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**Genotype 3-hepatitis C virus’ last line of defense**

Zarębska-Michaluk D. GT3 HCV last line of defense

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**Abstract**

Chronic infection with hepatitis C virus (HCV) is one of the leading causes of liver disease globally, affecting approximately 71 million people. The majority of them are infected with genotype (GT) 1 but infections with GT3 are second in frequency. For many years, GT3 was considered to be less pathogenic compared to other GTs in the HCV family due to its favorable response to interferon (IFN)-based regimen. However, the growing evidence of a higher rate of steatosis, more rapid progression of liver fibrosis, and lower efficacy of antiviral treatment compared to infection with other HCV GTs has changed this conviction. This review presents the specifics of the course of GT3 infection and the development of therapeutic options and the development of therapeutic options for GT3-infected patients in the era of direct-acting antivirals (DAA). The way from a standard of care therapy with pegylated IFN-alpha (pegIFNα) and ribavirin (RBV) through a triple combination of pegIFNα + RBV and DAA to the highly potent IFN-free pangenotypic DAA regimens is discussed along with some treatment options which appeared to be dead ends. Although the implementation of highly effective pangenotypic regimens is the most recent stage of revolution in the treatment of GT3 infection, there is still room for improvement, especially in patients with liver cirrhosis and those who fail to respond to DAA therapies, particularly those containing inhibitors of HCV nonstructural protein 5A.

**Key Words:** Hepatitis C virus; Genotype 3; Antiviral treatment; Interferon; Direct-acting antivirals; Pangenotypic

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**Core Tip:** Genotype 3 which is second in frequency worldwide, is unique among genotypes of hepatitis C virus in its higher rate of steatosis, accelerated fibrosis progression, and lower cure rates. This paper describes the genotype-specific mechanisms of liver injury and provides an overview of therapeutic options. Currently, available highly potent pangenotypic regimens have revolutionized the treatment of genotype 3 infection, however, patients with liver cirrhosis and those who fail to response to direct-acting antiviral therapy still present a therapeutic challenge.

**INTRODUCTION**

Chronic infection with hepatitis C virus (HCV) is assumed to be one of the leading causes of liver disease globally, affecting approximately 71 million people[1]. Due to the high genetic diversity of the viral nucleic acid sequence, six major genotypes (GT), differing from each other by 30% at the nucleotide level, comprising multiple subtypes of HCV, have been identified[2]. The majority of patients worldwide are infected with GT1, but infections of GT3 are also common in some regions. GT3 is defined by a higher rate of steatosis, increased risk of liver cirrhosis, and different response to antiviral drugs compared to other GTs. In the era of treatment with pegylated interferon alpha (IFNα) and ribavirin (RBV), patients infected with GT3 were considered "easy to treat" due to an efficacy rate of 70%, compared to less than 50% in GT1 and GT4 infected patients. The introduction of direct-acting antivirals (DAA) has changed the management of HCV infection, allowing a substantial increase in the treatment efficacy, however, the improvement for GT3 infection was not as pronounced as for other GTs, particularly in treatment-experienced patients and those with liver cirrhosis.

**The global spread of GT3**

GT3 infections are widely distributed worldwide and are estimated to be the second in frequency accounting for approximately 25%-30% of all HCV cases globally[2]. The distribution of GT3 varies between different countries and continents. The highest global prevalence (exceeding 70%) is found in South Asian countries, while a rate of approximately 20% is reported in Central and Southeast Asia, a few percent in East Asia, and only 0.4% in the Asia-Pacific region. A relatively high frequency of 36% is documented in Australia[3]. GT3 infection accounts for 14.2% of HCV cases in South America, 2.1% in Central America, and 15.7% in North America, ranging from 8.9% in the United States to 22.3% in Canada[3]. In Europe, the distribution of GT3 infections is also heterogeneous with the highest frequency exceeding 40% in Scandinavia and England, over 30% in Ireland, Greece Russia, and Slovenia, and more than 20% of infections in Germany, Switzerland, Montenegro, Belgium, Bosnia, and France[4-6]. The rate of a dozen percent is reported from Spain, Poland, Portugal, Bulgaria, and Croatia, whereas the lowest prevalence, below 10%, are documented in Italy, Albania, Hungary, and Romania[7-10]. The lowest proportional frequency of GT3 infections is found in Africa at an average of 5.3%, with the highest frequency at 7.4% in East Africa through 6.3% in North Africa to 0.8% in the central part of the continent[3].

