.7 439 5.9	14.8 403 6.3

Side effects: **Flu like symptoms**
Fatigue

NO: 8 **S.V.R** **age: 47y** **Male**

PCR				
Basal	3m	6m	12m	18m
2.3×10^4	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
54 89	144 126	95 44	62 66	27 39	0.9 0.2	0.6 0.1	0.8 0.1	1.0 0.4	0.9 0.2	121	137	133	55	79	0.9	1.2	1.6	1.9	0.8

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14 118 4.7	13 110 5.6	13 76 4.7	9.9 108 3	8.1 83 3.5	9.4 69 3	10.4 57 2.9	10 79 2.7

Side effects: **Flu like symptoms**
Fatigue

NO: 9 S.V.R age: 53y Male

PCR				
Basal	3m	6m	12m	18m
5.4×10^4	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
45 30	69 45	55 33	44 47	38 42	0.3 0.51	0.6 0.1	1.1 0.3	0.4 0.03	1.0 0.3	155	133	87	58	150	2.5	7.3	9.3	11.2	4.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.3	12.0	11.1	9.3	8.6	10.2	11.1	13.4
PLT	234	267	307	281	211	244	258	230
WBC	4.3	3.7	3.1	2.6	2	1.9	1.7	1.9

Side effects: Flu like symptoms
Hypothyroidism

NO: 10 **S.V.R** **age: 43y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
2.4×10^6	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
23 31	29 24	22 31	37 31	25 18	0.5 0.02	0.3 0.1	1.4 0.3	1.2 0.06	0.6 0.1	91	98	102	133	95	0.9	1.0	1.2	0.8	0.8

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	15.1	14.7	14.3	13.8	12.0	9.2	10.7	11.5
PLT	277	260	265	211	197	251	278	290
WBC	7.5	7.1	6.7	6.2	5.4	6.6	7.3	7.9

Side effects: **Flu like symptoms**
Bronchitis with spasm

NO: 11 S.V.R age: 32y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
2.1×10^5	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
74 40	80 43	99 55	66 33	35 23	1.3 0.1	1.2 0.09	0.9 0.1	1.0 0.4	0.7 0.2	68	66	57	76	77	1.8	1.9	1.8	1.8	1.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	16.5	11.2	9.2	8.0	10.3	12.2	12.4	14.5
PLT	216	199	187	177	198	218	230	277
WBC	5.7	5.1	4.4	4.4	4.0	4.7	4.6	4.9

Side effects: Flu like symptoms
Fatigue

NO: 12 S.V.R age: 45 y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
1.7 X 10^6	- ve	- ve	- ve	- ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
28 13	33 18	39 31	22 32	17 20	0.5 0.3	0.8 0.2	1.2 0.1	1.9 0.02	0.7 0.2	112	138	133	137	111	1.2	1.7	1.5	1.1	0.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	15.5	12.3	8.9	8.2	10.2	11.0	13.7	14.2
PLT	257	233	198	196	175	210	237	255
WBC	9.2	8.7	7.0	6.2	6.2	8.0	8.0	8.3

Side effects: Flu like symptoms
Arthralgia

NO: 13 Non responder age: 47y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
4.2×10^{7}	3.1×10^{6}	----	----	----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
31 28	32 17	----	-----	----	1.25 0.5	1.1 0.5	-----	-----	------	116	112	----	-------	-----	2.4	3.1	-----	-------	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	13.20 233 7.2	13.1 233 7.1	12.7 197 9.2	11.0 188 9.0	--------------	---------	--------	----------

Side effects: Flu like symptoms
Fatigue

NO: 14 S.V.R age: 57y Female

PCR				
Basal	3m	6m	12m	18m
4.3×10^5	- ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
53 41	55 31	40 42	44 31	37 18	1.20 0.02	1.30 0.03	1.20 0.03	1.40 0.2	1.01 0.1	78	77	67	73	98	1.4	1.4	1.3	1.7	2.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.7	14.3	12.2	9.4	8.7	8.5	10.0	11.2
PLT	166	157	177	163	177	166	189	203
WBC	5.2	5.0	4.2	4.0	3.2	3.2	4.3	4.7

Side effects: Flu like symptoms
Fatigue
Dizziness

NO: 15 **Stopped treatment at 24 w** **age: 53y** **Male**

PCR				
Basal	3m	6m	12m	18m
2.3×10^4	-ve	-ve	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
41 31	43 35	----	-----	-----	0.6 0.03	0.7 0.1	---	------	------	128	137	------	-------	------	0.7	1.2	-----	-------	-------

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.7 230 4.1	12.3 210 4.0	9.1 188 3.8	9.0 187 3.2	8.7 192 3.4	-------------	-------------	-------

Side effects: Flu like symptoms
Sever fatigue
Stopped treatment at 24 w due to sever incapacitating fatigue

NO: 16 **S.V.R** **age: 55y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.6×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
50 42	43 29	20 18	26 25	27 18	0.6 0.02	0.6 0.02	0.7 0.01	0.4 0.03	0.4 0.03	75	77	87	115	94	1.5	1.3	1.9	2.1	1.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.8 206 8.1	13.2 199 7.2	11.7 159 5	10.6 143 3.8	10.6 164 2.3	10.3 155 2.3	11.6 177 3.4	11.9 199 4.2

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 17 **S.V.R** **age: 53y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.8X 10^6	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
61 50	75 43	73 45	45 33	42 25	0.9 0.03	1.0 0.02	1.2 0.01	1.0 0.03	1.3 0.03	112	119	93	84	84	1.2	1.3	1.6	2.3	1.8

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	14.6 170 4.8	13.8 198 5	14.0 187 4.9	14.3 180 5	14.9 183 5	14.5 163 5.3	11.7 144 2.8	11.9 160 2.9

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 18 **S.V.R** **age: 40y** **Male**

PCR				
Basal	3m	6m	12m	18m
127.000	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
27 28	33 14	37 15	31 21	31 25	0.6 0.01	1.0 0.02	1.2 0.01	1.2 0.02	0.9 0.03	90	98	87	112	127	2.5	2.5	2.3	2.7	2.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	5.6	13.2	10.3	10.0	9.4	8.3	11.3	12.0
PLT	208	210	260	197	139	159	195	219
WBC	7.4	6.5	6.3	6.1	4.3	4.1	4.2	4.0

Side effects: **Flu like symptoms**
Fatigue
Headache

NO: 19 S.V.R age: 48y Female

PCR				
Basal	3m	6m	12m	18m
607.652	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
117 95	102 83	79 47	44 36	32 27	0.5 0.01	0.7 0.01	0.4 0.02	0.6 0.01	0.6 0.03	56	53	64	68	58	2.89	2.9	1.7	1.8	2.01

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.6 201 5.4	11.3 187 5.2	9.2 172 4.8	8.0 167 4.9	8.0 169 3.4	8.4 198 4.7	9.79 210 5.1	10.2 233 5.1

Side effects: Flu like symptoms
Fatigue

NO: 20 S.V.R age: 32y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
861.123	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
36 38	39 42	43 37	43 25	43 23	1.02 0.02	1.03 0.02	1.2 0.01	0.9 0.03	1.02 0.04	86	88	90	113	93	2.4	2.2	1.7	1.9	108

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	16.3 263 8.3	16.6 215 7.7	14.0 198 7.2	13.3 757 5.7	11.4 238 5.1	9.9 210 4.8	11.7 730 4.9	11.8 279 5.7

Side effects: **Flu like symptoms**
Fatigue

NO: 21 **S.V.R** **age: 29y** **Male**

PCR				
Basal	3m	6m	12m	18m
468.000	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
51 22	66 33	42 35	41 32	40 32	1.1 0.5	1.2 0.05	1.03 0.01	1.07 0.2	1.0 0.1	62	76	68	77	65	2.3	2.7	3.0	3.4	311

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.4 244 10	15.0 197 6.2	15.2 174 3.9	13.7 188 3.7	13.5 172 2.9	12.5 207 2.9	11.9 200 3.5	11.0 213 5.2

Side effects: Flu like symptoms
Fatigue

NO: 22 **S.V.R** **age: 45y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
172.073	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
41 39	43 33	41 25	47 28	42 27	0.7 0.18	0.7 0.19	0.7 0.13	1.1 0.02	0.9 0.03	97	93	101	85	95	2.1	2.3	2.4	1.9	1.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	14.6 269 4.8	14.2 215 4.2	13.0 247 5.0	13.8 337 5.2	13.5 294 5.9	13.8 291 5.3	14.0 313 5.7	14.5 340 5.0

Side effects: **Flu like symptoms**
Fatigue
Body aches

NO: 23 **Relapse** **age: 53y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
2.3×10^5	-ve	-ve	-ve	+ve 1.3×10^4

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 91	37 97	35 35	33 27	133 76	0.8 0.01	0.9 0.02	1.7 0.1	1.3 0.1	0.8 0.09	290	211	137	119	133	1.6	2.7	1.45	2.0	2.1

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	12.3	11.0	9.7	8.2	9.5	10.0	11.0	11.7
PLT	164	153	140	197	213	256	230	277
WBC	4.2	3.7	3.8	3.8	4.3	4.3	4.0	4.11

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 24 **S.V.R** **age: 53y** **Female**

PCR				
Basal	3m	6m	12m	18m
3.4×10^5 343507	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
63 31	81 42	77 33	45 33	40 37	0.8 0.02	0.8 0.01	1.2 0.01	1.2 0.02	0.9 0.01	129	132	130	116	123	1.4	1.3	2.4	2.2	1.8

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.4 169 7.3	12 269	12.5 279 8.6	11.9 288	11.9 293 7.8	11.4 203 5.8	9.7 707 7.1	9.1 157 6.0

Side effects: **Flu like symptoms**
Fatigue
Body aches

NO: 25 **S.V.R** **age: 53y** **Female**

PCR				
Basal	3m	6m	12m	18m
46769 4.6×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
76 47	62 33	45 43	42 41	41 29	0.4 0.01	0.5 0.02	0.5 0.03	0.6 0.03	0.6 0.03	112	113	117	122	104	3.5	3.7	3.5	2.9	2.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.9	14.0	4.4	12.7	12.0	12.1	10.4	11.6
PLT	169	168	162	167	167	175	129	131
WBC	5.1	4.2	4	5.4	5	4.4	3.4	3.1

Side effects: **Flu like symptoms**
Fatigue
Dizziness
Nausea

NO: 26 **S.V.R** **age: 48y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
6.2×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
53 33	56 42	41 23	42 27	39 29	1.01 0.03	1.02 0.07	0.9 0.03	0.9 0.08	0.9 0.1	153	156	153	155	155	2.1	2.1	3.4	3.2	2.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	15.3	12.0	9.6	9.4	8.9	10.8	11.6	11.9
PLT	246	233	211	169	198	201	233	246
WBC	5.4	5.4	5.1	9.6	4.3	4.5	5.2	5.3

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 27 **S.V.R** **age: 22y** **Male**

PCR				
Basal	3m	6m	12m	18m
7.2 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
32 27	32 23	44 35	41 18	31 29	0.6 0.08	0.7 0.03	0.6 0.08	1.1 0.1	1.1 0.2	56	68	57	66	68	1.8	1.9	1.8	2.1	2.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.0	13.7	12.7	13.2	11.0	10.2	12.7	13.0
PLT	193	239	232	195	177	219	235	264
WBC	12.5	8	3.6	3.9	3.2	4.7	5.9	7.2

Side effects: **Flu like symptoms**
Fatigue
Headache

NO: 28 **Non responder** **age: 40y** **Male**

PCR				
Basal	3m	6m	12m	18m
2.1×10^{6} 2144584	7.7×10^{5} 773390	-	-	-

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
78 95	66 83	----	-----	-----	0.8 0.07	0.9 0.03	----	-----	----	88	97	----	----	----	3.2	3.7	----	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.8 258 4.5	12.5 304 401	10.1 346 6.2	8.2 389 5.5	--------	----------	--------	

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 29 **S.V.R** **age: 54y** **Male**

PCR				
Basal	3m	6m	12m	18m
8.4×10^5 847574	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
43 37	45 33	42 13	37 17	32 18	0.5 0.08	0.7 0.01	0.7 0.02	0.9 0.1	1.1 0.1	73	77	82	73	75	1.9	1.8	1.6	1.2	1.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	16.4	13.0	12.2	10.5	9.5	9.7	10.0	12.3
PLT	142	133	96	82	104	138	166	195
WBC	6.8	6.2	6.1	5.6	6.3	6.6	7.0	7.0

