

Chronic Hepatitis C Virus Infection: Epidemiology, Treatment and Barriers of Management in Non Type 1 Genotypes infection

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Abstract Chronic Hepatitis C (HCV) infection occurs in more than 130 to 150 million individuals world wide. Twenty percent of patients chronically infected with HCV progress to cirrhosis. Other than cirrhosis, Chronic HCV infection is strongly associated with liver cancer and end-stage liver disease requiring transplantation. However, as with the approval of the first generation protease inhibitors telaprevir and boceprevir, we see significant progress in the treatment of chronic hepatitis c infection. however this has benefited many but not all patients with HCV infection as protease inhibitors have never been approved for genotype 2 and 3. No direct acting antiviral agents have ever been approved until recently. Very recently sofosbuvir, a direct acting antiviral agent which is a nucleotide polymerase inhibitor, has been approved for genotypes 2, 3, (and genotypes 1 and 4), where as multiple direct acting agents are approved and used for genotype 1 which includes but is not limited to Simeprevir. Now patients with genotype 3 have emerged among the hardest to treat. The reason behind this treatment failure of genotype 3 infections is that genotype 3 still remains a challenge to the efficacy of even newer regimen Also genotype 3 is associated with a more rapid progression of the disease. In addition, genotype 4 is increasing in Europe. Thus we want to emphasize the ongoing need for new, simpler therapeutics using direct –acting antivirals that target various stages of the HCV lifecycle to eradicate HCV without concomitant INF.

Keywords: chronic hepatitis C, non type 1 genotypes, epidemiology, direct acting anti virals, sofosbuvir

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1. Introduction

Chronic Hepatitis C (HCV) infection occurs in more than 130 to 150 million individuals world wide [1]. Twenty percent of patients chronically infected with HCV progress to cirrhosis. Other than cirrhosis, Chronic HCV infection is strongly associated with liver cancer and end-stage liver disease requiring transplantation.

However,as with the the approval of the first generation protease inhibitors telaprevir and boceprevir, we see significant progress in the treatment of chronic hepatitis c infection. however this has benefited many but not all patients with HCV infection [2] as protease inhibitors have never been approved for genotype 2 and 3 [3,4]. No direct acting antiviral agents have ever been approved until recently. Very recently sofosbuvir, a direct acting antiviral agent which is a nucleotide polymerase inhibitor, has been approved for genotypes 2, 3, (and genotypes 1 and 4), where as multiple direct acting agents are approved and used for genotype 1 which includes but is not limited to Simeprevir. Now patients with genotype 3 have emerged among the hardest to treat. The reason behind this treatment failure of genotype 3 infections is that genotype 3 still remains a challenge to the efficacy of

even newer regimen Also genotype 3 is associated with a more rapid progression of the disease [5]. In addition, genotype 4 is increasing in Europe [6,7]. Thus we want to emphasize the ongoing need for new, simpler therapeutics using direct –acting antivirals that target various stages of the HCV lifecycle to eradicate HCV without concomitant INF [8].

2. Discussion

Epidemiology of non type 1 genotypes of Hepatitis C Virus Infection

World Wide Prevalence of non type 1 HCV infection

The fundamentals of HCV management is to identify HCV genotypes and subtypes. In one hand this is of epidemiological interest, on the other hand it determines the type and duration of anti viral therapy where the risk of selecting resistance-associated variants during therapy is an important concept [6,7]. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described. Genotype 1 is the most prevalent genotype world wide, with a higher proportion of subtype 1b in Europe [6,7] and and 1a in the USA [6,7]. In India high prevalence of genotype 3 (> 76 %) and very low prevalence of genotype 2 (< 2 %) are seen [9]. Also

genotype 3a is highly prevalent in the European population of people who inject drugs (PWID). The incidence and prevalence of infections among PWID with HCV genotype 4 is currently growing [6,7] (prevalence of HCV 4 in Europe accounts for 14 to 20 % of HCV infections in some countries, which is mostly associated with immigration and intravenous drug use). Nevertheless, HCV genotype 4 which accounts for roughly 13 % of HCV infections, is common in the Middle East, North Africa, and Sub-Saharan Africa and is responsible for more than 90 % of HCV infections in Egypt. Also genotype 4 is the most common Hepatitis C virus genotype world wide. The spread of chronic HCV infection in Egypt is thought to be largely, but not only due to needle reuse during mass treatment programs for schistosomiasis during the late 1950's through the early 1980s. Unfortunately transmission continues to occur primarily through iatrogenic sources, such as blood transfusions, injections, and dental care. This seems related to poverty and lack of education [10-15].

