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A STEP FORWARD TOWARDS COMBINATION THERAPY FOR THE PREVENTION OF HCV

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Abstract

Chronic hepatitis C is very common condition prevailing worldwide. In Pakistan, its prevalence is about 5.9%. Now, there is no vaccine available for HCV prophylaxis, so focus must be toward the treatment of HCV through combination therapy. Combination of peg-interferon alpha and ribavirin exhibits strong potential for treating Hepatitis C and at present, reported as standard treatment. Patients infected with genotype 1 and do not have any previous HCV treatment are subjected to 8 week course of treatment with ledipasvir and sofobuvir so; the treatment is limited according to fibrosis stage and baseline viral load. Ribavirin free regimens-oral interferon and elbasvir-grazoprevir are presenting as a new therapeutic treatment for HCV. End point of this therapy is sustained virological response which is aviremia condition developed after 24 weeks of therapy however, end treatment response is a condition after completion of therapy. The main goal of anti-HCV combination therapy is to eliminate HCV infection and complications associated with extrahepatic tissues and liver diseases including cirrhosis, fibrosis, hepatocellular cancer and death.

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Introduction

A habitual condition caused by hepatitis C virus throughout the world is persistent hepatitis C infection. Development of this chronic infection results in cirrhosis which is characterized by different complications including encephalopathy and ascites hepatic cell carcinoma. Occurrence of antibodies in Eastern Europe ranges between 1.5%-5%, in Asia less than 2.5%, in western pacific areas 2.5- 4.9 % , in middle east about 1% and in central Asia >12% (Flamm, 2003).

In Pakistan prevalence of HCV is 5.9% (Lavanchy, 2011). Up till now there is no any vaccine present for HCV infection so now a days the main focus in developing world is to prevent the spreading of infection by using safe methods of blood transfusion, by reducing the numbers of individuals who commence the use of injectable and also use of injection in most safe way in health care institutes (Shepard *et al.*, 2005).

Standard treatment of HCV infection as documented in research is the incorporation of Peg-interferon alpha and Ribavirin in combined form (Reddy *et al.*, 2008). Recently accepted therapy is combination of body weight dependent oral ribavirin and peginterferon (IFN)-α subcutaneous taken once per week (Naik and Tyagi, 2012). For HCV 2&3 related patients who have infection ranging between 75-90% these strategies are beneficial but not in chronic patients with HCV1&4 with infection range 45% -52% (Deutsch and Hadziyannis, 2007). The synergistic action of ribavirin and interferon protect from relapse to hepatitis C infection (Labesque*et al.*, 2011).

It is estimated that this Hepatitis C therapy not only has limited success but also has unwanted multiple side effects (Huang *et al.*, 2006). These side effects adversely act on all the individuals with chronic hepatitis C infection who treated with this therapy. Adverse effects that occur commonly include fatigue and muscular pain. Besides this psychological effects including anxiety, irritability, depression, insomnia and difficulty in concentration occur and they are very difficult to treat. Approximately in 8.7% cases these side effects result in premature stoppage of therapy (Ogawa *et al.*, 2011).

In considerable ratio of patients one of the side effects of riboflavin is anemia (Franceschi*et al.*, 2000). Anemia is a state in which hemoglobin level is decreased from baseline concentration up to 2gm/dl (Brochot*et al.*, 2010). The literature elaborated that the chances of prevalence of anemia in hepatitis infection increase by every 1mg reduction in hemoglobin level and every 10 years of age (Reau*et al.*, 2008).

The guidelines provided by European Association for the Study of Liver (EASL) include identification of disease, objectives for therapy and proper treatment, endpoint of therapy, safe treatment in health care systems and upgrade success points of treatment.

Acknowledgement of therapy is calculated in terms of various specifications including Early Virological Response EVR, described as RNA of HCV that is unnoticeable at week 12 and Rapid Virological Response (RVR), described as HCV RNA that remains undetectable at week 4 (Franceschi*et al.*, 2000).

