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REVIEW

Advancements in combination therapy of Hepatitis C virus

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Abstract: Hepatitis C virus (HCV) is a primary cause of chronic liver disease along with various complications like liver cirrhosis and malignancy which leads to death. It has infected more than 185 million people worldwide. There is no congruence established for the treatment of various genotypes of HCV infection owing to diversity in prevalence globally. Assessment of affected individuals with HCV by polymerase chain reaction (PCR), viral load of HCV and liver enzyme levels (i.e., ALT and AST) are the foundation to evaluate the safety and efficacy of HCV therapies. The antiviral efficacy has been greatly improved and sustained viral response (SVR) rates increased from 6% with interferon monotherapy to 50-80% with PEG-interferon/ribavirin combination therapy to >95% after the approval of all interferon free oral direct acting antiviral agents. The main objective of this review article is to compile data from reference sources regarding the old and current therapeutic strategies used to manage HCV infection. It is accepted that chronic HCV infection increases patient's thrombocytopenia and neutropenia risk and complications increased in co-morbid disorders like in tuberculosis, HIV, diabetes etc. In past treatment associated side effects were the major consequences and many patients have to stop the treatment. But after the approval of direct acting antiviral drugs create a revolution in the treatment of HCV infection. So, it could be concluded that current combination therapies are a promising hope to eradicate and to control HCV but some safety concerns required more considerations Therefore, this review focus on the available latest combination therapies and their effectiveness to eradicate HCV infection.

Keywords: Sustained viral response, interferon; ribavirin; direct acting antiviral agents, safety, efficacy.

INTRODUCTION

It is widely accepted that hepatitis C virus (RNA in nature and member of the family flaviviridae) infection exists in various genotypes forms throughout the world. Progression of acute HCV infection to chronic infection result in cirrhosis, which ultimately leads to hepatic cell carcinoma if not treated timely. Socioeconomic issues (low literacy rate, poor hygiene, inefficient blood screening and less awareness) are playing major role in the spread of HCV infection and lack of awareness regarding the treatment and managements of hepatitis C virus patient in developing countries (Raja and Janjua, 2008). Occurrence of anti-HCV antibodies in Eastern Europe region ranges between 1.5%-5%, in Asia region less than 2.5%, in the western pacific region 2.5- 4.9%, in middle east region about 1% and in central Asia region>12%. World health organization (WHO) reported region wise epidemics for HCV as Western Pacific region 6.2%, African region 6.1%, Eastern Mediterranean region 3.3%, South-East Asia 2%, European region 1.6% and American region 0.7% (WHO, 2017). In Pakistan prevalence of HCV is 5.9% (Lavanchy, 2011). Still there is not any available vaccine to manage HCV infection, so now a days the main focus in developing world is to prevent the spread of infection by using safe methods of blood transfusion, by reducing the numbers of individuals who commence the use of injectable drugs and also use of injection in most safe way in health care institutes.

Pegylated interferon alpha and ribavirin were the treatment used for HCV with maximum SVR up to 75% having various side effects till 2011 but after the approval and recommendations of interferon free direct acting antiviral agents, the use of pegylated interferon and ribavirin has been discontinued (Naik and Tyagi, 2012). The synergistic action of ribavirin and interferon protect from relapse to hepatitis C infection (Labesque *et al*., 2011). but also has unwanted multiple side effects. These side effects adversely act on all the individuals with chronic HCV infection who was treated with this therapy. Adverse effects that occur commonly include anemia, fatigue and muscular pain. Besides this psychological effect, 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). The guidelines provided by European Association for the study of liver include identification of disease, objectives for therapy and proper treatment,

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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, described as RNA of HCV that was undetectable at week 12 and rapid virological response, described as HCV RNA that remains undetectable at week 4. However, the main objective of combination therapy (anti-HCV) is to suppress chronic HCV infection as well as to prevent various associated complications like fibrosis, hepatocellular carcinoma, cirrhosis, extrahepatic disorders and death. The SVR is indicated the successful results of combination therapy and it should be undetectable after 24 weeks of anti-HCV therapy (Mutimer *et al*., 2013).