Genotype 2 is found in clusters in the Mediterranean region. Genotypes 5 and 6 are rare in Europe [16]. Genotype 5, which has only one subtype 5a, can be found in South Africa and genotype 6 can be found in South – east Asia [9,17,18]. When analyzing prevalences of different genotypes in Asian countries, in Beijing, China, of 63 HCV –RNA samples, 52 % were genotype 2 and 29 % type 3 [9,13,14] where as in Thailand, HCV 3a was the most common genotype (50-60 %) with 1a, 1b, and 6 comprising the rest (10 – 20 % each) [9,17,18]. Now the novel genotype 7 has originated from Central Africa [16].

Several factors may contribute to the high incidence of HCV relative to that of other blood –borne infections among IDUs [19]. One important reason is the more frequent persistence of HCV compared to that of HBV. In general we see over 80 % of HCV infections persist [16]. Thus, among IDUs there is a large reservoir of HCV from which new injection drug users are infected. Persistence is even higher for HIV infection than for HCV infection. However, the prevalence of HIV is less than that of HCV among drug using populations, as HIV is less transmissible through parenteral route. Statistically approximately 0.3% persons exposed accidentally to HIV by being stuck with a needle become infected [20], but for HCV the frequency is at least 10-fold higher [19,21,22].

In a study performed in Belgium, an important difference in HCV seroprevalence among drug users in a methadone maintenance programs across two geographic regions, rural and urban settings was demonstrated [23]. This was explained not only by variations in drug-related risk behavior, but also by differences in sexual risk behavior and socio-economic and immigration status, which still need to be carefully reanalyzed in future studies [24].

However, in non injectors the sexual transmission of hepatitis C might contribute the highest prevalence rates of hepatitis C when compared to the general population [24]. Since non injectors often have (ex) injecting sexual partners of whom most are infected with hepatitis C, exposure to hepatitis C in this group is evidently much more frequent than in general population where the background prevalence varies around 1 % [24]. Goldberg et al [25] documented a HCV prevalence of 15 % among non-IDU women with an injecting sexual partner.

Special population

While most of the studies are centered around injection drug users or patients attending sexually transmitted diseases clinics it has been well documented that dialysis patients also have a higher rate of HCV infection [26]. In the 90's anti HCV prevalence rates was 10 to 50 % among Hemodialysis world wide with lower rates of 1.7% was found in Ireland [27,28,29,30,31]. In past rates in Europe were as high as 20 -30 % [27]. A more recent report from Saudi Arabia showed a prevalence rate of HCV among hemodialysis patients to be 9.24 % compared to 0.30 % among blood donors [26,29]. A survey of Hepatitis B and Hepatitis C virus prevalence among dialysis patients in Bahrain and Saudi Arabia were performed. Hemodialysis patients were consecutively recruited from tertiary medical centers in Bahrain and Saudi Arabia and the majority of patients received blood transfusion [29]. HBsAg (5.88% vs 0.31%) and anti –HCV (9.24 vs 0.30 %) were higher among patients than donors ($p < .001$) while antibody to HBcAg (anti HBc) was higher among blood donors (4.60%) than patients (1.7%)($P = 0.01$). The majority of Bahraini patients (4/6) had a high viral loads ($>500,000$ IU/ ML), compared with Saudi patients [32]. All Saudi Arabia patients tested positive for HCV 4, and 2 each carried in addition HCV -2 or each carried in addition HCV -2 or HCV -2a, while Bahraini patients were positive for HCV -1a and 1-b, in addition to -2a and -4, and most cases (4/6) were double positive, a distinct finding of this unique study [32].

The prevalence of HCV has been noted to be higher in kidney transplant populations as well. Among kidney transplants we found the prevalence was as high as 33.3 % in Italy. The frequency was higher prior to 1990 (50 %) than after 1990 (27 %) [33]. Definitely, most of these kidney transplant patients underwent dialysis as well.

Evolution of chronic hepatitis C treatment

The standard of care for all patients with HCV infection included 24 to 48 weeks of treatment with peginterferon –alfa 2b and ribavirin. First-generation NS3 protease inhibitors Telaprevir (TVR) and Boceprevir [34] was approved since 2011 as the new standard of care treatment for HCV genotype 1 patients only. But efficacy of TVR/BOC has been shown to be largely dependent on Peginterferon plus ribavirin backbone antiviral activity, as with this treatment regimen SVR rates were disappointing in difficult to treat patients such as previous non responders to dual therapy and used for genotypes 4,5 and 6 [34]. Also because of treatment with interferon is associated with troublesome side effects, the safety and efficacy of various interferon sparing and interferon –free regimens for the treatment of genotype 2 or 3 infection is significant [2].