However the main objective of combination therapy (anti-HCV) is to suppress chronic HCV infection as well as to prevent various complexities liver like fibrosis, liver diseases, hepatocellular carcinoma, cirrhosis, extra-hepatic disorders and death.

The Sustained Virological Response (SVR), is the end point of combination therapy and it is actually unnoticeable HCV RNA within 24 weeks after end of anti-HCV therapy but after accomplishment of therapy the undetectable RNA of HCV is known as End Treatment Response (Mutimer*etal.*, 2013). To minimize the disorders related to combinational therapy and to maximize the required therapeutic results different symptomatic monitoring of chronic HCV patients and efficacious laboratory tests must be performed during the therapy (Horner *et al.*, 2015).

Glecaprevir and Pibrentasvir for HCV Treatment

Worldwide infections caused by 1& 3 genotypes of hepatitis C virus is around 70% effecting 71-80 million people (Gower *et al.*, 2014). In majority of HCV genotypes the antiviral agents has been acting as standard for HCV treatment and also represent elevated level of virologic response (Asselah*et al.*, 2016). Among genotype 1 infected patients the capability of approved and antiviral agents (directly acting) ranges between 94%-99% within 12 weeks of treatment (Horner *et al.*, 2015). Patients who are infected with genotype 1 and they neither receive any treatment previously nor have cirrhosis can be treated with 8-week course of sofosbuvir–ledipasvir combination. The treatment depend upon the fibrosis stage and viral load at basal line (Grebely*et al.*, 2017).According to Most accepted guidelines of regimens 12 week treatment is enough for HCV infected patients although cohesiveness of patient goes to decline stage within last 4 weeks of therapy, which indicates that cohesiveness can be improved by short duration treatments (Townsend *et al.*, 2016).

For the treatment of patients in 12 weeks course cofounded pibrentasvir- glecaprevir or 60mg daclatasvir or 400mg sofosbuvir is given but patients treated in 8 week course of treatment received only glecaprevir–pibrentasvir in co-formulated form. In flowchart Panel B show the temperament of patients for the populations involved in statistical investigation for both trials. About 352 individuals infected with HCV genotype-1 are treated for 8 weeks by receiving glecaprevir–pibrentasvir in co-formulated form and 1 is not given any treatment similarly around 116 patients with chronic HCV infection by genotype-3 are treated for 12 weeks by giving glecaprevir–pibrentasvir and only 1 has not received therapy so, both patients were not involved in the objective to treat population (Landau *et al.*, 2000).

For conducting primary efficacy investigation a fixed-sequence procedure is used for testing. If first primary investigation succeed it would lead to secondary analysis and if results of secondary survey are successful than third survey would begin. According to the presumption of prolonged viral reaction of 97% for 12weeks, we estimated that around 270 individuals are mono infected with genotype-1 of HCV and they have not use any therapy previously with sofosbuvir hence they need to be provided greater than 90% strength for investigation (Landau *et al.*, 2000).

The investigation of primary efficacy of first ranked is defined as capability analysis during 12 weeks course of treatment.The 95% confidence interval of two sides can be calculated by using normal concentration to binomial expressions for patients percentage have viralogical reaction within 12 weeks and treated for 12 weeks after that it was analogize with 91% threshold rate. Threshold rate normally based upon virological reaction of 97% that was noticed among genotype 1 infected patients and patients who don't receive any antiviral therapy and treated for 12 weeks. Threshold level can be determined by using 6-percentage margins points (Pak, 2015).

The primary investigation at secondary level is a non-inferiority evaluation of 8 weeks course treatment as compared to treatment of 12 weeks particularly to check the ratio of persistent virological response after 12 weeks. In the investigated population 5 percentage points are used as non-inferiority margins to conduct this analysis. Patients with virological failure over 8 weeks course treatment and those who don't have virological failure and their data is also missing about persistent virological response of HCV RNA at 12 weeks treatment as well as patients who had terminated the treatment untimely are all excluded from this analysis. During the treatment of both groups patients undergo week 8 cannot assigned to treatment ultimately it will not appraise the non-inferiority analysis (Piaggio *et al.*, 2012).