Worldwide, infections caused by 1 and 3 genotypes of hepatitis C virus are around 70% effecting 71-80 million people (Gower *et al*., 2014). Among genotype 1 infected patients the capability of approved antiviral agents (directly acting) ranges between 94%-99% within 12 weeks of treatment (Horner *et al*., 2015). In the majority of HCV genotypes the antiviral agents have been acting as standard for HCV treatment (Asselah *et al*., 2016). According to most accepted guidelines of regimens 12-week treatment is enough for HCV infected patients, (Townsend *et al*., 2016). 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 depends upon the fibrosis stage and viral load at basal line (Grebely*et al*., 2017). To minimize the disorders related to combination 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. The main focus of this review article is to describe the various anti-HCV therapeutic strategies currently used as combination therapies after first FDA approved interferon free all oral antiviral agent in 2011 to date, their specificities, efficacy and safety concerns.

Different Combination therapies, their mode of actions and Viral specificities

Glecaprevir and Pibrentasvir for HCV Treatment

AbbVie®,and Enanta®, recognize the Glecaprevir as a protease inhibitor occurs in non-structural protein 3/4A form and pibrentasvir as NS5A inhibitor. The effective ratios for 1-6 HCV genotypes of Pibrentasvir and Glecaprevir lie within 1-5nmol/liter and 0.85-2.8nmol/ liter respectively. ENDURANCE-1(a study that involved the capability, efficacy and safety of ABT-493/ABT-530 in individuals with genotype 1 infection) study co-infection of those people with HCV genotype 1 infection and also those who have immunodeficiency virus type 1 (HTLV-1) and ENDURANCE-3 (a study that compare safety of ABT-493/ABT- 530 to Sofosbuvir dosed with Daclatasvir in adult people infected with genotype 3 involved the patients infected with genotype 3 and not formly received any treatment, we estimated the capability, safety and efficacy of both 8 and 12 week course therapy with ribavirin free treatment, taken one time per day glecaprevir-pbrentasvir in individuals without cirrhosis (Wyles *et al*., 2015; Afdhal *et al*., 2014). Patients with less than 18 years age are qualified for contributing in these trials only if they have an infection due to 1or 3 genotypes and also has elevated levels of HCV RNA up to 1000 IU/ml at the screening. People having HCV and HIV coinfection and had not previously received any kind of treatment with sofosbuvir plus ribavirin and with pegylated interferon either with or without ribavirin could receive this therapy instead of genotype-3 infected individuals (Kwo *et al*., 2017; Gane*et al*., 2013). The presence or absence of cirrhosis in patients was recorded by serum marker assessment, liver biopsy and transient elastography. Patients that have coinfection (infected with more than one genotype) and have positive surface antigens of hepatitis were also inhibited for this therapy so; the description of eligibility criteria is available in a supplementary appendix at the organization of New England Journal of Medicine.

Patients in ENDURANCE-1 are roughly allocated in ratio 1:1 hence to sustain coformulated concentration (120mg of Pibrentasvir and 300mg of Glecaprevirz) of glecaprevir-pibrentasvir for about 8-12 weeks. The time period of post-treatment viral response after 12 weeks and open label therapy is also shown. However, two roughly formulated treatment groups of 12 weeks and one non-randomly formed group of 8 weeks that is sequentially registered after completing the enrollment of 12 weeks are also registered in ENDURANCE-3. For the treatment of patients in the 12-weeks course coformulated Pibrentasvir- Glecaprevir or 60mg Daclatasvir or 400mg Sofosbuvir was given, but patients treated in the 8-week course of treatment received only Glecaprevir-Pibrentasvir in combination form. In flowchart Panel-B shows 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 with 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.

In all those patients who took minimally one dose of a trial drug statistical tests are conducted to treat them. In that 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 the 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 SVR 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 a difference of 6 percentage points in non-inferiority margins (Nelson *et al*., 2015).

During primary efficacy analysis to take control over rate of type I error Hochberg procedure (Adjusting the rate helps to control for the fact that sometimes small p-values (less than 5%) happen by chance, which could lead you to incorrectly reject the true null hypotheses. In other words, the B-H Procedure helps you to avoid Type I errors (false positives) and fixed-sequence testing procedure has been used. 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. 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 these 157 patients infected with genotype 3 provided with glecaprevir-pibrentasvir co-formulation for 8 weeks (Piaggio *et al*., 2012).