Side effects: **Flu like symptoms**
Fatigue
Nausea

NO: 30 **S.V.R** **age: 33y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
246.660 2.4 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
34 31	37 28	42 27	33 17	31 28	1.04 0.01	1.1 0.08	1.1 0.09	1.2 0.1	0.9 0.03	133	121	134	97	138	2.0	2.1	2.7	2.0	1.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	14.2	11.6	11.6	12.5	11.7	11.1	12.7	13.6
PLT	229	209	205	189	163	185	199	205
WBC	5.7	6	6.1	5.5	3.2	3.3	3.4	4.1

Side effects: **Flu like symptoms**
Fatigue
Headache

NO: 31 **S.V.R** **age: 48y** **Female**

PCR				
Basal	3m	6m	12m	18m
3.6×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
27 16	46 28	33 31	31 22	16 28	1.3 0.03	1.5 0.09	1.6 0.1	0.9 0.1	1.2 0.02	56	58	66	69	64	2.3	2.4	2.7	20	1.8

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.9 239 5.2	11.6 237 5.1	10.0 144 5.3	8.7 154 4.3	9.2 230 4.0	11.8 237 4.1	11.9 233 4.0	12.1 241 4.5

Side effects: **Flu like symptoms**
Nausea

NO: 32 **S.V.R** **age: 52y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.4×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
32 27	44 53	37 32	31 18	57 48	0.9 0.1	1.0 0.1	1.6 0.09	1.6 0.2	1.6 0.3	133	127	135	138	140	0.5	0.6	0.5	1.1	1.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.6	10.2	10.1	9.3	10.8	11.0	11.6	11.6
PLT	133	154	121	96	134	135	133	117
WBC	6.4	6.0	6.0	6.2	5.9	5.2	4.7	4.0

Side effects: **Flu like symptoms**
Fatigue
Arthralgia
Weight loss

NO: 33 **Non responder** **age: 46y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.3×10^6	2.5×10^7	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
36 33	75 46	-----	-----	-----	0.8 0.01	1.1 0.04	----	----	----	83	87	-----	------	----	1.6	1.9	----	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.0 177 7.6	10.6 158 7.1	9.2 143 6.8	9.1 157 6.1	--------	------	------	------

Side effects: **Flu like symptoms**
Fatigue
Arthralgia
Rash

NO: 34 Stopped treatment at 24 w age: 32y Female

PCR				
Basal	3m	6m	12m	18m
$1.6 X 10^4$	-ve	-ve	----	----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
41 38	57 42	31 17	----	---	1.1 0.1	1.6 0.2	1.9 0.2	----	----	144	137	133	----	----	0.4	0.4	0.3	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	10.7 247 4.7	9.2 230 4.3	9.1 211 3.1	8.5 198 3.9	8.5 187 3.8	------	------	------

Side effects: Flu like symptoms
Fatigue

Stopped treatment at 24 w due to sever fatigue

NO: 35 **S.V.R** **age: 48y** **Male**

PCR				
Basal	3m	6m	12m	18m
$7.4X\ 10^5$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
37 32	43 41	57 43	38 17	27 18	0.9 0.08	1.3 0.1	1.6 0.1	1.5 0.2	1.4 0.2	89	82	79	83	87	1.9	1.8	1.9	1.9	2.1

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.0 179 8.3	11.7 142 8.3	9.2 155 7.4	8.7 159 6.1	9.1 167 6.1	11.1 166 6.0	11.8 188 6.0	12.0 182 6.0

Side effects: **Flu like symptoms**
Fatigue
Nausea .
Rash

NO: 36 **S.V.R** **age: 52y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.3×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
32 11	43 31	65 42	31 27	33 16	0.7 0.1	1.2 0.1	1.7 0.2	1.7 0.2	1.8 0.3	117	122	124	119	112	0.9	0.9	0.8	0.9	0.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.7 199 7.1	12.1 210 6.8	10.2 187 6.8	9.7 183 5.0	9.7 190 5.2	10.8 211 5.9	11.3 233 6.1	12.0 241 6.0

Side effects: **Flu like symptoms**
Fatigue
Arthralgia

NO: 37 **S.V.R** **age: 58y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
1.9×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
41 36	58 44	33 21	17 15	22 11	0.5 0.09	0.9 0.1	1.5 0.08	1.5 0.08	13 0.03	83	86	91	87	93	2.1	2.1	3.2	3.4	2.7

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	14.0 302 7.8	12.7 263 6.2	11.2 251 5.0	9.5 279 5.1	10.8 286 4.3	10.8 288 5.2	11.6 290 5.8	12.3 297 5.9

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 38 S.V.R age: 38y Female

PCR				
Basal	3m	6m	12m	18m
1.3×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
53 41	66 52	32 16	21 26	12 11	0.7 0.03	0.9 0.03	1.3 0.1	1.6 0.08	1.6 0.08	56	53	57	16	57	1.7	1.7	1.8	1.7	1.8

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	10.5 277 4.9	8.9 256 4.7	8.1 241 3.8	8.1 203 3.9	9.3 247 4.1	9.7 232 4.5	9.7 244 5.1	10.2 251 5.3

Side effects : Flu like symptoms
Fatigue
Arthralgia

NO: 39 **S.V.R** **age: 49y** **Male**

PCR				
Basal	3m	6m	12m	18m
6.3×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 17	43 28	77 51	41 28	33 17	1.2 0.1	1.2 0.1	1.3 0.13	1.6 0.15	1.9 0.13	114	114	113	101	107	5.7	5.7	5.7	5.9	5.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.3	11.2	9.6	9.3	10.8	11.0	11.0	11.3
PLT	168	161	163	142	134	152	168	179
WBC	6.9	6.1	6.1	6.5	6.8	7.2	7.2	7.2

Side effects : Flu like symptoms
Fatigue
Nausea
Rash

NO: 40 **Relapse** **age: 45y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.2×10^6	5.3×10^5	-ve	-ve	+ve 4.1×10^6

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
66 41	93 102	32 31	17 12	132 87	0.9 0.09	1.2 0.1	1.2 0.1	1.7 0.07	0.9 0.07	93	97	92	88	87	2.7	2.7	2.9	2.1	2.1

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	19.0 293 8.1	12.3 277 8.1	10.1 268 7.4	8.7 214 6.3	9.0 234 6.2	10.8 261 6.8	11.2 262 7.3	11.4 281 7.1

Side effects : Flu like symptoms
Fatigue
Arthralgia . nausea
Rash

NO: 41 **S.V.R** **age: 42y** **Female**

PCR				
Basal	3m	6m	12m	18m
1.6×10^3	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 26	57 63	41 27	23 14	23 16	1.2 0.03	1.4 0.09	1.7 0.17	1.7 0.18	1.8 0.19	52	57	52	51	50	0.9	0.9	0.8	0.9	.9 1

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.3 133 4.7	10.7 127 4.3	9.5 122 4.1	9.3 111 3.8	10.1 123 3.2	10.3 125 3.0	10.3 130 3.1	10.9 137 3.8

Side effects : Flu like symptoms
Fatigue
Vomiting

NO: 42 **S.V.R** **age: 56y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.2×10^{6}	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 27	52 47	41 37	27 22	19 12	0.6 0.09	0.9 0.13	1.3 0.17	1.9 0.17	1.2 0.2	113	117	117	113	112	2.4	2.1	2.2	2.1	2.1

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.6	13.0	11.2	9.7	10.3	10.4	10.5	10.5
PLT	213	201	197	172	199	210	203	234
WBC	7.2	7.2	7.0	6.4	6.1	5.8	6.3	6.3

Side effects : Flu like symptoms
Fatigue
Dizziness
Rash

NO: 43 **S.V.R** **age: 33y** **Female**

PCR				
Basal	3m	6m	12m	18m
$6.1 X 10^6$	$3.4 X 10^3$	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 27	82 47	47 32	33 28	17 11	1.2 0.1	1.7 0.1	1.7 0.091	1.9 0.08	1.1 0.1	74	76	71	70	77	0.8	0.8	0.7	0.9	1.3

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	10.7	10.3	9.5	9.3	9.7	10.2	10.2	10.2
PLT	341	303	318	309	211	277	301	300
WBC	4.5	4.5	4.2	3.9	4.1	4.1	4.0	4.0

Side effects : Flu like symptoms
Fatigue
Rash
Nausea

NO: 44 **S.V.R** **age: 52y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
1.6 X 10^6	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
110 82	197 103	63 52	37 21	22 17	1.1 0.09	1.5 0.1	1.6 0.1	1.9 0.2	1.3 0.08	88	88	86	91	86	2.2	2.2	2.7	2.5	2.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.0 183 5.4	13.2 166 5.4	11.1 147 5.1	10.1 132 5.0	11.3 157 4.7	12.9 173 4.9	12.8 177 4.9	13.1 187 5.0

Side effects : Flu like symptoms
Fatigue
Rash
Headache

NO: 45 **Relapse** **age: 58y** **Male**

PCR				
Basal	3m	6m	12m	18m
9.7 X 10^8	2.1 X 10^4	-ve	-ve	+ve 3.9 X 10^6

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 27	51 39	41 32	31 27	117 93	1.3 0.1	1.3 0.1	1.9 0..2	1.7 0.2	1.3 0.2	113	117	112	111	119	0.7	0.7	0.9	1.2	1.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.7 347 6.6	12.1 313 6.1	10.5 299 6.1	10.1 274 5.7	10.7 281 5.2	11.3 302 5.9	11.3 309 6.0	11.3 317 6.0

Side effects : Flu like symptoms
Fatigue
Headache
Dizziness

NO: 46 **S.V.R** **age: 53y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.6 X 10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
39 21	77 54	42 38	34 17	28 12	0.9 0.02	1.1 0.02	1.6 0.09	1.7 0.07	1.7 0.1	77	72	69	71	77	1.9	1.8	1.9	1.7	1.7

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	13.9 267 4.7	12.1 251 4.7	10.7 237 4.3	9.8 219 4.0	10.2 233 3.8	11.0 241 3.1	11.1 255 3.3	11.3 260 4.0

Side effects : Flu like symptoms
Fatigue
Vomiting
Rash

NO: 47 S.V.R age: 41 F

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
6.1 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
27 11	78 51	43 38	31 27	17 11	1.1 0.3	1.3 0.3	1.3 0.3	1.9 0.1	1.2 0.09	137	137	133	133	130	2.9	2.8	2.7	2.7	2.7

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	10.9 297 7.1	10.1 303 7.1	9.3 300 6.0	8.7 281 5.4	8.7 277 5.1	9.4 289 6.3	10.0 298 6.3	10.0 303 6.1

Side effects : Flu like symptoms
Fatigue
Rash

NO: 48 Stopped treatment at 30 w age: 56y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
6.9 X 10^3	-ve	-ve	----	----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
101 59	127 87	43 31	----	----	1.1 0.09	1.4 0.09	1.7 0.09	----	---	87	88	81	----	----	0.7	0.7	0.9	----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	14.0 147 4.7	13.2 148 4.7	12.0 133 4.3	11.3 112 4.1	11.7 121 4.0	12.1 137 4.0	------	----

Side effects : Flu like symptoms
Fatigue
Rash

Stopped treatment at 30 w due to right hemi plegia that started by gradual right hemi paresis

NO: 49 Break throught at 36w age: 36y Male

PCR				
Basal	3m	6m	12m	18m
6.4X 10^5	-ve	-ve	+ve 3.1 X 10^7	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
27 18	52 64	43 38	36 38	-----	0.5 0.08	0.9 0.08	0.9 0.1	1.3 0.1	----	92	91	91	97	----	1.7	1.7	1.9	2.0	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.1 139 7.2	12.0 114 7.2	10.3 89 6.8	9.1 77 5.3	10.1 123 5.9	10.0 131 5.9	10.3 133 5.2	----------- ----------- -----------

Side effects : Flu like symptoms
Fatigue
Rash
Vomiting
Headache

No: 50 **S.V.R** **age: 38y** **Female**

PCR				
Basal	3m	6m	12m	18m
7.1×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 18	77 49	52 41	38 27	18 12	1.1 0.09	1.3 0.09	1.7 0.1	1.6 0.1	1.2 0.1	113	111	118	118	113	2.3	2.3	2.9	2.8	2.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	10.1 93 3.8	10.0 93 3.7	8.2 87 3.0	8.5 81 3.0	8.5 99 3.1	8.9 98 3.9	9.6 107 4.1	9.3 133 4.1

Side effects: **Flu like symptoms**
Fatigue
Rash
Vomiting
Headache

NO: 51 **Relapse** **age: 52y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.4×10^5	9.3×10^3	-ve	-ve	+ve 7.2×10^6