**Good or bad in the HCV family**

For many years, GT3 was considered to be less pathogenic compared to other GTs in the HCV family due to its favorable response to an IFN-based regimen. However, the growing evidence of a higher rate of steatosis and more rapid progression of liver fibrosis compared to infection with other HCV GTs has changed this conviction.

Liver steatosis is a frequent histological finding in patients with chronic hepatitis C (CHC). Although this feature is common among all HCV infected individuals, with an average rate of 50%, the highest prevalence exceeding 70% is observed in patients infected with GT3[11-14]. In in-vitro studies, GT3 is also demonstrated to be much more likely to induce liver steatosis than other HCV GTs[15]. The pathogenesis of hepatic steatosis is complex and related to host and viral factors, as well as to alcohol consumption. Metabolic steatosis, which is associated with host risk factors including high body mass index, obesity, dyslipidemia, metabolic syndrome, insulin resistance and type 2 diabetes, is commonly found in patients infected with non-GT3 HCV, whereas in the GT3-infected individuals, virus-related hepatic steatosis is described as predominantly being induced by the direct cytopathic effect of the HCV is described[16-20]. Although the exact mechanism remains unknown, several pathways are linked to the pathogenesis of GT3-induced steatosis. A central role is played by the inhibition of microsomal triglyceride transfer protein function by HCV core protein, resulting in overall decreased hepatocyte lipid export with intracellular triglycerides accumulation. This effect is documented to be amplified with HCV-3 core proteins[21]. Another mechanism through which the virus modulates the host lipid metabolic pathways is inhibition of the peroxisome proliferator associated receptor-α (PPAR-α), a transcription factor inducing hepatic fatty acid oxidation and ketogenesis. A decrease in PPAR-α level leads to hepatic lipid collection. *In vitro* studies document inhibition of PPAR-α observed in the GT3 infections as being more efficient than in infections with GT1 HCV[22]. Viral-induced hepatic steatosis results not only from the reduction of the lipid excretion with subsequent intracellular lipid accumulation but also from the promotion of the neolipogenesis with fatty acid synthesis. This activity is proposed to be a consequence of an increase in function of sterol regulatory element-binding protein-1c activated by the HCV-3 core protein, however, the exact mode of activation is unknown[23]. The hypothesis of a pathogenic link between GT3 infection and steatosis is supported by a significant correlation of the steatosis score and intrahepatic titer of HCV RNA only in patients infected with GT3[16]. The improvement in liver steatosis in GT3-infected patients after successful antiviral therapy, which is not observed in patients infected with GT1, seems to indirectly confirm this association[24,25]. GT3 HCV was also identified as an independent predictor for the accelerated progression of liver fibrosis in addition to established risk factors including the age of infection, male gender, coinfection with hepatitis B virus and human immunodeficiency virus, insulin resistance, iron overload, alcohol and drugs intake[26]. Precise analysis of the influence of HCV GT on the more advanced liver disease is difficult due to the coexistence of the aforementioned predictors and the previously discussed higher prevalence of liver steatosis in GT3 infection, which contributes to more rapid progression of hepatic fibrosis[12,27,28]. However, the pooled analysis conﬁrmed a signiﬁcantly more severe liver disease in single-biopsy studies and a trend towards the faster progression of fibrosis in GT3 patients compared with the other GTs[29]. The strong association between GT3 infection and end-stage liver disease was documented in HCV-infected drug abusers in France and confirmed by a population-based study in a cohort of native Alaskans with CHC[30,31].

An increased risk not only of liver cirrhosis but also of hepatocellular carcinoma (HCC) among GT3 infected individuals compared to those infected with other GTs was reported in a large cohort (> 110000) of American patients from the Veterans Affairs Registry[32,33]. Consistent results of significantly higher incidence of HCC in GT3 patients were also obtained in French and Korean populations[34,35]. Nevertheless, the effect of HCV GT3 infection on the higher prevalence of liver cancer remains controversial because of the data demonstrated for GT1b as a major risk factor for HCC development[36,37].