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 direct acting antiviral therapies. For HCV genotypes (1,2,4,5,6) high potency is required but for genotype 3 its action is slow. Resistance-associated variants are frequently noticed after the failure of therapy in the presence of the first generation of protease inhibitors, but Grazoprevir preserve a substantial role against them (Howe *et al*., 2014).

Elbasvir defined as an NS5A inhibitor that is very active against genotypes like genotype (1, 2a, 3, 4, 5 and 6) even in the 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 have easy access for the treating HCV infection. However use of Grazoprevir-elbasvir is a new emerging option for HCV. 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 has also seemed to be similar with a 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).

In patients infected with genotype 4 Grazoprevir-elbasvir this therapy has high efficacy resulting the SVR12 rate 100%. In the treatment of native patients infected with genotype 4 from the combined state 2/3 grazoprevir-elbasvir database (54 of 56 [96%]) the visualized response rate is constant with rates of SVR12. Although the rates of SVR12 are constantly less than that seen in genotype 1 and 4 but the efficacy of grazoprevir- elbasvir is highly meaningful for genotype 6. In patients infected with genotype 1a genotype NS5A, NS3, GT1 RAVs are noticed during their population sequencing but most common agents for virologic failure are Y93H, NS3-Q80K, NS5A-M28V/A/G, D168A, L31M and Q30H/L/R. By taking grazoprevir- elbasvir patients with virologic failure can be treated and these discoveries have intimations for salvage therapy in a small proportion of individuals. For the treatment of non-cirrhotic and cirrhotic individuals infected with various genotypes of HCV including 1, 4 and 6 the combination of elbasvir 50 mg and grazoprevir 100 mg 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 genotype 1 and 6 failure is coupled with baseline NS5A, genotype 1a, 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 the baseline has been clearly pronounced. The NS3 RAVs baselinehas 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 gasterointestinal infected individuals whose baseline RAVs reveal a greater than 5-fold shift to elbasvir. Patients that have high viral load at baseline, develop a relation between both virologic failure and genotype 1a RAVs baseline since the number of individuals having NS5A RAVs baseline are considerably smaller. A second effect noticed in individuals of the 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 the safety profile of liver of grazoprevir–elbasvir are mostly similar. Less than 1% of patients accomplished the late advancement of ALT level, which is 5 times greater than the normal upper limit (Lawitz *et al*., 2015). So, in combination therapy single tablet is taken once in a 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, 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 filing the initial treatment SVR12 of 13 patients remain 100%, while in 63 patients out of 66 due to virologic failure its rate was 95.5% (Forns *et al*., 2015). From 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-cirrhotic and cirrhotic patients infected with sub-genotypes like 1a and 1b are similar.

After the 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 the protease inhibitor classes 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 reuse of ribavirin and among them 11 out of 12 study participantshave untimely eliminated their therapy because of drug intolerance. NS3 RAVs are present at baseline in about half of the patients for 1st generation protease-inhibitor but they uncommonly express elevated levels of of cross-resistance to grazoprevir in vitro (Howe *et al*., 2014). SVR12 rate has been conducted in all patients despite of 3 who have relapsed. People having failed treatment with PR and protease inhibitor if provided with regimen (interferon free) of ribavirin plus grazoprevir/elbasvir for 12 weeeks 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 the united states and greater than 90% individuals infected with genotype 1 and 4 have achieved sustained response against virus (Raedler, 2015). Ombitasvir can be defined as an NS5A inhibitor that involve in inhibition of viral assembly and RNA replication in viruses. 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 are 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*., 2016). Earlier studies reveal that this combination therapy has no 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, 2015).

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 (Feld *et al*., 2015; Rockstroh *et al*., 2015). 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 pharmacological 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). Because of minimum amount of comparator group up to n=2, concealment of allocation scheme n=2 and uncertain sequence generation bias risk was moderate.