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
44 31	52 47	40 38	27 11	53 47	1.0 0.08	1.1 0.1	1.3 0.1	1.3 0.09	1.8 0.1	83	81	80	77	82	0.9	0.9	1.1	1.1	1.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.8 307 5.2	12.0 300 5.1	11.0 283 5.1	9.8 271 5.0	9.7 206 4.3	10..2 241 4.0	10.7 268 4.0	11.0 298 4.1

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 52 **S.V.R** **age: 38y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.746.987	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 21	47 42	93 55	31 18	27 12	0.9 0.07	0.9 0.07	1.2 0.09	1.2 0.1	1.5 0.1	153	152	155	154	151	3.0	3.0	3.1	3.1	3.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.3	14.2	11.6	10.5	10.0	10.8	11.2	12.7
PLT	298	277	261	240	251	283	287	270
WBC	7.1	4.0	6.7	6.7	5.2	6.3	6.2	6.9

Side effects: **Flu like symptoms**
Fatigue
Headache
Gastritis

NO: 53 **S.V.R** **age: 32y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.9×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
61 52	116 89	73 31	22 18	12 19	0.8 0.07	0.8 0.07	1.3 0.1	1.5 0.1	1.3 0.1	99	91	98	97	93	1.3	1.3	1.3	1.4	1.4

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	10.7 155 5.9	9.3 143 5.2	9.0 132 4.3	8.3 117 3.2	9.7 128 3.4	9.8 133 3.1	10.1 147 3.8	10.0 158 3.7

Side effects: **Flu like symptoms**
Fatigue
Rash
Dizziness

NO: 54 **S.V.R** **age: 51y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.7 X 10^3	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 18	69 47	41 22	38 17	29 12	1.1 0.1	1.1 0.1	1.2 0.09	1.5 0.2	1.6 0.2	63	67	68	69	61	2.7	2.7	2.6	2.5	2.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	13.8	9.4	9.2	8.3	8.4	9.1	9.7	10.2
PLT	213	211	188	163	175	182	193	201
WBC	7.5	7.1	5.2	4.0	4.3	5.1	5.2	5.2

Side effects: **Flu like symptoms**
Fatigue . tinitus
Headache . rash
Gastritis

NO: 55 **S.V.R** **age: 47y** **Male**

PCR				
Basal	3m	6m	12m	18m
9.4 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
52 47	73 51	33 21	18 11	12 9	0.7 0.08	0.9 0.09	1.3 0.1	1.7 0.1	1.2 0.1	133	138	131	130	137	0.9	0.7	0.8	0.8	0.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.0 299 7.1	12.8 317 701	10.3 238 6.0	10.1 241 4.7	11.5 216 4.9	11.7 281 5.2	17.0 298 5.6	12.0 307 6.1

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 56 Non responder age: 42y Female

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.5×10^{7}	+ve 9.2×10^{6}	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
33 27	47 42	----	----	----	1.3 0.1	1.5 0.1	---	----	----	139	138	----	-----	----	1.4	1.7	---	-----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	11.0 241 3.8	10.3 233 3.1	9.3 219 2.9	9.3 221 2.7	-------	------	------	-----

Side effects: Flu like symptoms
Fatigue
Rash
Headache

NO: 57 **S.V.R** **age: 53y** **Female**

PCR				
Basal	3m	6m	12m	18m
1.2×10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
21 18	54 48	133 52	49 31	38 27	0.8 0.08	1.3 0.09	1.2 0.07	1.4 0.1	1.4 0.1	66	67	61	59	58	0.9	0.9	0.8	0.9	0.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.8 97 4.8	11.3 92 4.3	10.5 89 4.0	9.8 81 4.0	9.9 90 4.0	10.7 88 3.9	10.9 92 4.3	10.5 107 4.2

Side effects: **Flu like symptoms**
Fatigue
Gastritis

NO: 58 **S.V.R** **age: 47y** **Male**

PCR				
Basal	3m	6m	12m	18m
6.3×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
38 27	52 47	41 32	28 17	21 12	0.3 0.13	0.5 0.14	1.6 0.19	1.6 0.2	1.9 0.2	52	51	52	57	51	2.1	2.1	2.3	2.1	2.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	13.8	11.3	9.2	8.1	10.4	11.5	11.5	11.0
PLT	190	182	161	143	155	163	170	183
WBC	5.4	5.0	4.3	4.0	2.1	3.7	3.9	3.9

Side effects: **Flu like symptoms**
Fatigue
Nausea

NO: 59 **Relapse** **age: 37** **Female**

PCR				
Basal	3m	6m	12m	18m
3.1×10^7	9.6×10^5	-ve	-ve	+ve 6.1×10^9

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
28 51	53 77	31 38	23 17	117 83	0.8 0.09	0.8 0.09	1.4 0.1	1.6 0.1	1.8 0.1	83	87	84	84	81	0.9	0.9	1.0	1.2	1.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	10.2 183 4.7	9.0 167 4.3	9.0 145 4.1	9.3 104 4.0	9.3 123 4.0	9.2 157 4.0	9.1 155 4.2	9.7 173 4.3

Side effects: **Flu like symptoms**
Fatigue
Headache
Dizziness

NO: 60 **S.V.R** **age: 53** **Male**

PCR				
Basal	3m	6m	12m	18m
9.3×10^9	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
113 97	145 122	57 43	39 21	28 13	1.1 0.07	1.1 0.07	1.2 0.09	1.5 0.13	1.7 0.17	147	147	149	138	143	1.7	1.9	1.8	1.5	1.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	15.5	13.7	11.2	10.4	10.9	12.1	12.7	12.6
PLT	89	117	93	87	72	99	128	133
WBC	6.6	6.4	6.2	5.1	4.0	4.0	4.8	4.8

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 61 S.V.R age: 47 y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
1.4×10^{7}	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
42 31	67 51	43 38	37 21	31 18	0.9 0.09	0.8 0.07	1.3 0.1	1.7 0.12	1.3 0.19	97	98	90	91	101	3.0	3.0	3.1	2.9	2.7

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	13.2	11.4	9.7	8.1	8.5	10.2	10.3	11.7
PLT	374	338	302	293	314	333	32	350
WBC	7.2	7.2	6.3	6.0	5.0	5.7	6.1	6.0

Side effects: **Flu like symptoms**
Fatigue
Rash
Gastritis

NO: 62 **S.V.R** **age: 58y** **Female**

PCR				
Basal	3m	6m	12m	18m
6.2×10^5	7.9×10^3	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
47 58	82 91	63 47	31 22	27 11	1.1 0.08	1.0 0.03	1.6 0.1	1.9 0.3	1.0 0.1	118	112	123	116	113	2.4	2.3	2.4	2.1	2.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.0 157 4.9	10.4 133 4.9	9.1 122 4.2	9.7 98 3.7	10.3 113 3.1	10.3 178 3.4	10.3 143 3.4	10.3 140 3.5

Side effects: **Flu like symptoms**
Fatigue
Tinnitus. gastritis. dizziness

NO: 63 Stopped treatment at 12 w age: 32y Female

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
7.9 X 10^5	-ve	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
43 47	52 71	----	----	-----	0.8 0.1	0.8 0.1	----	----	-----	83	87	-----	-----	-----	1.7	1.9	----	-----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	10.5 214 5.9	9.3 203 5.2	8.6 188 5.0	8.4 162 5.1	--------	------	------	-----

Side effects: **Flu like symptoms**
Fatigue
Nausea . vomiting

Stopped treatment at 12 w due to pregnancy

NO: 64 **S.V.R** **age: 41y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
4.1 X 10^6	**-ve**	**-ve**	**-ve**	**-ve**

ALT / AST					Billrubin T / Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 / 39	62 / 76	113 / 94	42 / 33	37 / 24	0.7 / 0.09	0.9 / 0.08	1.4 / 0.13	1.6 / 0.18	1.1 / 0.1	143	148	148	147	140	2.3	2.1	2.2	2.4	2.4

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	**13.4**	**10.6**	**10.1**	**9.3**	**9.7**	**10.2**	**10.5**	**10.5**
PLT	**162**	**166**	**763**	**157**	**187**	**183**	**201**	**233**
WBC	**8.4**	8,2	8.0	7.6	7,2	5.5	5.3	4.8

Side effects: **Flu like symptoms**
Fatigue
Rash
Headache

NO: 65 **S.V.R** **age: 46y** **Male**

PCR				
Basal	3m	6m	12m	18m
2.4 X 10^6	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
35 43	67 53	41 36	38 29	32 17	1.2 0.07	0.9 0.08	0.9 0.08	1.3 0.1	1.0 0.09	128	122	128	121	130	0.8	0.8	0.7	1.2	1.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	13.7	12.2	10.9	8.5	9.4	10.5	11.2	11.7
PLT	310	257	233	199	230	279	970	275
WBC	6.4	6.4	5.9	5.3	5.0	4.5	4.7	5.5

Side effects: **Flu like symptoms**
Fatigue
Rash
wt loss of 7 kg

NO: 66 Stopped treatment at 14 w age: 52y Male

PCR				
Basal	3m	6m	12m	18m
8.1 X 10^6	-ve	-----	-----	----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
37 22	48 51	----	----	---	1.0 0.091	1.1 0.097	---	----	----	143	140	----	----	----	2.3	2.3	----	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.9 210 5.7	10.3 193 5.3	10.0 177 5.3	9.3 183 4.0	------	------	------	-----

Side effects: **Flu like symptoms**
Fatigue
Rash

Stopped treatment at 14 w due to visual field disturbance

NO: 67 S.V.R age: 28y Male

PCR				
Basal	3m	6m	12m	18m
5.3×10^6	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
54 38	77 49	32 28	31 22	27 16	0.5 0.1	0.5 0.1	0.7 0.1	0.7 0.1	0.7 0.1	133	127	131	128	128	1.6	1.6	1.8	1.6	1.6

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.8 317 7.6	11.0 301 7.6	9.3 279 6.1	7.6 241 5.2	10.2 263 5.2	10.5 281 5.6	10.4 287 5.6	10.7 280 5.3

Side effects: Flu like symptoms
Fatigue
Rash. arthralgia

NO: 68 **S.V.R** **age: 42y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.9×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
112 93	132 101	57 42	41 33	36 28	1.1 0.1	1.0 0.1	1.4 0.1	1.5 0.1	1.5 0.1	69	69	68	64	64	0.8	0.8	0.9	0.9	0.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	10.8	10.3	10.3	10.0	10.0	9.2	9.7	9.0
PLT	175	166	138	104	89	103	143	144
WBC	6.0	5.3	5.3	5.0	4.7	4.9	4.9	4.9

Side effects: **Flu like symptoms**
Fatigue
Dizziness. headache

NO: 69 **S.V.R** **age: 51y** **Male**

PCR				
Basal	3m	6m	12m	18m
1.2×10^{7}	6.3×10^{4}	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 28	52 41	31 28	29 17	22 11	0.9 0.09	0.9 0.09	1.0 0.1	1.3 0.1	1.6 0.2	59	52	51	58	57	2.0	2.0	2.0	2.1	2.3

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	15.0	13.7	11.8	9.3	8.0	8.2	9.7	11.2
PLT	113	127	111	145	193	197	143	211
WBC	8.1	8.2	7.8	6.1	5.0	5.1	4.9	5.1

Side effects: **Flu like symptoms**
Fatigue
Tinitus
Gastritis

NO: 70 Non responder age: 42y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
$4.3X\ 10^4$	+ve $9.3\ X\ 10^6$	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
51 63	72 59	----	----	----	1.2 0.1	1.4 0.1	----	-----	----	131	133	----	----	----	1.6	1.6	----	-----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	15.3 210 8.0	13.2 210 6.1	10.1 251 5.2	10.1 277 6.9	------	-----	-----	-----

Side effects: **Flu like symptoms**
Fatigue
Rash
Headache

NO: 71 S.V.R age: 38y Male

PCR				
Basal	3m	6m	12m	18m
9.3×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
39 31	72 48	33 29	31 18	32 21	1.1 0.1	1.0 0.1	1.3 0.1	1.6 0.1	1.3 0.1	93	94	90	93	91	2.4	2.3	2.4	2.4	2.1

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.3 333 7.3	11.8 289 7.1	9.2 271 7.0	9.2 223 6.3	9.7 204 5.0	9.7 207 4.3	10.1 251 5.2	10.1 277 6.9

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 72 **S.V.R** **age: 42y** **Male**