The regimen of 8 weeks will be taken as non-inferior to the regimen of 12 weeks if the subordinate bound of confidence interval is 5 percentage points above of non-inferiority margin due to difference in ratio of persistent viral response after 12 weeks (difference of

sustainable virological rate at 8 weeks and at 12 weeks). After the success of secondary analysis of non- inferiority within 8-12 weeks of treatment the third ranked analysis of primary efficacy is performed in same way. It included those individuals who are previously excluded from per-protocol community (Piaggio *et al.*, 2012).

In the patients infected with genotype 1 of HCV the concentration of sustained viral response after 12 weeks is analyzed in HIV co-infected individuals and in individuals whotreated with sofobuvir previously in order to treat population. ENDURANCE-3 has 90% power and is allocated to assess the non-inferiority of regimen of 12 weeks for pibrentasvir- glecaprevir to that of sofosbuvir–daclatasvir, by using 6 percentage points as margins in order to conduct analysis. After the treatment of 8 weeks of HCV genotype 3 infected patients by providing glecaprevir–pibrentasvir17 efficacy data of phase 2 elaborated that the rate of virological response is almost 97% in 12 weeks course treatment among patients. After the discussion with certain regulatory companies we enumerate 8 weeks treatment by glecaprevir–pibrentasvir to which patients are non-randomly delegated (Mannset *al.,* 2014).

In all those patients who take minimally one dose of a trial drug statistical tests are conducted to treat them. In those statistical analysis and respective protocol which are accepted by regulatory companies the results of statistical comparisons (between 8 week treatment and 12 week treatment groups) have been included. If the 6 percentage points of non-inferiority margin is below than the lower bound difference of confidence interval or if the level of confidence interval of lower bound in group rate becomes elevated up to 92% than non-inferiority of regimen (8weeks to 12 weeks) of glecaprevir–pibrentasvir at the rate of 12 week sustained virological response has been given with 80% power. This threshold is concurred to historical 98% proportion of virological reaction after 12 weeks of treatment and in the similar population it is related with sofosbuvir–daclatasvir, with difference of 6 percentage points in non-inferiority margins (Nelson *et al.*, 2015).

During primary efficacy analysis to take control over rate of type 1error Hochberg procedure and fixed-sequence testing procedure has been used so, further details related to these procedures are described in Supplementary Appendix. Regulatory agencies select the non-inferiority margins upto 5 or 6 percentage points according to the guidelines provided in non-inferiority trials and ensuring the minimum loss of efficacy (Piaggio*et al.*, 2012).

Approximately, out of 1410 patients 200 were eliminated from the screening trials due to improper eligibility standards like 185 out of 200 individuals has 92 percentage while all others are screened out between 21st Oct, 2015 and 4th May 2016. Inclusively, 1053 patients undergo randomization while 1051 patients were treated. 352 patients infected with genotype 1 of HCV and 233 of genotype 3 has been given glecaprevir–pibrentasviror co-formulation for 12 weeks, 351 patients infected with genotype 1 provided with glecaprevir–pibrentasvir co-formulation for 8 weeks and 115 individuals infected with genotype 3 has been given sofosbuvir–daclatasvir for about 12 weeks. In addition to this 157 patients infected with genotype 3 provided with glecaprevir–pibrentasvir co-formulation for 8 weeks. Panel A of the given figure shows that patients infected with genotype 1 of chronic HCV of and SVR12 rates during 8 and `12 weeks of treatment in primary subset. This subset eliminates the patients having HIV co-infection as well as previously treated patients with sofosbuvir(Summa *et al.*, 2012).