The SVR12 rates are less when 3 direct acting antiviral regimens 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 a 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 sofosbuvir declatasvir is also used which is an NS5A inhibitor. Patients with hepatic disorders have lower SVR rates up to 82% (Poordad *et al*., 2016). Once-daily oral daclatasvir plus sofosbuvir was associated with high rates of sustained virologic response among patients infected with HCV genotype 1, 2, or 3, including patients with no response to prior therapy with telaprevir or boceprevir. Daclatasvir is a first-in-class HCV NS5A replication complex inhibitor and sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor. Both have potent antiviral activity and broad genotypic coverage and are administered orally once daily (Sulkowski *et al*., 2014).

Ledipasvir-Sofosbuvir

Only one dosage is given per day of sofosbuvir and ledipasvir (NS5A inhibitor) in combined formulation. 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; Charlton *et al*., 2015 Velpatasvir-Sofosbuvir.

Sofosbuvir and Velpatasvir are provided to patients in co-formulated from once in a 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 showedelevated 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

Six studied patients infected with HCV genotype 2 are enrolled while out of 3 studies 1 has a medium bias risk and 2 have less bias risk also assessed velpatasvir-sofosbuvir in fixed dose combination (Feld *et al*., 2015; Wyles *et al*., 2015). 3 studies with medium bias risk are assessed by sofosbuvir and daclatasvir co-formulation (Poordad *et al*., 2106 El Raziky *et al*., 2017). In phase 2 trials, treatment with the combination of the nucleotide polymerase inhibitor sofosbuvir and the NS5A inhibitor velpatasvir resulted in high rates of sustained virologic response in patients chronically infected with hepatitis C virus (HCV) genotype 2 or 3. Among patients with HCV genotype 2, the rate of sustained virologic response in the sofosbuvir–velpatasvir group was 99% (95% confidence interval [CI], 96 to 100), which was superior to the rate of 94% (95% CI, 88 to 97) in the sofosbuvir-ribavirin group (P=0.02). Among patients with HCV genotype 3, the rate of sustained virologic response in the sofosbuvir-velpatasvir group was 95% (95% CI, 92 to 98), which was superior to the rate of 80% (95% CI, 75 to 85) in the sofosbuvir–ribavirin group. The most common adverse events in the two studies were fatigue, headache, nausea, and insomnia (Foster *et al*., 2015).

Daclatasvir and sofosbuvir

According to ALLY-2 studies 13 patients having HIV coinfection and genotype 2 infection has been treated for

12 weeks attained SVR (Raziky *et al*., 2017). Another study reveals that out of 26 the 24 HIV seronegative, non-cirrhotic and treatment naive patients were 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 non-cirrhotic patients have been treated either with or without ribavirin for 24 weeks assessed SVR [56] (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 treated 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 is superior to ribavirin and sofosbuvir co-formulation 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 with 12-week regimen ultimately achieving 100% SVR rate. It indicated that the occurrence of NS5VR cannot affect SVR [47] (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, SVR rates are 100% in patients infected with genotype 4 both in treatment experienced (n=44) and in treatment *natıve* (n=42) patients. Due to absence of bibavirin SVR rate are 91% (Menon *et al*., 2015).

Simeprevir and sofosbuvir

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

HCV Genotype 5 and 6 Infection

Currently, six studies have been conducted with genotype 5 and 6 infected individuals (Rockstroh *et al*., 2015; Lawitz *et al*., 2016).

Ledipasvir-Sofosbuvir

Ledipasvir-Sofosbuvir combination results in elevated level of SVR rates 95% (n=41) in people with HCV genotype5, while for genotype 6 infection SVR is 96% (n=25) (Abergel *et al*., 2016). The patient numbers for treatment are less than SVR, which is high up to 95 % in treatment experienced persons and 89% in those having cirrhosis (Abergel *et al.,* 2016).

Velpatasvir-sofosbuvir

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

CONCLUSION

Hepatitis C virus (HCV) is a primary cause of chronic liver disease along with various complications like liver cirrhosis and malignancy which leads to death. The major cause of chronic HCV is injectable drugs uses and it has infected more than 185 million people worldwide. Pegylated Interferon and ribavirin associated side effects have been eradicated after the introduction and use of all interferon free oral direct acting antiviral agents with more than 95% SVR which is great revolution in the treatment of HCV infection. So, it could be concluded that current combination therapies are a promising hope to eradicate and to control HCV but some safety concerns required more considerations.

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