PCR				
Basal	3m	6m	12m	18m
$3.1X\ 10^{7}$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
111 83	143 97	62 43	41 32	29 17	0.7 0.09	0.8 0.09	1.2 0.1	1.5 0.2	1.5 0.2	113	113	116	118	114	2.0	2.0	2.1	2.4	2.1

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.3 134 4.9	9.2 115 4.3	8.7 102 4.0	8.3 133 3.1	8.5 144 3.7	8.5 140 4.5	9.1 147 4.5	9.0 154 4.5

Side effects: **Flu like symptoms**
Fatigue
Tinitus
Vomiting

NO: 73 S.V.R age: 37y Male

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
7.3 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
73 83	93 87	51 42	34 21	36 18	1.1 0.1	1.1 0.1	1.2 0.1	1.7 0.1	1.3 0.3	87	81	82	87	89	0.7	0.7	0.7	0.8	1.4

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	13.7 343 4.7	10.4 317 4.7	8.9 301 4.2	8.1 288 3.8	10.3 289 3.9	10.4 310 4.0	10.0 300 4.0	10.5 327 4.1

Side effects: Flu like symptoms
Fatigue
Rash
Gastritis

NO: 74 **Relapse** **age: 48** **Male**

PCR				
Basal	3m	6m	12m	18m
8.2×10^4	-ve	-ve	-ve	+ve 1.3×10^7

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
32 29	56 43	41 38	32 26	27 12	1.0 0.09	1.2 0.09	0.6 0.1	1.7 0.1	1.7 0.1	78	72	77	77	71	1.4	1.4	1.3	1.5	1.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.0 153 7.0	11.3 132 7.2	9.5 89 6.7	9.5 113 6.1	9.3 121 6.0	10.4 143 6.4	11.2 157 6.9	11.0 12 6.9

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 75 **S.V.R** **age: 56y** **Male**

PCR				
Basal	3m	6m	12m	18m
$6.3 X 10^5$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6 m	12 m	18 m	Basal	3m	6m	12 m	18 m	Basal	3m	6m	12 m	18 m	Basal	3m	6 m	12 m	18m
41 32	53 42	33 25	31 18	27 13	1.0 0.07	1.0 0.08	1.3 0.1	1.6 0.2	1.9 0.2	147	14 2	14 0	143	145	3.0	3.0	3.1	3.4	3.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	14.7	13.0	11.2	9.7	10.5	10.5	11.3	11.5
PLT	105	99	81	80	93	117	113	103
WBC	9.3	9.1	7.5	6.0	6.0	6.2	6.5	7.4

Side effects: Flu like symptoms
Fatigue
Gastritis
Vomiting
Arthralgia

NO: 76 **S.V.R** **age: 38y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.5×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
38 41	53 67	41 49	33 31	37 22	0.9 0.1	0.9 0.1	1.3 0.2	1.2 0.2	1.6 0.2	83	111	91	82	102	2.7	2.1	2.3	2.7	2.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.0 201 4.7	11.2 179 4.2	8.4 145 4.0	8.5 198 3.8	9.6 219 3.1	10.3 203 3.0	10.8 211 3.8	10.8 200 4.0

Side effects : Flu like symptoms
Fatigue
Headache
Rash

NO: 77 **S.V.R** **age: 47y** **Female**

PCR				
Basal	3m	6m	12m	18m
$3.9 X 10^7$	$1.4X 10^5$	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
113 73	144 82	55 43	32 31	28 16	0.7 0.1	0.9 0.1	1.4 0.2	1.9 0.2	1.3 0.2	73	81	75	79	80	2.4	2.4	2.5	2.3	2.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.3 163 7.2	10.0 154 5.9	9.2 132 5.2	8.5 127 4.9	8.7 101 3.2	9.1 93 3.7	9.3 130 4.1	9.7 148 4.1

Side effects : Flu like symptoms
Fatigue
Vomiting

NO: 78 **S.V.R** **age: 51y** **Female**

PCR				
Basal	3m	6m	12m	18m
7.3 X 10^4	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
95 81	103 92	54 43	38 27	21 18	1.1 0.08	1.1 0.09	1.3 0.1	1.6 0.1	1.3 0.1	156	158	150	161	159	3.1	3.2	3.0	3.1	3.1\

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	10.3 93 8.1	9.1 87 7.2	9.0 95 6.5	8.7 114 6.1	9.0 123 7.4	9.0 147 7.3	9.0 132 7.4	9.5 143 7.5

Side effects: Flu like symptoms
Fatigue
Headache
Nausea

NO: 79 **S.V.R** **age: 42y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
9.2 X 10^3	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12 m	18 m	Basal	3m	6m	12 m	18 m	Basal	3m	6m	12 m	18 m	Basal	3m	6m	12 m	18 m
43 37	51 76	38 41	31 28	26 16	1.0 0.03	1.3 0.08	1.4 0.1	1.7 0.1	1.9 0.2	113	125	101	98	102	2.3	3.9	4.1	5.9	5.3

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	15.1 391 4.8	14.3 302 4.2	12.0 213 4.0	10.4 241 3.5	9.5 295 3.1	10.5 310 4.0	10.5 300 4.0	11 278 4.0

Side effects: Flu like symptoms
Fatigue
Rash

NO: 80 **Non responder** **age: 58y** **Female**

PCR				
Basal	3m	6m	12m	18m
4.1 X 10^6	+ve 9.2 X 10^5	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
53 61	87 70	-----	-----	-----	1.2 0.1	1.2 0.09	-----	-----	-----	53	59	----	-----	-----	1.7	1.6	----	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.0 175 7.2	11.1 143 6.9	9.7 107 6.0	10.2 89 6.0	--------	-------	------	-------

Side effects: **Flu like symptoms**
Fatigue
Nausea

NO: 81 **S.V.R** **age: 46y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
7.9 X 10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 27	53 48	42 37	30 21	22 12	1.0 0.08	1.4 0.09	1.8 0.1	1.7 0.1	1.5 0.1	150	134	143	151	155	0.9	0.8	1.2	1.5	1.3

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	10.5 312 8.3	10.1 278 8.0	9.0 241 6.5	9.0 203 6.0	8.7 197 6.0	10.3 141 6.3	10.0 158 7.0	10.0 171 7.0

Side effects: **Flu like symptoms**
Fatigue
Rash
Gastritis
Dizziness

NO: 82 **Break through at 24 w** **age: 55y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.9 X 10^7	-ve	3.2 X 10^9	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
48 31	32 28	117 75	----	---	0.8 0.07	0.9 0.07	0.8 0.07	-----	----	152	147	135	-----	----	3.5	3.7	3.1	----	----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.8 93 5.9	12.8 71 5.1	10.9 75 4.3	9.7 113 4.5	10.3 134 4.5	------	-------	-------

Side effects: **Flu like symptoms**
Fatigue
Headache
Nausea

NO: 83 **S.V.R** **age: 32y** **Male**

PCR				
Basal	3m	6m	12m	18m
3.2×10^5	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
41 40	52 63	37 30	29 17	13 10	1.0 0.09	1.0 0.09	1.3 0.1	1.4 0.1	1.5 0.1	79	61	72	78	66	0.9	0.9	1.0	1.5	1.6

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.0 304 8.5	11.2 281 7.1	10.7 207 6.2	8.3 203 6.2	10.5 238 5.3	10.5 241 6.0	10.5 293 6.1	11.3 289 6.1

Side effects: **Flu like symptoms**
Fatigue
Rash
Wt loss

NO: 84 **Stopped treatment at 13 w** **age: 52y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
2.6 X 10^5	-ve	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
33 21	41 46	-----	-----	-----	1.2 0.09	1.2 0.07	-----	-----	-----	91	111	-----	-----	----	3.1	3.8	----	----	----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	12.3 153 8.2	10.1 103 7.1	8.1 97 6.3	9.7 114 6.0	------	------	-----	------

Side effects: Flu like symptoms
Fatigue
Rash

Stopped treatment at 13 w due to chest pain (I H D)

NO: 85 **Break throught at 24 w** **age: 43y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
3.5X 10^4	-ve	1.9 X 10^5	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
31 27	68 41	40 28	----	----	1.1 0.1	1.1 0.1	1.4 0.2	-----	----	92	116	128	----	----	2.9	3.1	3.4	-----	-----

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb **PLT** **WBC**	10.0 91 4.8	9.0 79 4.1	8.0 71 3.7	7.2 85 3.0	9.3 113 3.0	-----	-----	-----

Side effects: **Flu like symptoms**
Fatigue
Anorexna
Headache

NO: 86 **S.V.R** **age: 32y** **Male**

PCR				
Basal	3m	6m	12m	18m
$9.3X\ 10^4$	-ve	ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
115 93	147 133	51 38	32 19	21 7	0.9 0.09	1.2 0.1	1.5 0.4	1.8 0.2	1.9 0.2	55	67	58	51	54	3.2	3.9	4.5	5.3	5.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.7 204 5.1	12.1 235 5.0	11.1 201 3.5	9.2 179 3.1	9.5 233 3.0	10.3 234 4.0	121 209 4.2	12.0 217 4.5

Side effects: **Flu like symptoms**
Fatigue
Nausea
Headache

NO: 87 **S.V.R** **age: 51y** **Male**

PCR				
Basal	3m	6m	12m	18m
4.4X 10^6	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 21	61 42	43 38	32 21	27 15	1.1 0.09	1.4 0.1	1.6 0.2	1.9 0.2	1.5 0.2	143	157	153	133	147	0.7	0.9	1.1	1.1	0.9

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.7 379 8.1	10.0 351 8.0	10.0 319 8.0	9.1 297 6.5	9.6 280 6.1	9.9 295 6.3	103 340 6.1	10.2 301 7.2

Side effects: **Flu like symptoms**
Fatigue
Rash
Dizziness

NO: 88 **S.V.R** **age: 48y** **Female**

PCR				
Basal	3m	6m	12m	18m
$7.3X\ 10^5$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
118 57	137 66	61 52	38 25	30 17	0.7 0.08	0.9 0.08	1.3 0.1	1.4 0.2	1.5 0.3	87	81	90	83	89	3.1	4.2	5.9	5.1	5.3

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	12.0	10.4	9.3	9.4	9.5	10.1	10.5	10.3
PLT	137	103	144	153	131	139	141	138
WBC	6.0	6.0	5.1	4.3	3.8	3.8	4.0	4.1

Side effects: **Flu like symptoms**
Fatigue
Gastritis

NO: 89 **S.V.R** **age: 29** **Male**

PCR				
Basal	3m	6m	12m	18m
$3.4X\ 10^4$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
43 41	55 52	31 28	27 11	18 9	1.2 0.09	1.1 0.08	1.4 0.1	1.5 0.1	1.5 0.1	153	149	150	147	153	2.3	2.3	2.6	2.7	2.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.7 210 6.4	13.0 207 6.2	11.1 189 5.8	10.2 161 5.1	10.7 203 4.7	10.7 210 4.9	10.9 228 5.0	11.5 231 5.0

Side effects: Flu like symptoms
Fatigue
Rash
Mild depression

NO: 90 **Relapse** **age: 49y** **Male**

PCR				
Basal	3m	6m	12m	18m
$9.3X\ 10^6$	-ve	-ve	-ve	+ve $1.4X\ 10^4$

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
125 83	183 101	62 47	41 23	153 113	1.2 0.1	1.4 0.1	1.6 0.2	1.9 0.2	1.3 0.1	87	99	101	93	81	3.1	3.0	3.2	4.1	4.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	14.7 210 6.4	13.0 207 6.2	11.1 189 5.8	10.2 161 5.1	10.7 203 4.7	10.7 210 4.9	10.9 228 5.0	11.5 231 5.0

Side effects: **Flu like symptoms**
Fatigue
Rash
Anorexia

NO: 91 **S.V.R** **age:42y** **Female**

PCR				
Basal	3m	6m	12m	18m
$7.8X\ 10^4$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
31 28	53 37	41 18	26 17	21 7	0.9 0.08	0.9 0.08	1.1 0.1	1.3 0.2	1.3 0.1	161	155	153	148	153	1.6	1.6	1.9	3.2	2.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.3 134 9.3	11.1 112 9.0	10.0 89 9.0	10.0 91 8.1	10.5 123 6.2	11.3 132 6.2	11.2 142 6.3	1101 155 6.4

Side effects: **Flu like symptoms**
Fatigue
Rash
Wt loss

NO: 92 **S.V.R** **age:51y** **Female**

PCR				
Basal	3m	6m	12m	18m
$3.9X\ 10^7$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
62 41	77 51	41 38	32 30	29 18	1.0 0.09	1.0 0.07	1.2 0.09	1.6 0.1	1.4 0.2	81	83	90	87	83	3.6	3.1	3.0	3.3	3.2