Within the primary subset those patients are excluded who have terminated the treatment untimely, treatment results in virological failure before week 8 and those patients in which assessment window SVR12 don't show any type of HCV RNA means without virologic failure. In group of week 8 patients during primary subset just one patient infected with genotype 1a and had received treatment for HCV ultimately developed the virological failure at 29th day of treatment. However, due to non-adherence one

patient terminate at second day and the data of SVR12 had missed of one patient included in 12 week group. SVR12 rates of patients infected with genotype 3 of HCV and don't take any previous treatment for HCV and have no cirrhosis are categorized in panel B .In bar 1 about 95% confidence interval (2-sided) is determined by using normal to binomial proportions. Fig 1 shows the rate of patients infected with genotype 1 and 3.

Grazoprevir–Elbasvir Combination Therapy for HCV Treatment

The developing cause of liver decompensating, liver carcinoma, liver transplantation and cirrhosis is the infection caused by hepatitis C virus (Hajarizadeh*et al.*, 2014). Mortality rate and severe complications related to liver had been move towards decline due to effectiveness of therapy (Pearlman and Traub, 2011).

For HCV genotypes GT (1, 2, 4, 5, and 6) high potency is required but for GT3 its action is slow (Summa *et al.*, 2012). Resistance-associated variants are frequently noticed after the failure of therapy in the presence of first generation of protease inhibitors but Grazoprevir preserve substantial role against them (Howe *et al.*, 2014).

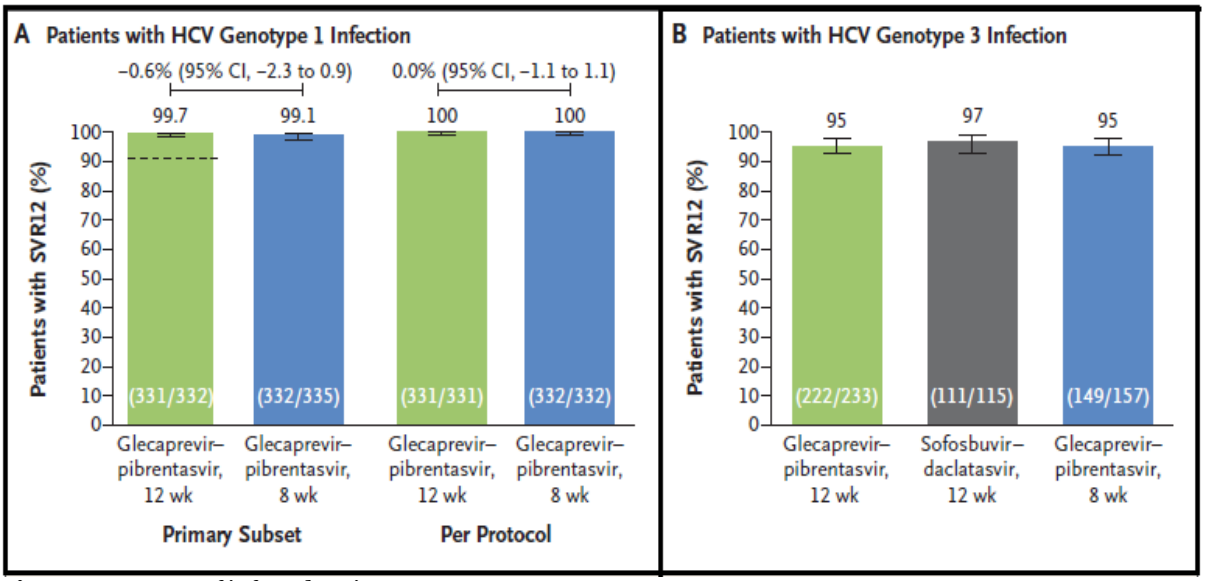

Fig. 1. SVR12 rate of infected patients.