Treatment Issues

Thus over decades several efforts had been made and steps were taken in patients with genotypes 2 and 3 chronic hepatitis C (CHC) to assess whether shortening the duration of therapy with peg –IFN and RBV might preserve the efficacy of the standard 24 week treatment duration while decreasing side effects and improving tolerability [35].

As we understand both the effectiveness of IFN in blocking production of the virus in the first phase of viral decline (rapid decline) and the rate of decline in the second phase (slower decline) differ in patients with

hepatitis C virus (HCV) genotype 2 or 3 [35], several investigators came to the hypothesis that in patients with CHC genotype 2 or 3 and rapid virologic response (RVR, ie, HCV RNA undetectable after 4 weeks of therapy), 12 - 16 weeks of treatment with PEG – IFN and RBV may be as effective as a course of 24 weeks. This hypothesis is reinforced by Accelerate study. This study left an open question - whether a higher weight –based dose of RBV still permit a shorter duration of treatment [31] of genotype 2 and 3 patients with RVR without increasing the risk of relapse [33]. But accelerate study was challenged by North-C trial [32] with lower SVR (81% vs 91%) and higher relapse rates (11% vs 5%) in those treated for 14 weeks (as compared to a 24 week regimen) using RBV 800-1400 mg daily dose [36]. Not much studies have been conducted on other genotypes, 5, 6 and 7.

As duration of treatment could not be truncated with IFN and RBV regimen, this subsequently implicated a thought whether HCV genotype 2 or 3 could be treated without IFN. A phase 2 trial in patients with chronic HCV infection (either genotype 2 or 3) found the success of treatment with sofosbuvir plus ribavirin resulted in a SVR in 100% of previously untreated patients and 50 to 73% of previously treated patients [2,37]. Sofosbuvir, a direct acting agent which is active against all hepatitis C virus genotypes plus ribavirin for 12 weeks may be effective in previously untreated patients with HCV genotype 2 or 3 infection (100% who received sofosbuvir plus RBV without IFN had a SVR at 24 weeks) [2]. Sofosbuvir and weight based ribavirin alone has replaced IFN- containing therapy for HCV genotypes 2 and 3.

Current Treatment of Hepatitis C, non type 1 genotypes Genotypes 2 and 3

Patients with HCV genotypes 2 and 3, representing 20-29% of US HCV infections, should receive sofosbuvir and RBV alone when indicated. In a randomized, controlled, open-label phase 3 non –inferiority trial (**Fission trial**) among treatment- naïve, cirrhotic and non cirrhotic patients with chronic HCV genotypes 2 or 3, receiving sofosbuvir-ribavirin for 12 weeks, response rates were lower among patients with GT 3 infection than among patients with GT 2 infection (SVR at 12 weeks after the end of therapy is 56% vs 97%) and were lower for patients with cirrhosis than for without cirrhosis (47% vs 72%) [38]. High rates of sustained virologic response were observed among patients who have been historically been less likely to have a sustained response, including black patients and those with the unfavorable IL 28 CT /TT genotypes [38]. This study did not detect the S 28 T mutation (the only variant known to be associated with resistance to sofosbuvir) on deep-sequencing assays in any patient receiving sofosbuvir [36]. As no detectable resistance to sofosbuvir was found, this is against the rapid emergence of viral resistance that has been observed with other classes of direct acting anti HCV agents in patients who had virologic break through during treatment or relapse after completion of therapy [38]. Current recommendation for GT 2 infection in cirrhotic patients is to treat with Sofosbuvir and Ribavirin for 16 weeks. This recommendation is based on likely due to high virologic failure when treated with 12 weeks duration, even though there is no study performed yet to support this fact.

With Sofosbuvir and RBV regimen, viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, IL 28 B status, and presence or absence of IFN in the regimen [2]. All patients have undetectable level of HCV by week 4, with viral suppression sustained through the end of treatment. No virologic breakthrough was observed in any patient during the dosing period. The presence or absence of Peg – IFN alfa 2a appeared to have no effect on viral kinetics or rate of SVR [2,38].