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.5 213 6.0	10.1 193 7.0	9.3 187 5.2	9.1 113 4.0	9.0 131 3.8	10.3 154 4.9	10.5 183 5.3	10.7 197 5.8

Side effects: **Flu like symptoms**
Fatigue
Rash
Headache

NO: 93 Stopped treatment at 20 w age: 57y Male

PCR				
Basal	3m	6m	12m	18m
1.2X 10^4	-ve	-----	-----	-----

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
33 38	47 41	-----	-----	-----	1.0 0.08	1.0 0.08	-----	-----	-----	82	87	-----	-----	-----	1.5	1.3	-----	-----	-----

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.3 357 5.9	9.7 319 5.4	6.4 302 5.1	7.0 291 9.6	6.2 342 4.3	-----	-----	-----

Side effects : Flu like symptoms
Fatigue
Rash
Dizziness

Stopped treatment at 20 w due to sever anaemia required repeated blood transfusion and EPO therapy but no adequate response

NO: 94 **S.V.R** **age: 57y** **Male**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
$2.5X\ 10^5$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**	**Basal**	**3m**	**6m**	**12m**	**18m**
28 13	44 39	32 30	28 17	21 12	1.1 0.07	1.3 0.09	1.3 0.1	1.9 0.1	1.6 0.2	87	93	111	115	98	2.9	2.8	2.7	2.9	2.9

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb PLT WBC	12.5 193 5.8	10.3 182 5.1	9.7 160 9.2	7.1 135 3.1	8.2 143 3.1	9.3 172 3.0	9.5 199 4.5	10.4 210 4.9

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 95 **S.V.R** **age:48y** **Female**

PCR				
Basal	3m	6m	12m	18m
$9.7X\ 10^4$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
82 51	1.6 64	43 31	38 30	31 27	0.8 0.09	0.8 0.09	1.2 0.1	1.3 0.1	1.5 0.1	132	144	135	141	140	3.1	3.0	3.2	3.0	3.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	11.3 253 7.8	10.0 271 7.0	9.2 300 6.2	9.0 291 6.0	10.4 317 5.1	10.5 332 5.0	10.7 307 5.3	10.7 301 6.1

Side effects: **Flu like symptoms**
Fatigue
Rash
Headache

NO: 96 **S.V.R** **age:35y** **Female**

PCR				
Basal	3m	6m	12m	18m
7.3X 10^7	9.2X 10^3	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
44 53	62 71	41 32	28 13	17 12	1.0 0.1	1.3 0.1	1.4 0.1	1.7 0.2	1.9 0.2	94	101	92	112	93	0.7	0.9	1.2	1.4	1.7

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	12.0 185 5.9	11.3 173 5.1	10.5 175 5.1	8.7 182 3.0	10.1 193 4.2	11.2 204 5.2	11.5 173 5.5	11.5 171 5.5

Side effects: **Flu like symptoms**
Fatigue
Nausea
Arthralgia

NO: 97 **S.V.R** **age:52y** **Male**

PCR				
Basal	3m	6m	12m	18m
$1.4X\ 10^5$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
28 17	52 48	31 28	29 11	29 7	1.2 0.1	1.3 0.09	1.5 0.2	1.5 0.2	1.3 0.2	63	69	71	68	75	3.0	3.0	3.2	3.1	3.5

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	15.0 93 9.1	14.0 81 8.0	12.7 72 7.2	10.2 66 7.1	10.0 55 6.5	11.3 73 6.5	11.5 89 7.9	12.7 101 8.0

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 98 **S.V.R** **age: 48y** **Female**

PCR				
Basal	**3m**	**6m**	**12m**	**18m**
$2.6X\ 10^{7}$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
113 82	144 89	58 38	41 22	20 21	1.0 0.1	1.0 0.1	1.04 0.1	1.1 0.1	1.3 0.2	147	153	166	143	140	2.7	2.9	3.6	3.5	5.5

CBC								
	Basal	**2W**	**4W**	**12W**	**20W**	**28W**	**36W**	**44W**
Hb	15.0	14.0	12.7	10.2	10.0	11.3	11.5	12.7
PLT	93	81	72	66	55	73	89	101
WBC	9.1	8.0	7.2	7.1	6.5	6.5	7.9	8.0

Side effects: **Flu like symptoms**
Fatigue
Rash

NO: 99 **S.V.R** **age: 41y** **Male**

PCR				
Basal	3m	6m	12m	18m
$3.7X 10^4$	-ve	-ve	-ve	-ve

ALT AST					Billrubin T Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
43 81	51 38	41 27	26 11	17 13	1.1 0.09	1.0 0.09	1.2 0.1	1.4 0.1	1.5 0.3	77	81	68	90	107	1.9	2.8	2.7	3.0	3.0

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb PLT WBC	13.0 138 7.5	12.5 117 6.0	11.1 110 5.3	10.7 123 4.2	11.5 135 3.0	12.1 142 3.0	12.0 151 4.5	12.5 153 4.3

Side effects: **Flu like symptoms**
Fatigue
Rash
Nausea

NO: 100 **S.V.R** **age: 42y** **Female**

PCR				
Basal	3m	6m	12m	18m
$5.3X\ 10^9$	-ve	-ve	-ve	-ve

ALT / AST					Billrubin T / Billrubin D					ALK P					TSH				
Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m	Basal	3m	6m	12m	18m
81 93	133 104	52 41	38 22	29 18	0.7 0.08	0.9 0.09	1.2 0.1	1.5 0.2	1.7 0.2	163	158	160	155	143	1.7	1.7	2.1	2.0	2.4

CBC								
	Basal	2W	4W	12W	20W	28W	36W	44W
Hb	11.0	9.5	9.1	8.4	9.7	9.1	9.0	9.0
PLT	183	141	113	154	133	172	189	201
WBC	4.5	4.1	3.7	3.2	3.2	3.0	3.0	4.5

Side effects: **Flu like symptoms**
Fatigue
Dizziness
Syncope

RESULTS

Table (1): Distribution of the studied cases according to demographic data

	No.	%
Sex		
Male	68	68.0
Female	32	32.0
Age		
Range	22.0 – 58.0	
Mean ± SD.	45.57 ± 8.38	
Median	47.0	

Table (2): Distribution of the studied cases according to some lab investigations basal

Basal	Range	Mean ± SD.	Median
PCR for HCV ($\times10^6$) (iu/ml)	0.007 – 9300.0	160.6 ± 1068.17	0.62
ALT (u/l)	12.0 – 183.0	54.14 ± 33.21	41.0
AST (u/l)	10.0 – 150.0	43.90 ± 25.88	37.0
Billrubin T (mg/dl)	0.08 – 1.30	0.91 ± 0.26	1.00
Billrubin D (mg/dl)	0.01 – 0.51	0.10 ± 0.09	0.09
ALP (u/l)	52.0 – 290.0	103.79 ± 36.02	93.0
TSH (mu/l)	0.30 – 5.70	1.90 ± 0.93	1.90
HB (g/dl)	10.0 – 16.0	13.47 ± 1.84	13.80
PLT ($X10^9$/l)	89.0 – 794.0	215.52 ± 94.06	202.50
WBC ($X10^9$/l)	2.80 – 12.50	6.47 ± 1.65	6.40

Table (3): Distribution of the studied sample regarding their response to treatment in relation to their sex and age

	Patients								Total (n = 93)	
	S.V.R (n = 71)		Relapse (n = 11)		Non Responder (n = 7)		Break through (n = 4)			
	No.	%	No.	%	No.	%	No.	%	No.	%
Sex										
Male	46	64.8	9	81.8	5	71.4	3	75.0	63	67.7
Female	25	35.2	2	18.2	2	28.6	1	25.0	30	32.3
Age										
Range	22.0 – 58.0		33.0 – 58.0		40.0 – 58.0		36.0 – 55.0		22.0 – 58.0	
Mean ± SD	44.92 ± 8.44		46.64 ± 7.49		47.57 ± 7.52		47.0 ± 9.13		45.41 ± 8.22	
Median	47.0		47.0		46.0		48.50		47.0	

Table (4): Distribution of the studied cases according to side effects

	No.	%
Side effect		
Flu like symptoms	100	100.0
Fatigue	93	93.0
Hypothyroidism	1	1.0
Bronchitis with spasm	1	1.0
Arthralgia	13	13.0
Dizziness	12	12.0
Headache	21	21.0
Body aches	2	2.0
Nausea	15	15.0
Weight loss	4	4.0
Rash	45	45.0
Vomiting	18	18.0
Tinitus	4	4.0
Anorexna	2	2.0
Milddepression	1	1.0
Syncope	1	1.0

Table (5): Comparison between different stages according to some lab investigations in patients who achieved S.V.R

	Basal	3m	6m	12m	18m
PCR (×10^6) (iu/ml)					
Range	0.002 – 9300.0	0.003 – 0.14	**undetectable-**	**undetectable-**	**undetectable-**
Mean ± SD.	209.73 ± 1261.90	0.045 ± 0.059	-	-	-
Mean diff. (p_1)		↓26.1 (0.124)	-	-	-
ALT (u/l)					
Range	21.0 – 118.0	1.60 – 197.0	11.0 – 133.0	8.0 – 66.0	12.0 – 133.0
Mean ± SD.	52.13 ± 27.86	71.37 ±36.23	49.48 ± 20.97	34.69 ± 8.98	29.21 ± 15.26
Mean diff. (p_1)		↑19.25 (<0.001*)	↓2.65 (0.472)	↓17.44 (<0.001*)	↓22.915 (<0.001*)
Mean diff. (p_2)			↓21.90 (<0.001*)	↓14.79 (<0.001*)	↓5.48 (0.003*)
AST(u/l)					
Range	11.0 – 97.0	14.0 – 133.0	0.50 – 94.0	11.0 – 66.0	7.0 – 48.0
Mean ± SD.	42.24 ± 23.82	55.63 ± 26.11	35.68 ± 12.96	24.27 ± 8.95	18.80 ± 8.43
Mean diff. (p_1)		↑13.39 (<0.001*)	↓6.56 (0.026*)	↓17.97 (<0.001*)	↓23.44 (<0.001*)
Mean diff. (p_2)			↓19.95 (<0.001*)	↓11.42 (<0.001*)	↓5.46 (<0.001*)
Billrubin T (mg/dl)					
Range	0.08 – 1.30	0.08 – 1.70	0.40 – 1.80	0.40 – 1.90	0.01 – 1.90
Mean ± SD.	0.88 ± 0.27	0.98 ± 0.30	1.25 ± 0.30	1.40 ± 0.37	1.28 ± 0.39
Mean diff. (p_1)		↑0.11 (<0.001*)	↑0.37 (<0.001*)	↑0.53 (<0.001*)	↑0.40 (<0.001*)
Mean diff. (p_2)			↑0.27 (<0.001*)	↑0.15 (<0.001*)	↓0.12 (0.006*)
Billrubin D (mg/dl)					
Range	0.01 – 0.51	0.01 – 0.30	0.01 – 2.20	0.01 – 0.40	0.01 – 0.30
Mean ± SD.	0.09 ± 0.09	0.09 ± 0.05	0.15 ± 0.27	0.13 ± 0.08	0.14 ± 0.08
Mean diff. (p_1)		↓0.007 (0.449)	↑0.054 (0.103)	↑0.036 (0.008*)	↑0.049 (<0.001*)
Mean diff. (p_2)			↑0.06 (0.036*)	↓0.18 (0.587)	↑0.01 (0.208)
ALP (u/l)					
Range	52.0 – 163.0	51.0 ± 158.0	51.0 – 166.0	16.0 – 161.0	78.0 – 1585.0
Mean ± SD.	102.58 ± 33.02	102.76 ± 32.63	102.44 ± 32.61	101.92 ± 33.56	120.79 ± 179.22
Mean diff. (p_1)		↑0.18 (0.920)	↓0.14 (0.916)	↓0.66 (0.779)	↑18.21 (0.375)
Mean diff. (p_2)			↓0.32 (0.863)	↓0.52 (0.782)	↑18.87 (0.359)
TSH (mu/l)					
Range	0.46 – 5.70	0.60 – 7.30	0.50 – 9.30	0.80 – 20.0	0.55 – 311.0
Mean ± SD.	2.0 ± 0.93	2.21 ± 1.26	2.31 ± 1.36	2.66 ± 2.59	8.12 ± 38.58
Mean diff. (p_1)		↑0.214 (0.063)	↑0.318 (0.007*)	↑0.67 (0.021*)	↑6.12 (0.185)
Mean diff. (p_2)			↑0.10 (0.275)	↑0.33 (0.160)	↑5.45 (0.238)