Elbasvir defined as an NS5A inhibitor that is very active against genotypes like GT(1, 2a, 3, 4, 5 &6) even in occurrence of RAVs that involved in the non-fulfillment of NS5A inhibitors like ledipasvir and daclatasvir(Yeh*et al.*, 2013).During the substantial phase 2 clinical development program Grazoprevir–elbasvir had been assessed (Manns*et al.*, 2014).As elaborated by C-WORTHY study cirrhotic, non-cirrhotic, HIV co-infected and monoinfected individuals grazoprevir–elbasvir treatment either included ribavirin or not for 12 weeks has been providing a well-tolerated treatment and elevated level of efficacy (Lawitz*et al.*, 2015). Regimens free of ribavirin and oral interferon has easy access for the treating hepatitis C virus infection. However use of Grazoprevir–elbasvir is a new emerging option for HCV. The rate of total elimination of virus through razoprevir–elbasvir regimen for 12 weeks is 4% as demonstrated by C-EDGE Treatment-Naive study. The study of phase 3 encourage the results of phase 2 with grazoprevir– elbasvir(Lawitz*et al.*, 2015).

According to C-WORTHY study the SVR12 rates by using grazoprevir– elbasvir within 12 weeks in cirrhotic patients are 97% and in non-cirrhotic patients 98% (Sulkowski*et al.*, 2015). Its efficacy is also seem to be similar with fixed dose of sofosbuvir–ledipasvir provided for 12 weeks and SVR12 rates for cirrhotic patients are 94% and in non-cirrhotic patients 99% in this therapy (Afdhal*et al.*, 2014).

For the treatment of non- cirrhotic and cirrhotic individuals infected with various genotypes of HCV including GT 1, 4 & 6 the combination of elbasvir 50 mg and grazoprevir 100mg in the form of fixed dose is recommended by C-EDGE Treatment-Naive study which is a randomized, international, placebo-controlled, blinded and parallel- group trial. The study reveals that in patients infected with GT1 & 6 failure is coupled with baseline NS5A, GT1a RAVs with the emergence of NS5A and NS3 RAVs.

However, the occurrence of NS3-RAVs at baseline is about 40% and there is no relationship between virologic failure and NS3-RAVs of baseline has been clearly pronounced. NS3 RAVs baseline has adverse effect on regimens like protease inhibitor for example Q80K common baseline polymorphism has negative effects on the effectiveness of ribavirin and simeprevir/peginterferon having rate of SVR12 without Q80K 84% and with Q80K is 58% (McConachie*et al.*, 2016).

In 13% patients infected with genotype 1 NS5A RAVs baselines have perceived. Data elaborated a relation between baseline NS5A RAVs and virologic failure most commonly occur in GT1a infected individuals whose baseline RAVs reveal a greater than 5-fold shift to elbasvir(Zeuzem*et al.*, 2015). Patients that have high viral load at baseline develop a relation between both virologic failure and GT1a RAVs baseline since the number of individuals having NS5A RAVs baseline are considerably small. A second effect noticed in4 individuals of immediate treatment group about baseline efficacy with NS5A regimens is increased up to 5 times than normal and no any patient was having hyperbilirubinemia (Zeuzem*et al.*, 2015).

The abnormalities occurred have no any clinical consequences and are reversible. Findings of phase 2C-WORTHY and safety profile of liver of grazoprevir–elbasvir are mostly similar. In it less than 1% of patients accomplished the late advancement of alanine aminotransferase enzyme level which is 5 times greater than the normal upper limit (Lawitz*et al.*, 2015). So, in combination therapy single tablet is taking once in day and the combination of 2 drugs is more vigorous treatment for HCV infection (Zeuzem*et al.*, 2015).

Open-label C-Salvage trial for efficacy of Grazoprevir–Elbasvir Combination Therapy for HCV

In this C-Salvage trial, HCV genotype 1 infected 79 patients of which 84% with virologic failure and 43% patients with cirrhosis was failed the combination therapy by protease inhibitor and PR then they treated with ribavirin and grazoprevir/elbasvir. Despite of elevated occurrence of NS3 RAVs at baseline the levels of HCV RNA at the end of therapy were less than the detected assay limit among all the patients.

The comprehensive rates of SVR12 were 96.2% and within 12 weeks of treatment 3.8% relapses have occurred. Due to some non-virologic conditions of failing the initial treatment SVR12 of 13 patients remains 100% while in 63 patients out of 66 due to virologic failure its rate was 95.5% (Forns*et al.*, 2015).