**IFN and RBV couple**

The standard of care therapy of pegylated (peg) IFNα and RBV established in 2000 has resulted in a sustained virologic response (SVR) of approximately 70% in GT3-infected patients[38-42]. Such a high effectiveness compared to the SVR below 50% achieved by patients with GT1 and GT4 infection was the basis for the GT3 being deemed "easy to treat" and has led to attempts to shorten the treatment course to 16, 14, and even 12 wk. However, the reduction in the SVR rate was reported in patients who did not achieve the so-called rapid virologic response (RVR) defined as undetectability of HCV RNA after 4 wk of therapy[38,39,42-44]. The meta-analysis of twelve clinical trials performed by Andriulli *et al*[45] documented a wide variance in response to pegIFNα and RBV in GT3-infected patients depending on the baseline viral load. Individuals with a high baseline level of HCV RNA demonstrated a significantly lower SVR rate of 58% compared to 75% in those with a low baseline viral load. The strongest predictive factor for treatment response was RVR and this finding provided the basis for the conclusion that patients without RVR may need a longer therapy duration. The negative impact of cirrhosis on treatment response among subjects infected with GT3, leading to poor antiviral effectiveness was documented by Powis *et al*[46], suggesting that such patients also require an alternative management strategy. However, the extension of the treatment course did not result in higher effectiveness, nor was there an improvement in the SVR rate on increasing the dose of RBV[47-49].

**The couple with a little help of DAA**

The registration of the first DAAs in 2011, which were inhibitors of the HCV serine protease (non-structural protein 3/4A, NS3/4A), started a revolution in the treatment of CHC. The combination of telaprevir or boceprevir with pegIFNα and RBV significantly increased the SVR rate, but only in patients infected with GT1[50,51]. Those infected with other GTs, including GT3, were still treated with pegIFNα and RBV because no significant improvement was demonstrated after the addition of telaprevir or boceprevir[52,53]. Therefore, at the beginning of the DAA era GT3 emerged as a "difficult-to-treat" GT. New hopes for higher effectiveness were raised with the introduction of the next-generation DAAs for possible combination with pegIFNα and RBV. Unfortunately, clinical trials demonstrated that simeprevir, a second-wave protease inhibitor with documented in-vitro pangenotypic activity has limited efficacy in GT3-infected patients, and the effectiveness of daclatasvir (DCV), acting through inhibition of the HCV nonstructural protein 5A (NS5A), has proven to be also disappointing, with SVR rates of 45% and 74% in GT3 patients with and without liver cirrhosis, respectively[54,55]. However, the expectations of a higher response rate among GT3-infected patients have been met by sofosbuvir (SOF), a new DAA class representative, HCV polymerase (NS5B) inhibitor. The addition of SOF to pegIFNα and RBV (SPR) leads to better outcomes when compared to standard of care therapy, regardless of liver fibrosis and history of previous antiviral therapy. Phase 2 clinical trials documented a response of 83% among treatment-experienced patients with liver cirrhosis participating in the LONESTAR-2 study, while non-cirrhotic, treatment-naïve individuals treated in the QUANTUM study responded in 92% of cases[56,57].

Patients included in the BOSON phase 3 clinical trial achieved an SVR of 93%, specifically 88% among individuals with liver cirrhosis and 95% in those without; the lowest efficacy of 86% was demonstrated for patients with liver cirrhosis who failed to respond to previous antiviral therapy[58]. An open-label clinical study evaluating the outcome of SOF-containing treatments reported 100% efficacy among GT3-infected treatment naïve patients without cirrhosis treated with triple therapy[59].

Those results from clinical trials were supported by real-world experience (RWE) data that documented an SVR rate higher than that following dual therapy. The best response of 93% was reported for non-cirrhotics among Americans treated in the Veterans Affairs health care system[60]. Scandinavian patients responded in 96% of cases, an efficacy of 98% was obtained in the Polish EpiTer-2 study and an SVR reached 99% in a German cohort[6,61,62]. The effectiveness of the SPR regimen in cirrhotic individuals in these RWE studies was also promising, reaching 92%, 81%, 91%, and 88%, respectively[6,60-62].