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \le 0.05$

Table (6): Comparison between different stages according to some lab investigations in S.V.R

	Basal	2W	4W	12W	20W	28W	36W	44W
HB (g/dl)								
Range	10.10 – 16.50	8.90 – 16.60	4.40 – 15.20	7.10 – 14.30	8.0 – 14.90	8.20 – 14.50	9.0 – 121.0	9.0 – 14.70
Mean ± SD.	13.47 ± 1.70	11.88 ± 1.68	10.47 ± 1.73	9.71 ± 1.59	10.07 ± 1.31	10.53 ± 1.27	13.85 ± 16.95	11.32 ± 1.33
Mean diff. (p_1)		↓1.60 (<0.001*)	↓3.0 (<0.001*)	↓3.76 (<0.001*)	↓3.40 (<0.001*)	↓2.94 (<0.001*)	↑0.39 (0.850)	↓2.15 (<0.001*)
Mean diff. (p_2)			↓1.40 (<0.001*)	↓0.76 (<0.001*)	↑0.63 (0.004*)	↑0.46 (<0.001*)	↑3.32 (0.104)	↓ 2.53 (0.212)
PLT ($X10^9$/l)								
Range	89.0–391.0	81.0-351.0	72.0-763.0	66.0-757.0	55.0-317.0	69.0-333.0	32.0-970.0	79.0-350.0
Mean ± SD.	210.28±76.74	198.63±69.83	192.11±97.16	182.32±95.74	180.89±64.82	192.76±65.71	211.49±142.15	211.08±65.65
Mean diff. (p_1)		↓11.65 (<0.001*)	↓18.17 (0.074)	↓27.96 (0.003*)	↓29.39 (<0.001*)	↓17.52 (<0.001*)	↑11.21 (0.459)	↑0.80 (0.861)
Mean diff. (p_2)			↓6.52 (0.478)	↓9.79 (0.421)	↓1.44 (0.860)	↑11.87 (<0.001*)	↑28.73 (0.054)	↓10.41 (0.488)
WBC ($X10^9$/l)								
Range	3.80 – 12.50	1.20-701.0	3.0-9.20	2.60-9.60	2.0-7.80	1.90-8.0	1.70-8.0	1.90-8.30
Mean ± SD.	6.65 ± 1.69	15.96±83.08	5.56±1.45	4.98±1.39	4.56±1.32	4.76±1.29	5.06±1.38	5.28±1.40
Mean diff. (p_1)		↑9.32 (0.351)	↓1.09 (<0.001*)	↓1.66 (<0.001*)	↓2.10 (<0.001*)	↓1.89 (<0.001*)	↓1.59 (<0.001*)	↓1.37 (<0.001*)
Mean diff. (p_2)			↓ 10.44 (0.296)	↓0.54 (<0.001*)	↓0.47 (<0.001*)	↑ 0.21 (0.011*)	↑0.30 (<0.001*)	↑0.22 (0.001*)

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \leq 0.05$

Table (7): Comparison between different stages according to some lab investigations in relapse

	Basal	**3m**	**6m**	**12m**	**18m**
PCR ($\times10^6$) (iu/ml)					
Min. – Max.	0.038 – 970.0	0.004 – 0.96	-	-	0.013 – 6100.0
Mean ± SD.	92.98 ± 291.01	0.31 ± 0.43	-	-	557.23 ± 1838.3
Mean diff. (p_1)		↓200.9 (0.355)	-	-	↑464.3 (0.432)
ALT (u/l)					
Min. – Max.	12.0 – 183.0	36.0 – 183.0	27.0 – 75.0	17.0 – 76.0	13.0 – 133
Mean ± SD.	73.0 ± 57.80	65.55 ± 42.05	43.64 ± 15.40	36.82 ± 15.57	79.18 ± 44.05
Mean diff. (p_1)		↓7.45 (0.716)	↓29.36 (0.142)	↓36.18 (0.072)	↑6.18 (0.807)
Mean diff. (p_2)			↓21.91 (0.084)	↓6.82 (0.128)	↑42.36 (0.021*)
AST (u/l)					
Min. – Max.	10.0 – 150.0	29.0 – 102.0	31.0 – 49.0	11.0 – 131.0	12.0 – 113.0
Mean ± SD.	57.91 ± 41.04	58.91 ± 29.08	37.91 ± 5.59	36.91 ± 33.51	62.73 ± 30.16
Mean diff. (p_1)		↑1.0 (0.947)	↓20.0 (0.133)	↑21.0 (0.047*)	↓4.81 (0.726)
Mean diff. (p_2)			↓21.00 (0.041*)	↓1.00 (0.923)	↑25.82 (0.118)
Billrubin T (mg/dl)					
Min. – Max.	0.60 – 1.30	0.50 – 1.40	0.43 – 1.90	0.82 – 1.90	0.80 – 1.80
Mean ± SD.	0.98 ± 0.20	0.98 ± 0.29	1.17 ± 0.48	1.41 ± 0.324	1.25 ± 0.38
Mean diff. (p_1)		↓0.0 (1.000)	↑0.18 (0.248)	↑0.429 (0.003*)	↑0.27 (0.041*)
Mean diff. (p_2)			↑0.18 (0.147)	↑0.24 (0.076)	↓0.16 (0.231)
Billrubin D (mg/dl)					
Min. – Max.	0.01 – 0.20	0.02 – 0.30	0.10 – 0.030	0.07 – 0.40	0.07 – 0.30
Mean ± SD.	0.11 ± 0.05	0.11 ± 0.07	0.15 ± 0.08	0.18 ± 0.11	0.13 ± 0.07
Mean diff. (p_1)		↑0.0036 (0.795)	↑0.049 (0.066)	↑0.072 (0.053)	↑0.027 (0.179)
Mean diff. (p_2)			↑0.05 (0.046*)	↑0.02 (0.269)	↓0.05 (0.243)
ALP (u/l)					
Min. – Max.	78.0 – 290.0	72.0 – 211.0	77.0 ± 137.0	77.0 – 199.0	71.0 – 143.0
Mean ± SD.	113.18 ± 60.07	114.36 ± 39.26	94.0 ± 17.86	105.18 ± 35.38	101.09 ± 24.10
Mean diff. (p_1)		↑1.18 (0.903)	↓19.18 (0.200)	↓8.0 (0.403)	↓12.09 (0.447)
Mean diff. (p_2)			↓20.36 (0.043*)	↑11.18 (0.113)	↓4.09 (0.674)
TSH (mu/l)					
Min. – Max.	03.0 – 3.10	0.30 – 3.0	0.90 – 3.20	0.90 – 4.10	0.70 – 4.50
Mean ± SD.	1.42 ± 0.86	1.55 ± 0.90	1.73 ± 0.80	1.80 ± 0.95	1.78 ± 1.10
Mean diff. (p_1)		↑0.127 (0.248)	↑0.313 (0.029*)	↑0.38 (0.054)	↑0.36 (0.043*)
Mean diff. (p_2)			↑0.186 (0.316)	↑0.068 (0.734)	↓0.018 (0.882)

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \le 0.05$

Table (8): Comparison between different stages according to some lab investigations in relapse

	Basal	2W	4W	12W	20W	28W	36W	44W
HB (g/dl)								
Range	10.20 – 19.0	9.0 – 14.90	9.0 – 14.70	8.20 – 13.70	9.0 – 13.0	9.20 – 12.60	9.10 – 13.70	9.70 – 15.0
Mean ± SD.	14.15 ± 2.34	12.32 ± 1.75	11.28 ± 2.0	10.15 ± 1.76	10.20 ± 1.12	10.84 ± 1.0	11.03 ± 1.43	11.96 ± 1.64
Mean diff. (p_1)		↓1.83 (0.012*)	↓2.86 (0.003*)	↓3.99 (0.001*)	↓3.95 (<0.001*)	↓3.31 (<0.001*)	↓3.12 (0.002*)	↓2.18 (0.009*)
Mean diff. (p_2)			↓1.036 (0.002*)	↓1.127 (0.050)	↑0.045 (0.895)	↑0.64 (0.026*)	↑0.190 (0.643)	↑0.936 (0.080)
PLT ($X10^9$/l)								
Range	131.0-347.0	132.0-313.0	89.0-322.0	104.0-419.0	121.0-300.0	127.0-377.0	130.0-439.0	12.0-4036.0
Mean ± SD.	224.55±72.69	216.36±63.68	207.45±75.47	210.27±88.57	198.64±59.16	223.73±73.96	235.27±86.22	233.64±103.97
Mean diff. (p_1)		↓8.18 (0.311)	↓17.09 (0.190)	↓14.27 (0.488)	↓25.91 (0.104)	↓0.82 (0.962)	↑10.73 (0.581)	↑9.09 (0.688)
Mean diff. (p_2)			↓8.91 (0.232)	↑2.82 (0.843)	↓11.64 (0.419)	↑25.09 (0.004*)	↑11.55 (0.106)	↓1.64 (0.921)
WBC ($X10^9$/l)								
Range	4.20 – 8.60	3.70-8.80	3.80-9.20	2.30-6.50	2.90-6.20	3.20-6.80	3.10-7.30	2.60-7.10
Mean ± SD.	6.45 ± 1.35	6.13±1.52	6.05±1.50	4.98±1.26	4.75±0.96	4.75±1.16	5.28±1.33	5.42±1.48
Mean diff. (p_1)		↓0.32 (0.284)	↓0.400 (0.295)	↓1.46 (0.012*)	↓1.69 (0.003*)	↓1.69 (0.005*)	↓1.16 (0.029*)	↓1.03 (0.076)
Mean diff. (p_2)			↓0.08 (0.645)	↓1.06 (0.107)	↓0.23 (0.147)	↓0.00 (1.000)	↑0.53 (0.088)	↑0.14 (0.259)

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \le 0.05$

Table (9): Comparison between different stages according to some lab investigations in non responder patients

	Basal	**3m**
PCR (×10)[6] (iu/ml)		
Range	0.043 – 42.0	0.66 – 25.0
Mean ± SD.	12.88 ± 17.68	6.99 ± 8.81
Mean diff. (p_1)		↓5.9 (0.472)
ALT (u/l)		
Range	31.0 – 78.0	32.0 – 75.0
Mean ± SD.	45.86 ± 16.54	56.0 ± 16.04
Mean diff. (p_1)		↑10.14(0.153)
AST (u/l)		
Range	27.0 – 95.0	17.0 – 83.0
Mean ± SD.	49.86 ± 24.77	53.14 ± 21.19
Mean diff. (p_1)		↑3.29(0.493)
Billrubin T (mg/dl)		
Range	0.80 – 1.30	0.90 – 1.50
Mean ± SD.	1.11 ± 0.21	1.19 ± 0.20
Mean diff. (p_1)		↑0.079(0.262)
Billrubin D (mg/dl)		
Range	0.01 – 0.50	0.03 – 0.50
Mean ± SD.	0.15 ± 0.16	0.14 ± 0.16
Mean diff. (p_1)		↓0.017(0.321)
ALP (u/l)		
Range	53.0 – 139.0	59.0 – 138.0
Mean ± SD.	96.86 ± 32.49	98.86 ± 30.78
Mean diff. (p_1)		↑2.0 (0.299)
TSH (mu/l)		
Range	0.90 – 3.20	1.20- 3.70
Mean ± SD.	1.83 ± 0.75	2.11 ± 0.92
Mean diff. (p_1)		↓0.29(0.033)

p_1: p value for Paired t-test for comparing between basal with each other stages
*: Statistically significant at $p \le 0.05$

Table (10): Comparison between different stages according to some lab investigations in non responder patients

	Basal	2W	4W	12W	20W
HB (g/dl)					
Range	11.0 – 17.30	10.30 – 14.60	9.20 – 14.60	8.20 – 14.0	9.20 –16.20
Mean ± SD.	13.66 ± 2.10	12.20 ± 1.58	10.81 ± 2.04	10.27 ± 1.87	12.5± 0.0
Mean diff. (p_1)		↓1.46 (0.005*)	↓2.84 (0.002*)	↓3.39 (0.001*)	-
Mean diff. (p_2)			↓1.39 (0.015*)	↓0.54 (0.169)	-
PLT ($X10^9$/l)					
Range	172.0 – 258.0	143.0-304.0	107.0-346.0	89.0-389.0	120.0-395.0
Mean ± SD.	211.0 ± 33.90	203.57±59.38	199.71±82.07	204.14±103.88	257.0±0.0
Mean diff. (p_1)		↓7.43 (0.511)	↓11.29 (0.608)	↓6.86 (0.825)	-
Mean diff. (p_2)			↓ 3.86 (0.766)	↑4.43 (0.655)	-
WBC ($X10^9$/l)					
Range	2.80 – 8.0	3.10-8.0	2.90-9.20	2.70-9.0	3.0-9.00
Mean ± SD.	5.996 ± 2.0	5.59±149.41	5.70±2.09	5.59±2.21	6.0±0.0
Mean diff. (p_1)		↑56.20 (0.360)	↓0.29 (0.671)	↓0.40 (0.463)	-
Mean diff. (p_2)			↓56.49 (0.355)	↓0.11 (0.735)	-