Of 32 patients 29 have SVR12 rate 90.6% and they have decreased vulnerability at baseline to telaprevir, boceprevir and simeprevir because of virologic failure possessing virus documented as NS3 RAVs.SVR12 achieved in both non-cirrhotics and cirrhotics patients infected with sub-genotypes like 1a and 1b are similar. After failure of treatment used for viral infections the exposure of class resistance within drugs has been sharing a common mechanism of action. Luckily, in antiretroviral therapy when first protease inhibitor has failed its activity then various drugs of protease inhibitor class are adequate to use in combination therapy. People infected with genotype 1 of HCV that failed the triple therapy including PR integrated with protease inhibitor (earlier generation) can be treated with regimen anchored by protease inhibitor because the newly provided inhibitor is comparatively more effective and it is not cross- resistant to already used protease inhibitor (Forns*et al.*, 2015).

Patients who cannot tolerate the previously used interferon-combination therapy has high tolerability of regimen is also demonstrated by this trial. In 11 studied patients the dose of ribavirin needed to be reduced but in 78 of 19 patients the rate of SVR12 was 98.7% without reusage of ribavirin and among them 11 out of 12 study participants have untimely eliminate their therapy because of drug intolerance (Lawitz*et al.*, 2015).

NS3 RAVs are present at baseline in about half of the patients for 1st generation protease- inhibitor but they uncommonly express elevated level of cross-resistance to grazoprevir in vitro (Howe *et al.*, 2014). SVR12 rate has been conducted in all patients despite of 3 who have relapse. People having failed treatment with PR and protease inhibitor if provided with regimen (interferon free) of ribavirin plus grazoprevir/elbasvir for 12 weeks through oral route then chronic HCV infection can be successfully treated (Lawitz*et al.*, 2015).

Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir

For treating HCV in December 2014 Ombitasvir-paritaprevir-ritonavir-dasabuvir have been accepted for use in United States (US) and greater than 90% individuals infected with genotype 1&4 have achieved sustained response against virus (Raedler and Viekira, 2015). Ombitasvir can be defined as a NS5A inhibitor that involve in inhibition of viral assembly and RNA replication in virus. Paritaprevir is a protease inhibitor that interrupts the cleavage necessary for replication. Its efficacy can be enhanced by ritonavir along CYP3A inhibition.NS5B gene codes RNA polymerase which is HCV RNA dependent and Dasabuvir directly targets the replication of HCV by inhibiting this enzyme. The combination of these four drugs is particularly protein bounded as well as has increased distribution volume (Deeks, 2015).

Ombitasvir-paritaprevir-ritonavir-dasabuvir involve in inhibition of different proteins including UGT1A1, CYP3A4 and SLCO1B3. By the induction of CYP2C19 the interactions of significant drugs have restricted its use. Metabolism of drugs is carried out in liver and then excreted out through feces so renal damage presumed to affect the level of drugs (Pockros*et al.*, 2015). Earlier studies reveals that this combination therapy has no any side effects but the recent study demonstrated that regimen have association in liver failure in those patients infected with C cirrhosis and Child-Pugh B (Flisiak*et al.*, 2016). Side effects during treatment of patients are nausea, fatigue, elevated level of bilirubin, diarrhea and rashes (Raedler&Viekira., 2015).

HCV Genotype 1 Infection

Regimens That Include NS3/4A Protease Inhibitors

Elbasvir is a NS5A inhibitor and grazoprevir is an NS3 inhibitor and both are obtainable in fixed dose combination. The following regimen is studied within the 4 multicenter randomized trials that were published in 6 articles (Rockstroh *et al.*, 2015; Feld *et al.*, 2015; Kwo*et al.*, 2017).Because of lack of n=2 selective reporting and n=1comparator group the possibility of bias in these 3 studies is moderate. In treatment native patients that are infected with 1a and 1b genotypes the checked SVR12 rate after providing grazoprevir– elbasvirat at 12 week course treatment is 92% while in treatment experienced rate is 99-100% (Kwo *et al.*, 2017).