Out of 50, 10 patients with HCV genotype 2 or 3 infection who received sofosbuvir alone suggest a role for RBV in the maintenance of an antiviral response. Although all 10 patients had a rapid response in this recent study and had an undetectable level of HCV RNA by week 4 of treatment, which was maintained for the duration of treatment, 4 patients had a relapse after the end of treatment. Sofosbuvir monotherapy led to a SVR in the other 6 patients [38]. The exact mechanism by which RBV prevents relapse when added to IFN / DAA remains uncertain, but Ribavirin is added with Sofosbuvir.

However, this success of treatment in genotype 2 or 3 infection is limited. In future RBV free treatment regimen can be used for non type 1 genotypes. We are exploring effective treatment options in the use of INF free and RBV free regimen in previously untreated chronic Hepatitis C patients; There is a success now in this area with the use of Ledipasvir and sofosbuvir for previously treated HCV genotype 1 and genotype 4 infections [39]. Even though studies did not include chronic Hepatitis C genotypes 2 and 3, a similar study, ALLY trail demonstrates high cure rates for investigational Daclatasvir and Sofosbuvir combination among genotype 3 chronic Hepatitis C patients [40,41]. Daclatasvir and sofosbuvir regimen achieves SVR 12 in 90% of treatment – naïve and 86% of treatment –experienced genotype 3 patients. The efficacy was not tested in previously treated patients with IFN, specially non- responder patients with Hepatitis C virus genotype 2/3 infection (a 12 week vs 24 – week treatment study). As a direct acting agent, Daclatasvir seems promising, as Daclatasvir has shown pan-genotypic activity in bench research, a factor which is becoming increasingly important as we learn more about the complexity of HCV [40]. Further, Daclatasvir's potential to be combined with many other agents, including Sofosbuvir, is significant in continuing to develop additional treatment options that may help patients of all genotypes achieve cure [40,41].

Genotype 4:

Because interferon –containing treatments for genotype 4 infection have low efficacy and poor tolerability, efficacy and safety of an oral interferon free regimen, Ombitasvir, an NS5A inhibitor, and paritaprevir plus ritonavir have been recommended now for genotype 4 infection. Based on **PEARL -1** trail (which included non cirrhotic CHC Genotype 4 patients [42]), this regimen achieved high sustained virological response rates at 12 weeks after the end of treatment and was well tolerated, with low rates of anemia and treatment discontinuation. Interestingly in previously untreated patients, SVR 12 rates were 100% in the ribavirin containing regimen and 90.9% in ribavirin free regimen. Even though no statistically significant differences in SVR 12 between

the treatment naïve groups were noticed (after adjusting for IL 28 B), currently Ribavirin is included in the regimen for treatment naïve patients with genotype 4 infection. All treatment experienced patients achieved SVR 12 of 100 %. No virologic failures were recorded in ribavirin containing regimen [42]. Another treatment option of treatment naïve HCV GT 4 infected patients is a 24 –week course of Sofosbuvir and Ribavirin. A recent study performed on the Egyptian Ancestry Genotype 4, investigators found

that SVR 12 rates were 90 % with 24 weeks and 77 % with 12 weeks of sofosbuvir and ribavirin therapy [43]. In a single-group study of sofosbuvir combined with peginterferon–ribavirin (Neutrino Trial) [38,44], patients with predominantly genotype 1 or 4 HCV infection had a rate of sustained virologic response of 90% at 12 weeks and patients with genotype 2 or 3 infection who received either sofosbuvir or peginterferon with ribavirin had nearly identical rates of response (67%) (Table 1) [38,44].

Table 1. Response during and after treatment period [39]

Response	NEUTRINO Study		FISSION Study	
	SOF+PEG+RBV for 12Wk (N=327)	SOF+RBV for 12Wk (N=253)	PEG+RBV for 12Wk (N=243)	
HCV RNA<25 IU/ml –no./total no.(%)				
During treatment	299/327 (91)	231/251 (92)	76/241 (32)	
At 2 wk	321/325 (99)	249/250 (>99)	158/236 (67)	
At 4 wk	326/253 (>99)	249/253 (98)	217/243 (89)	
At last observed measurement				
After end of treatment	302/327 (92)	187/253 (74)	181/243 (74)	
At 4 wk	295/327 (90)	170/253 (67)	162/243 (67)	
At 12 wk	0	1 (<1)	18 (7)	
Virologic breakthrough during treatment—no. (%)				
Relapse in patients with HCV RNA < 25 IU/ml at end of treatment—no./total no. (%)				
Patients who completed treatment	25/320 (8)	71/242 (29)	37/188 (20)	
Patients who did not complete treatment	3/6 (50)	3/7 (43)	9/29 (31)	