RWE data revealed a failure of previous therapy, with a history of treatment with IFN and RBV shown to be a negative prognostic factor of the response to SPR treatment. This triple regimen was still recommended by the guidelines of the European Association for the Study of the Liver in 2015 for GT3-infected noncirrhotic patients and those with compensated liver cirrhosis, regardless of treatment history[63]. Irrespective of the high effectiveness of SPR, accompanied by reasonable tolerability due to the short treatment period, any IFN-based therapy was refused by patients[61]. Therefore, further research on the treatment of GT3 infections has focused on highly efficient IFN-free therapeutic options.

**DAA home alone**

The first available IFN-free regimen, SOF and RBV, used in GT3-infected patients for 12 wk or 16 wk, did not result in increased efficacy when compared to standard of care therapy, which demonstrated significantly lower response rates in patients with liver cirrhosis, especially in those who had previously failed IFN and RBV therapy (Table 1)[40,58,64].

The extension of treatment duration to 24 wk enabled effectiveness of up to 95%, however, the difference in response rates between patients without and with liver cirrhosis was significant[58,65]. The results of phase 3 clinical trials confirmed by RWE data became a basis for treatment guidelines, according to which IFN-ineligible GT3-infected patients should receive SOF/RBV for 24 wk. However, this regimen was recognized as suboptimal, due to unsatisfactory effectiveness for those with liver cirrhosis who had previously failed IFN and RBV therapy[66-68].

Searching for the optimal antiviral regimen, the combinations of SOF and another DAA with a different mechanism of action were studied. Promising results were obtained with a SOF and DCV combination administered for 12 wk and 24 wk, with or without RBV[69-71]. Although the difference in response rates with SOF + DCV ± RBV between non-cirrhotic and cirrhotic patients was still noticeable, this regimen was recommended for the treatment for GT3-infected patients regardless of liver fibrosis and history of previous therapy and has been widely used in RWE settings[66,72-74]. High efficacy and good tolerability demonstrated in both clinical trials and real-world cohorts have made this regimen a reasonable choice for therapy for GT3 infection as long as highly potent pangenotypic options became broadly available[75-77].

**Better is the enemy of good enough**

The final stage of the revolution in antiviral treatment which improved the outcome and simplified the management of GT3-infected patients was the implementation of potent pangenotypic regimens (Table 1).

According to the most recent guidelines, two basic options of DAAs are currently approved for the treatment of GT3 infection; a fixed-dose combination of SOF and velpatasvir (VEL), and dual treatment with glecaprevir (GLE), an NS3/4A protease inhibitor, and pibrentasvir (PIB), an NS5A inhibitor (Table 2)[78,79]. A single-tablet regimen containing SOF and VEL was registered based on the results of the ASTRAL-3 study, which confirmed effectiveness exceeding 93% in noncirrhotic and 89% in cirrhotic patients[80]. The 12-wk regimen is recommended for non-cirrhotics and patients with compensated cirrhosis, regardless of the previous treatment history. The addition of RBV may be considered in compensated individuals.

It is noteworthy that SOF/VEL combined with RBV is the only option recommended for patients with decompensated liver cirrhosis[81,82]. Data on the high efficacy and favorable safety profile of SOF/VEL achieved in clinical trials were supported by RWE studies reporting comparable SVR rates. Prior treatment-experience, as well as advanced liver fibrosis, were significant predictors of reduced effectiveness[83-87]. As resistance-associated substitutions at the NS5A position can be responsible for a reduction in the efficacy of the NS5A inhibitors, the resistance-associated substitutions testing at baseline should be considered for treatment-experienced patients and cirrhotic individuals, irrespective of treatment history, for whom SOF/VEL is being considered. The identification of the Y93H substitution indicates the need for RBV addition or an alternative regimen administration[78,79].