Paritaprevir–Ritonavir–Ombitasvir and Dasabuvir

NS3 protease inhibitor also called Paritaprevir has co-formulated with an NS5A inhibitor (ombitasvir) and ritonavir used for pharmacologic boosting. But those patients that are infected with genotype 1 an NS5B polymerase inhibitor has also added called dasabuvir. Studies have been conducted in which 9 individuals have received 3-DAA regimens for 12-24 weeks because 4 have moderate and 5 have low bias risk while 1 received 2 DAA regimen because of low risk of bias (Pockros*et al.*, 2016; Sulkowski*et al.*, 2015). The SVR12 rates are less when 3-DAA regimen is provided without ribavirin in HCV type 1a infected individuals (90%) as compared to persons infected with 1b infection (99%). Fortunately by adding ribavirin the rate of SVR12 in persons infected with genotype 1a has become 97%. In comparison with placebo, ribavirin commonly results in fatigue, anemia,

insomnia and rashes. When cirrhotic patients infected with genotype 1a are provided with three DAA regimens for 24 weeks in addition to ribavirin the level of SVR12 increased 94.2% vs 88.6% (Poordad*et al.*, 2014). By providing ribavirin and three DAA regimens in genotype 1b infected patients for 12 weeks the SVR12 rate lies between 97% to 100% (Kwo*et al.,* 2017; Lawitz*et al.*, 2016).

Simeprevir (NS3 protease inhibitor) and sofobuvir (NS5B polymerase inhibitor) has been taken in combined form once in day. In patients infected with HCV genotype 1a the SVR12 rates are minimum due to the resistance linked substitutions at 28, 30, 31, and 93 positions of NS5A region (Rockstroh*et al.*, 2015; Sulkowski*et al.*, 2015). There are greater chances of fatigue, anemia and nausea as 3% to 16% vs 0% due to ribavirin (Sulkowski*et al.*, 2015). Except those patients infected with HCV genotype 1a with baseline RASs the rate of VR12 are same either they treated in the presence or absence of ribavirin. Cirrhosis has no link with low SVR rates (Poordad*et al.*, 2016).

Regimens That Do Not Include NS3/4A Protease Inhibitors

Daclatasvir and Sofosbuvir

With sofosbuvirdeclatasvir is also used which is a NS5A inhibitor. Patients with hepatic disorders have lower SVR rates up to 82% (Poordad*et al.*, 2016).

Ledipasvir–Sofosbuvir

Only one dosage is given per day of sofosbuvir and ledipasvir (NS5A inhibitor) in combined form. Total 8 studies have been demonstrated by providing various treatment durations like 8, 12 and 24 weeks and in the presence of ribavirin (Poordad*et al.*, 2016; Kowdley *et al.*, 2014; Charlton *et al.*, 2015; Manns*et al.*, 2016). The medium bias risk is due to allocation scheme concealment n=2 and lack of comparator n=1.

Velpatasvir–Sofosbuvir

Sofosbuvir and Velpatasvir are provided to patients in co-formulated form once in day. This Velpatasvir is a pangenotypic NS5A inhibitor. Patients having 1a and 1b infection, with cirrhosis and prior treatment experience when received this regimen for 12 weeks have elevated rates of SVR up to 97% to 99% (Feld *et al.*, 2015). The patients that sustain placebo and velpatasvir–sofosbuvir have similar adverse events as examined in placebo controlled which is a double line trial having less bias risk (Sulkowski*et al.*, 2015).

HCV Genotype 2 Infection

Daclatasvir and Sofosbuvir

Acoording to ALLY-2 studies 13 patients having HIV coinfection and genotype 2 infection has been treated for 12 weeks attained SVR (Razikyet *al.*, 2017). Another stusy reveals that out of 26 the 24 HIV seronegative, non-cirhhotic and treatment native patients was treated for24 weeks both in the presence and absence of ribavirin attained SVR but 2 patients have lost to follow up (Sulkowski*et al.,* 2014).