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \leq 0.05$

Table (11): Comparison between different stages according to some lab investigations in break through group

	Basal	3m	6m	12m
PCR $(\times 10)^6$ (iu/ml)				
Range	0.04 – 49.0	-	0.19 – 3200.0	0.24 – 51.0
Mean ± SD.	12.51 ± 24.33	-	1066.82 ± 1847.39	25.620 ± -
Mean diff. (p_1)		-	↑1050.35 (0.423)	-
ALT (u/l)				
Range	27.0 – 154.0	32.0 – 96.0	40.0 – 138.0	36.0 – 161.0
Mean ± SD.	65.0 ± 60.3	62.0 ± 27.03	84.50 ± 50.40	98.0 ± -
Mean diff. (p_1)		↓ 3.0 (0.898)	↑19.50 (0.355)	-
Mean diff. (p_2)			↑22.50 (0.443)	-
AST (u/l)				
Range	18.0 – 73.0	28.0 – 64.0	28.0 – 75.0	38.0 – 117.0
Mean ± SD.	37.25 ± 24.45	44.50 ± 14.89	49.0 ± 20.61	77.5 ± -
Mean diff. (p_1)		↑ 7.25 (0.672)	↑11.75 (0.441)	-
Mean diff. (p_2)			↑4.50 (0.797)	-
Billrubin T (mg/dl)				
Range	0.50 – 1.10	0.80 – 1.10	0.70 – 1.40	0.8 – 1.45
Mean ± SD.	0.73 ± 0.29	0.93 ± 0.13	0.95 ± 0.31	1.10 ± -
Mean diff. (p_1)		↑0.20 (0.116)	↑0.23 (0.078)	-
Mean diff. (p_2)			↑0.03 (0.809)	-
Billrubin D (mg/dl)				
Range	0.07 – 0.10	0.07 – 0.10	0.07 – 0.20	0.08 – 0.20
Mean ± SD.	0.09 ± 0.02	0.08 ± 0.02	0.12 ± 0.07	0.14 ± -
Mean diff. (p_1)		-	↑0.04 (0.321)	-
Mean diff. (p_2)			↑0.04 (0.321)	-
ALP (u/l)				
Range	79.0 – 152.0	88.0 – 147.0	81.0 – 135.0	97.0 – 156.0
Mean ± SD.	103.75 ± 32.75	110.50 ± 27.38	108.75 ± 26.74	126.5 ± -
Mean diff. (p_1)		↑6.75 (0.373)	↑5.0 (0.684)	-
Mean diff. (p_2)			↓1.75 (0.759)	-
TSH (mu/l)				
Range	1.30 – 3.50	1.70 – 3.70	1.40 – 3.40	2.0 – 4.7
Mean ± SD.	2.35 ± 1.02	2.83 ± 0.84	2.45 ± 0.95	3.35 ± -
Mean diff. (p_1)		↑0.48 (0.262)	↑0.10 (0.630)	-
Mean diff. (p_2)			↓0.38 (0.414)	-

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \le 0.05$

Table (12): Comparison between different stages according to some lab investigations in break through group

	Basal	2W	4W	12W	20W	28W	36W
HB (g/dl)							
Range	10.0 – 15.20	9.0 – 13.20	8.0 – 12.50	7.20 – 11.10	9.30 – 13.20	9.5 – 13.7	10.30 – 13.90
Mean ± SD.	13.03 ± 2.44	11.75 ± 1.90	10.43 ± 1.86	9.28 ± 1.62	10.73 ± 1.71	11.6 ± -	12.10 ± -
Mean diff. (p_1)		↓1.28 (0.068)	↓2.60 (0.012*)	↓3.75 (0.006*)	↓2.30 (0.063)	-	-
Mean diff. (p_2)			↓1.33 (0.019*)	↓1.15 (0.003*)	↑1.45 (0.033*)	-	-
PLT ($X10^9$/l)							
Range	91.0 – 794.0	71.0 – 173.0	71.0 – 154.0	77.0 – 153.0	113.0 – 153.0	131.0 – 265.0	197.0 – 398.0
Mean ± SD.	279.25 ± 343.88	109.25 ± 46.42	97.25 ± 38.61	107.0 ± 34.33	130.75 ± 17.13	198.0 ± -	297.0 ± -
Mean diff. (p_1)		↓170.0 (0.340)	↓182.0 (0.319)	↓172.3 (0.353)	↓148.5 (0.433)	-	-
Mean diff. (p_2)			↓12.0 (0.157)	↑9.75 (0.434)	↑23.75 (0.088)	-	-
WBC ($X10^9$/l)							
Range	4.80 – 7.20	4.10 – 7.20	3.50 – 6.80	3.0 – 5.30	3.0 – 5.90	3.90 – 5.70	4.20 – 6.80
Mean ± SD.	5.70 ± 1.12	5.15 ± 1.44	4.58 ± 1.52	4.23 ± 0.96	4.20 ± 1.30	4.80 ± -	5.50 ± -
Mean diff. (p_1)		↓0.55 (0.059)	↓1.13 (0.023*)	↓1.48 (0.010*)	↓1.50 (0.001*)	-	-
Mean diff. (p_2)			↓0.58 (0.011*)	↓0.35 (0.510)	↓0.03 (0.931)	-	-

p_1: p value for Paired t-test for comparing between basal with each other stages
p_2: p value for Paired t-test for comparing between two successive stages
*: Statistically significant at $p \leq 0.05$

Table (13): Comparison between the different studied groups according to

	S.V.R (n = 71)		Relapse (n = 11)		Non Responder (n = 7)		Break through (n = 4)		Test of Sig.	P
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**		
PCR basal $(\times 10)^6$ (iu/ml)										
Negative	0	0.0	0	0.0	0	0.0	0	0.0	-	-
Positive	71	100.0	11	100.0	7	100.0	4	100.0		
Range	0.002 – 9300.0		0.038 – 970.0		0.043 – 42.0		0.04 – 49.0		F=0.119	0.949
Mean ± SD.	209.7 ± 1261.9		92.98 ± 291.01		12.88 ± 17.68		12.51 ± 24.33			
PCR 3m (iu/ml)										
Negative	66	93.0	6	54.5	0	0.0	4	100.0	χ^2=33.678*	^{MC}p=<0.001*
Positive	5	7.0	5	45.5	7	100.0	0	0.0		
Range	0.003 – 0.14		0.004 – 0.96		0.66 – 25.0		-		F=2.877	0.090
Mean ± SD.	0.045 ± 0.059		0.31 ± 0.43		6.99 ± 8.81		-			
PCR 6m (iu/ml)										
Negative	71	100.0	11	100.0	7	100.0	1	25.0	χ^2=20.201*	^{MC}p<0.001*
Positive	0	0.0	0	0.0	0	0.0	3	75.0		
Range	-		-		-		0.19 – 3200.0		-	-
Mean ± SD.	-		-		-		1066.8 ± 1847.4			
PCR 12m (iu/ml)										
Negative	71	100.0	11	100.0	7	100.0	3	75.0	χ^2=8.949*	^{MC}p=0.041*
Positive	0	0.0	0	0.0	0	0.0	1	25.0		
Range	-		-		-		31.0 – 31.0		-	-
Mean ± SD.	-		-		-		31.0 ± -			
PCR 18m (iu/ml)										
Negative	71	100.0	0	0.0	7	100.0	4	100.0	χ^2= 59.291*	^{MC}p=<0.001*
Positive	0	0.0	11	100.0	0	0.0	0	0.0		
Range	-		0.013 – 6100.0		-		-		-	-
Mean ± SD.	-		557.23 ± 1838.3		-		-			

χ^2: Chi square test
MC: Monte Carlo test
F: F test (ANOVA)
t: Student t-test
*: Statistically significant at $p \le 0.05$

Table (14): Comparison between the different studied groups according to ALT

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
ALT basal (u/l)						
Range	21.0 – 118.0	12.0 – 183.0	31.0 – 78.0	57.0 – 154.0	F=1.518	0.215
Mean ± SD.	52.13 ± 27.86	73.0 ± 57.80	45.86 ± 16.54	65.0 ± 60.03		
ALT 3m (u/l)						
Range	1.60 – 197.0	36.0 – 183.0	32.0 – 75.0	32.0 – 96.0	F=0.500	0.683
Mean ± SD.	71.37 ±36.23	65.55 ± 42.05	56.0 ± 16.04	62.0 ± 27.03		
ALT 6m (u/l)						
Range	11.0 – 133.0	27.0 – 75.0	-	40.0 – 138.0	F=5.309*	0.007*
Mean ± SD.	49.48 ± 20.97	43.64 ± 15.40	-	84.50 ± 50.40		
ALT 12m (u/l)						
Range	8.0 – 66.0	17.0 – 76.0	-	85.0 –1 96.0	t=0.654	0.515
Mean ± SD.	34.69 ± 8.98	36.82 ± 15.57	-	140.5 ± -		
ALT 18m (u/l)						
Range	12.0 – 133.0	13.0 – 133	-	-	t=3.728*	0.004*
Mean ± SD.	29.21 ± 15.26	79.18 ± 44.05	-	-		

F: F test (ANOVA)
t: Student t-test
*: Statistically significant at $p \leq 0.05$

Table (15): Comparison between the different studied groups according to AST

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
AST basal (u/l)						
Range	11.0 – 97.0	10.0 – 150.0	27.0 – 95.0	18.0 – 73.0	F=1.316	0.274
Mean ± SD.	42.24 ± 23.82	57.91 ± 41.04	49.86 ± 24.77	37.25 ± 24.45		
AST 3m (u/l)						
Range	14.0 – 133.0	29.0 – 102.0	17.0 – 83.0	28.0 – 64.0	F=0.324	0.808
Mean ± SD.	55.63 ± 26.11	58.91 ± 29.08	53.14 ± 21.19	44.50 ± 14.89		
AST 6m (u/l)						
Range	0.50 – 94.0	31.0 – 49.0	-	28.0 – 75.0	F=2.157	0.122
Mean ± SD.	35.68 ± 12.96	37.91 ± 5.59	-	49.0 ± 20.61		
AST 12m (u/l)						
Range	11.0 – 66.0	11.0 – 131.0	-	38.0 – 38.0	t=1.244	0.241
Mean ± SD.	24.27 ± 8.95	36.91 ± 33.51	-	38.0 ± 0.0		
AST 18m (u/l)						
Range	7.0 – 48.0	12.0 – 113.0	-	-	t=4.801*	0.001*
Mean ± SD.	18.80 ± 8.43	62.73 ± 30.16	-	-		

F: F test (ANOVA)
t: Student t-test
*: Statistically significant at $p \leq 0.05$

Table (16): Comparison between the different studied groups according to Bilirubin T

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
Bilirubin T basal (mg/dl)					F=2.691	0.051
Min. – Max.	0.08 – 1.30	0.60 – 1.30	0.80 – 1.30	0.50 – 1.10		
Mean ± SD.	0.88 ± 0.27	0.98 ± 0.20	1.11 ± 0.21	0.73 ± 0.29		
Bilirubin T 3m (mg/dl)					F=1.145	0.335
Min. – Max.	0.08 – 1.70	0.50 – 1.40	0.90 – 1.50	0.80 – 1.10		
Mean ± SD.	0.98 ± 0.30	0.98 ± 0.29	1.19 ± 0.20	0.93 ± 0.13		
Bilirubin T 6m (mg/dl)					F=1.788	0.174
Min. – Max.	0.40 – 1.80	0.43 – 1.90	-	0.70 – 1.40		
Mean ± SD.	1.25 ± 0.30	1.17 ± 0.48	-	0.95 ± 0.31		
Bilirubin T 12m (mg/dl)					t= 0.060	0.952
Min. – Max.	0.40 – 1.90	0.82 – 1.90	-	1.30 – 1.30		
Mean ± SD.	1.40 ± 0.37	1.41 ± 0.324	-	1.30 ± 0.0		
Bilirubin T 18m (mg/dl)						
Min. – Max.	0.01 – 1.90	0.80 – 1.80	-	-	t=0.224	0.823
Mean ± SD.	1.28 ± 0.39	1.25 ± 0.38	-	-		