Genotypes 5 and 6

Not much data on treatment of genotypes 5 and 6. Now we treat chronic hepatitis C patients infected with genotype 5 with daily sofosbuvir (400 mg) and weight –based ribavirin (1000 mg (< 75 Kg) to 1200 mg (> 75 kg) plus weekly Peg – IFN for 12 weeks in treatment naïve patients with HCV genotype 5 infection [45]. Neutrino trial supports this current recommendation because of rapid virologic response and sustained virologic response at 12 weeks and low discontinuation rate [36]. Though Atomic trial also suggests that there is no additional benefit of extending treatment beyond 12 weeks, investigators concluded that these findings would have to be substantiated in Phase 3 trials [46]. The result of the

Atomic study was limited by the fact that neither treatment experienced patients nor cirrhotic patients nor patients with genotypes 5 were not enrolled in this study [47].

In summary, In various studies, the primary end point was sustained virologic response (HCV RNA < 25 IU / ML) at 12 weeks post treatment (SVR 12). (Table 2) [48].

Compensated cirrhosis at baseline was found in 17 % of patients in the Neutrino study, 21 % in Fission study, 18 % in Positron, and 33 % in Fusion [48].

In all studies, SVR 12 was higher in patients without cirrhosis. Patients with genotype 2 experienced higher SVR 12 than those with genotype 3.

SVR 24 rates were similar to SVR 12 rates (Table 3) [48].

Table 2. 12-week SVR rates [48]

	GT 1,4,5,6		GT 2 and 3				
	NEUTRINO	FISSION	POSITRON	FUSION			
	SOF/PEG/RBV (n = 327)	SOF/RBV (n = 253)	PEG/RBV (n = 243)	SOF/RBV (n = 207)	Placebo (n = 71)	SOF/RBV 12 week (n = 100)	SOF/RBV 16 week (n = 95)
Overall	91%	67%	67%	78%	0%	50%	73%
GT 2	N/A	97%	78%	93%	0%	86%	94%
GT 3	N/A	56%	63%	61%	0%	30%	62%
Noncirrhotic	93%	72%	74%	81%	0%	61%	76%
Cirrhotic	80%	47%	38%	61%	0%	31%	66%

Nonresponders

Never the less another unresolved issue in treatment of Chronic Hep C non type 1 genotypes is the lack of effective treatment regimen in case of non responders. For retreatment of nonresponders with IFN with or without RBV, SVR in a large trial in chr hepatitis C genotype 2 and 3 or non type 1 genotypes, was 82.5 % and 79.3 % on 24 weeks and 48 weeks respectively. Thus on chronic Hepatitis C non type 1 genotypes, the optimal duration of treatment with Interferon and ribavirin was 24 weeks [48]. From studies we see the non responders had significantly lower IFN concentrations as well as significantly greater mean age, body mass index, and viral load. Suboptimal drug concentrations may thus contribute to lack of

Table 3. SVR12 vs SVR24 [48]

	SVR12	SVR24
Treatment-naïve patients		
GT 1, 4, 5, 6 overall	91%	91%
GT 1	90%	90%
GT 4	96%	96%
GT 5 and GT 6	100%	100%
Treatment-naïve and experienced GT 2, 3 patients		
Treatment-naïve	67%	67%
Interferon unable	78%	78%
Previously treated (12 week regimen)	51%	50%
Previously treated (16 week regimen)	73%	72%

response to therapy in patients with infection due to genotype 2/3 [49].

3. Conclusion

Definitely more studies on chronic Hepatitis C non type 1 genotypes need to be performed in a systemic manner to generate more efficacious treatment plans for non responders and previously treated patients [19]. Given the associated morbidity and mortality and the lack of an HCV vaccine, efforts to prevent HCV infection must be focused on reducing injection drug use and practices involving sharing of drug use equipment [19]. Strategies such as needle exchange programs may be effective in this way [19,50,51]. Crudely, factors like a low level of education, unemployment, marginalization and a loose social network are considered to be main barriers to the management of hepatitis C infection in addition to lack of an effective treatment plan [24]. Prevention measures should not only be directed towards ceasing high risk drug related behavior but should also include measures to decrease sexual high risk behavior, certainly in populations where intravenous drug use is less common. Efforts should be made to gain a better understanding of how different social conditions influence variation of hepatitis C prevalence [24].

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Conflict of Interest

None.

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