HCV Genotype 3 Infection

Daclatasvir and Sofosbuvir

Out of 18 in phase 2 study 16 no-cirrhotic patients have been treated either with or without providing ribavirin for 24 weeks assessed SVR (Sulkowski*et al.*, 2014). While in ALLY-3 trail of single group people with medium bias risk, treatment experienced individuals and 94-97% non-cirrhotic patients also achieved SVR after 12 weeks of treatment (Nelson *et al.*, 2015).

Ledipasvir–Sofosbuvir

26 patients provide with ribavirin and ledipasvir–sofosbuvir for about 12 weeks attained SVR. Without ribavirin SVR rate is less up to 64% while in treatment experienced individuals it is 82 % (Gane*et al.*, 2015).

Velpatasvir–Sofosbuvir

RCT phase 3 shows that 12 weeks treatment with velpatasvir–sofosbuvir provided for 12 is superior to ribavirin and sofosbuvir co-formulation provided for 24 weeks having SVR 95% and 80% respectively. This treatment was conducted on 552 patents and demonstrated that it has less adverse effects mainly less anemia (Wyles*et al.*, 2015).

HCV Genotype 4 Infection

Grazoprevir–Elbasvir

According to C-EDGE study the efficiency of grazoprevir– elbasvir has been elaborated among 18 individuals infected with genotype 4 of HCV by providing those 12 weeks regimen ultimately achieving 100% SVR rate.

It indicated that the occurrence of NS5VR cannot affect SVR (Rockstroh*et al.*, 2015). However, in treatment experienced individuals who received regimen for 12 to 16 weeks either with or without ribavirin the rates of SVR are less than 95% except for those who gets regimen with ribavirin for 16 weeks (Kwo*et al.*, 2017).

Paritaprevir–Ritonavir–Ombitasvir

A trial with less bias risk, ribavirin and paritaprevir–ritonavir– ombitasvir leads to increased efficacy as SVR rates are 100% in patients infected with genotype 4 as in treatment experienced n=44 and in treatment natives n=42. Due to absence of bibavirin SVR rate are 91% (Abergel*et al.*, 2016).

Simeprevir and Sofosbuvir

According to RCT trial with moderate bias risk, 43 patients when treated with plus sofosbuvir for 12 weeks have achieved SVR 100% due to allocation scheme concealment and unclear sequence generation. While 20 patients have less SVR rate (75%) when treated for 8 weeks (Razaky*et al.*, 2017).

HCV Genotype 5 and 6 Infection

With genotype 5 and 6 infected individual's six studies have been conducted (Rockstroh*et al.*, 2015).

Ledipasvir–Sofosbuvir

Ledipasvir–Sofosbuvir combination results in elevated level of SVR rates in people with HCV genotype 5having SVR 95% and n=41 while for genotype 6 infections SVR is 96% and n=25 (Abergel*et al.*, 2016).

The patient numbers for treatment are less than SVR which is high up to 95 % in experienced persons and 89% in those having cirrhosis (Abergel*et al.*, 2016).

Velpatasvir–Sofosbuvir

During conducting of RCT trials with less bias risk, for patients having genotype 5 (n=350) and with genotype 6 (n=41) and provide with treatment of 12 weeks the SVR rates are high up to 97 and 100% respectively and only one patients cannot assess to SVR (death unrelated to treatment)(Lawitz*et al.*, 2016).

Conclusion

At present, monotherapy is not capable for treating advanced stages of hepatitis C so; combination therapy is capable of reducing the chances of resistance development of a pathogen against multiple drugs simultaneously. Combination of different drugs showed effective clinical efficacy against HCV. The novel findings of multiple drugs will have implications not only on maximizing its clinical utilization, but also improving therapeutic outcomes. As it is very encouraging therapy so, future research must be continued to unravel the role of combination therapy.

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