F: F test (ANOVA)
t: Student t-test

Table (17): Comparison between the different studied groups according to Bilirubin D

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
Bilirubin D basal (mg/dl)					F=0.972	0.410
Range	0.01 – 0.51	0.01 – 0.20	0.01 – 0.50	0.07 – 0.10		
Mean ± SD.	0.09 ± 0.09	0.11 ± 0.05	0.15 ± 0.16	0.09 ± 0.02		
Bilirubin D 3m (mg/dl)					F=1.448	0.234
Range	0.01 – 0.30	0.02 – 0.30	0.03 – 0.50	0.07 – 0.10		
Mean ± SD.	0.09 ± 0.05	0.11 ± 0.07	0.14 ± 0.16	0.08 ± 0.02		
Bilirubin D 6m (mg/dl)					F=0.018	0.982
Range	0.01 – 2.20	0.10 – 0.030	-	0.07 – 0.20		
Mean ± SD.	0.15 ± 0.27	0.15 ± 0.08	-	0.12 ± 0.07		
Bilirubin D 12m (mg/dl)					t=1.751	0.084
Range	0.01 – 0.40	0.07 – 0.40	-	0.10 – 0.10		
Mean ± SD.	0.13 ± 0.08	0.18 ± 0.11	-	0.10 ± 0.0		
Bilirubin D 18m (mg/dl)					t=0.411	0.682
Range	0.01 – 0.30	0.07 – 0.30	-	-		
Mean ± SD.	0.14 ± 0.08	0.13 ± 0.07	-	-		

F: F test (ANOVA)
t: Student t-test

Table (18): Comparison between the different studied groups according to ALP

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
ALP basal (u/l)						
Range	1.20 – 163.0	78.0 – 290.0	53.0 – 139.0	79.0 – 152.0	F=0.341	0.796
Mean ± SD.	101.02 ± 35.12	113.18 ± 60.07	96.86 ± 32.49	103.75 ± 32.75		
ALP 3m (u/l)						
Range	51.0 ± 158.0	72.0 – 211.0	59.0 – 138.0	88.0 – 147.0	F=0.498	0.685
Mean ± SD.	102.76 ± 32.63	114.36 ± 39.26	98.86 ± 30.78	110.50 ± 27.38		
ALP 6m (u/l)						
Range	51.0 – 166.0	77.0 ± 137.0	87.0 – 87.0	81.0 – 135.0	F = 0.382	0.766
Mean ± SD.	102.44 ± 32.61	94.0 ± 17.86	87.0 ± 0.0	108.75 ± 26.74		
ALP 12m (u/l)						
Range	16.0 – 161.0	77.0 – 199.0	77.0 – 77.0	97.0 – 97.0	t=0.298	0.766
Mean ± SD.	101.92 ± 33.56	105.18 ± 35.38	77.0 ± 0.0	97.0 ± 0.0		
ALP 18m (u/l)						
Range	78.0 – 1585.0	71.0 – 143.0	-	-	t=0.362	0.718
Mean ± SD.	120.79 ± 179.22	101.09 ± 24.10	-	-		

F: F test (ANOVA)
t: Student t-test

Table (19): Comparison between the different studied groups according to TSH

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
TSH basal (mu/l)						
Range	0.46 – 5.70	03.0 – 3.10	0.90 – 3.20	1.30 – 3.50	F=1.580	0.200
Mean ± SD.	2.0 ± 0.93	1.42 ± 0.86	1.83 ± 0.75	2.35 ± 1.02		
TSH 3m (mu/l)						
Range	0.60 – 7.30	0.30 – 3.0	1.20- 3.70	1.70 – 3.70	F=1.438	0.237
Mean ± SD.	2.21 ± 1.26	1.55 ± 0.90	2.11 ± 0.92	2.83 ± 0.84		
TSH 6m (mu/l)						
Range	0.50 – 9.30	0.90 – 3.20	-	1.40 – 3.40	F=1.011	0.368
Mean ± SD.	2.31 ± 1.36	1.73 ± 0.80	-	2.45 ± 0.95		
TSH 12m (mu/l)						
Range	0.80 – 20.0	0.90 – 4.10	-	2.0 – 2.0	t=1.092	0.278
Mean ± SD.	2.66 ± 2.59	1.80 ± 0.95	-	2.0 ± -		
TSH 18m (mu/l)						
Range	0.55 – 311.0	0.70 – 4.50	-	-	t=0.542	0.590
Mean ± SD.	8.12 ± 38.58	1.78 ± 1.10	-	-		

F: F test (ANOVA)
t: Student t-test

Table (20): Comparison between the different studied groups according to HB

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
HB basal (g/dl)						
Range	5.60 – 16.50	5.0 – 19.0	11.0 – 17.30	10.0 – 15.20	F=0.538	0.657
Mean ± SD.	13.33 ± 1.92	13.24 ± 3.59	13.66 ± 2.10	13.03 ± 2.44		
HB 2W (g/dl)						
Range	8.90 – 16.60	9.0 – 14.90	10.30 – 14.60	9.0 – 13.20	F=0.381	0.767
Mean ± SD.	11.88 ± 1.68	12.32 ± 1.75	12.20 ± 1.58	11.75 ± 1.90		
HB 4W (g/dl)						
Range	4.40 – 15.20	9.0 – 14.70	9.20 – 14.60	8.0 – 12.50	F=1.122	0.345
Mean ± SD.	10.47 ± 1.73	11.28 ± 2.0	10.81 ± 2.04	10.43 ± 1.86		
HB 12W (g/dl)						
Range	7.10 – 14.30	8.20 – 13.70	8.20 – 14.0	7.20 – 11.10	F=0.548	0.651
Mean ± SD.	9.71 ± 1.59	10.15 ± 1.76	10.27 ± 1.87	9.28 ± 1.62		
HB 20W (g/dl)						
Range	8.0 – 14.90	9.0 – 13.0	11.20 – 11.20	9.30 – 13.20	F=0.547	0.651
Mean ± SD.	10.07 ± 1.31	10.20 ± 1.12	11.20 ± 0.0	10.73 ± 1.71		
HB 28W (g/dl)						
Range	8.20 – 14.50	9.20 – 12.60	-	10.0 – 10.0	t = 0.767	0.445
Mean ± SD.	10.53 ± 1.27	10.84 ± 1.0	-	10.0 ± -		
HB 36W (g/dl)						
Range	9.0 – 14.10	9.10 – 13.70	-	10.30 – 10.30	t =0.550	0.584
Mean ± SD.	13.85 ± 16.95	11.03 ± 1.43	-	10.30 – 0.0		
HB 44W (g/dl)						
Range	9.0 – 14.70	9.70 – 15.0	-	-	t=1.442	0.153
Mean ± SD.	11.32 ± 1.33	11.96 ± 1.64	-	-		

F: F test (ANOVA)
t: Student t-test

Table (21): Comparison between the different studied groups according to PLT

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
PLT basal (X10^9/l)						
Range	190.0 – 391.0	131.0 – 347.0	172.0 – 258.0	91.0 – 794.0	F=0.655	0.582
Mean ± SD.	207.87 ± 80.0	244.55±72.69	211.0 ± 33.90	279.25 ± 343.88		
PLT 2W (X10^9/l)						
Range	81.0-351.0	132.0-313.0	143.0-304.0	71.0 – 173.0	F=2.594	0.058
Mean ± SD.	198.63±69.83	216.36±63.68	203.57±59.38	109.25 ± 46.42		
PLT 4W (X10^9/l)						
Range	72.0-763.0	89.0-322.0	107.0-346.0	71.0 – 154.0	F=1.460	0.231
Mean ± SD.	192.11±97.16	207.45±75.47	199.71±82.07	97.25 ± 38.61		
PLT 12W (X10^9/l)						
Range	66.0-757.0	104.0-419.0	89.0-389.0	77.0 – 153.0	F=1.197	0.316
Mean ± SD.	182.32±95.74	210.27±88.57	204.14±103.88	107.0 ± 34.33		
PLT 20W (X10^9/l)						
Range	55.0-317.0	121.0-300.0	188.0-188.0	113.0 – 153.0	F=1.138	0.339
Mean ± SD.	180.89±64.82	198.64±59.16	188.0±0.0	130.75 ± 17.13		
PLT 28W (X10^9/l)						
Range	69.0-333.0	127.0-377.0	-	131.0 – 131.0	t=1.431	0.156
Mean ± SD.	192.76±65.71	223.73±73.96	-	131.0 ± -		
PLT 36W (X10^9/l)						
Range	32.0-970.0	130.0-439.0	-	133.0-133.0	t=0.312	0.756
Mean ± SD.	211.49±142.15	235.27±86.22	-	133.0±0.0		
PLT 44W (X10^9/l)						
Range	79.0-350.0	12.0-4036.0	-	-	t = 0.972	0.334
Mean ± SD.	211.08±65.65	233.64±103.97	-	-		

F: F test (ANOVA)
t: Student t-test

Table (22): Comparison between the different studied groups according to WBCs

	S.V.R (n = 71)	Relapse (n = 11)	Non Responder (n = 7)	Break through (n = 4)	Test of sig.	P
WBC basal ($X10^9/l$)						
Range	3.80 – 12.50	4.20 – 8.60	2.80 – 8.0	4.80 – 7.20	F=0.490	0.690
Mean ± SD.	6.65 ± 1.69	6.45 ± 1.35	5.996 ± 2.0	5.70 ± 1.12		
WBC 2W ($X10^9/l$)						
Range	1.20-10.0	3.70-8.80	3.10-9.0	4.10 – 7.20	F=0.075	0.973
Mean ± SD.	5.96±83.08	6.13±1.52	6.219±1.49	5.15 ± 1.44		
WBC 4W ($X10^9/l$)						
Range	3.0-9.20	3.80-9.20	2.90-9.20	3.50 – 6.80	F=3.245*	0.026*
Mean ± SD.	5.56±1.45	6.05±1.50	5.70±2.09	4.58 ± 1.52		
WBC 12W ($X10^9/l$)						
Range	2.60-9.60	2.30-6.50	2.70-9.0	3.0 – 5.30	F=3.335*	0.023*
Mean ± SD.	4.98±1.39	4.98±1.26	5.59±2.21	4.23 ± 0.96		
WBC 20W ($X10^9/l$)						
Range	2.0-7.80	2.90-6.20	9.0-9.00	3.0 – 5.90	F=4.522*	0.006*
Mean ± SD.	4.56±1.32	4.75±0.96	9.0±0.0	4.20 ± 1.30		
WBC 28W ($X10^9/l$)						
Range	1.90-8.0	3.20-6.80	-	5.90 – 5.90	t=0.021	0.983
Mean ± SD.	4.76±1.29	4.75±1.16	-	5.90 ± -		
WBC 36W ($X10^9/l$)						
Range	1.70-8.0	3.10-7.30	-	5.20-5.20	t=0.496	0.621
Mean ± SD.	5.06±1.38	5.28±1.33	-	5.20±0.0		
WBC 44W ($X10^9/l$)						
Range	1.90-8.30	2.60-7.10	-	-	t=306	0.760
Mean ± SD.	5.28±1.40	5.42±1.48	-	-		

F: F test (ANOVA)
t: Student t-test

Table (23): Distribution of the studied cases according to Hb, PLT and WBCs

	No.	%
Hb (g/dl)		
<10	69	69.0
<8	4	4.0
PLT ($X10^9/l$)		
<80	10	10.0
<50	2	2.0
<25	1	1.0
WBCs ($X10^9/l$)		
<4	40	40.0
<2	3	3.0

Table (24): Cases that had stopped treatment due to side effects or complications of therapy

Causes of stopping treatment		Number of cases	Percentage of cases
Neurological affection	Hemiplegia	1	1%
Sensory affection	Visual field disturbance(loss)	1	1%
Cardio-vascular affection	Ischemic heart diseases	1	1%
Haematological affection	Severe anaemia not responding to therapy	1	1%
Others	Severe incapacitating fatigue	2	2%
	Pregnancy	1	1%
Endocrine affection	------------------	0	0%
Psychiatric affection	-------------------	0	0%

Table (25): The overall cases that had stopped treatment in the study

Cause of stopping treatment	Number	Percentage of the cases
Non responder	7	7%
break through	4	4%
Side effects or complications of therapy	7	7%