The second potent pangenotypic option is a combination of GLE and PIB, which was approved for the treatment of patients without or with liver cirrhosis irrespective of previous therapy. As protease inhibitors containing regimens carry a risk of decompensation during antiviral treatment, GLE/PIB is not recommended for decompensated cirrhotic patients[88]. This regimen provides the opportunity for shortening therapy to 8 wk in the majority of patients[89]. Based on findings from the ENDURANCE-3, SURVEYOR-II, and EXPEDITION-8 clinical trials, an 8-wk regimen has been registered for all previously untreated patients, including those with compensated liver cirrhosis, whereas treatment-experienced GT3-infected individuals should be treated for 16 wk regardless of liver fibrosis[90-94]. RWE studies reported effectiveness for an 8-wk GLE/PIB regimen, which exceeded 96% in treatment-naïve patients without liver cirrhosis[95-99]. Since the shortening of therapy in previously untreated cirrhotic patients infected with GT3 has been approved very recently, the available RWE data are very limited and only include a small number of patients[100,101]. Therefore, further studies are needed to determine the treatment outcome in this subpopulation. Although the implementation of SOF/VEL and GLE/PIB regimens has resulted in a high efficacy rate among GT3-infected individuals, there is still room for improvement, especially in those who did not achieve SVR, particularly following NS5A containing regimens. For such patients, a 12-wk salvage therapy with a single-tablet combination of SOF/VEL and next-generation NS3/4A protease inhibitor voxilaprevir (VOX) is recommended[102]. Safety and efficacy of SOF/VEL/VOX in GT3-infected patients without and with liver cirrhosis, both treatment-naïve and treatment-experienced were demonstrated in the POLARIS studies (Table 1)[102,103].

The other option to address failed DAA treatment in GT3-infected patients is a combination of GLE/PIB plus SOF and RBV, as investigated in the MAGELLAN-3 study. This demonstrated a 100% SVR rate, however, the small number of patients enrolled may have limited the broad applicability of these findings[104].

**Something went wrong**

On the way to developing highly effective pangenotypic regimens against GT3, there were multiple paths that appeared to be dead ends. Some of them were not investigated despite showing encouraging initial results, due to disappointing treatment outcomes in selected subpopulations of GT3 patients. One good example is an open-label study of 12-wk treatment with an NS5A inhibitor—ledipasvir and SOF, plus RBV, which demonstrated a 100% SVR rate among treatment-naïve GT3 infected individuals. Unfortunately, due to limited efficacy in treatment-experienced patients, especially those with liver cirrhosis, as well as low antiviral potency without RBV against GT3, that direction of search has proved a blind alley[105]. Alisporivir, a cyclophilin inhibitor, applied alone or with RBV in treatment-naïve noncirrhotic patients has resulted in SVR rates of 76% and 93%, respectively, however, research involving other subgroups of patients was suspended due to a safety issue[106]. Efficacy was observed to be below expectations with the combination of the NS3/4A inhibitor grazoprevir (GZR) and the NS5A inhibitor elbasvir (EBR) with RBV, as well as with a regimen consisting of the NS5A inhibitor ruzasvir and the NS5B inhibitor uprifosbuvir[107,108]. The unsatisfactory outcome of the treatment with NS35A inhibitor ombitasvir, and NS3/4A inhibitor paritaprevir boosted by ritonavir with or without RBV, was subsequently improved by the addition of SOF, but ultimately these regimens were not further evaluated, because there were new potent pangenotypic options on the horizon[109,110]. For this same reason, investigations into a regimen of GZR/EBR combined with uprifosbuvir or SOF were discontinued, despite the high effectiveness demonstrated in phase 2 clinical trials. However, GZR/EBR + SOF is currently recommended by AASLD/IDSA as an alternative option for the specific subpopulation of pegIFNα+RBV-experienced patients with compensated liver cirrhosis[79,111-113].

**CONCLUSION**

Despite the high efficacy and safety of pangenotypic therapies, that may sooner or later cure all or at least almost all identified HCV infections, including GT3, there will still be many infections that go unrecognized and are therefore impossible to cure with even the best drug. The major problem that remains to be solved worldwide is screening people who are unaware of the risk of liver disease progression from a virus in their body. It is a shame for national governments that, despite having access to the perfect tool to eliminate a dangerous virus and rule out one of the most difficult-to-treat cancers, are not doing enough.

**REFERENCES**

1 **World Health Organization**. Global Health Sector Strategy on Viral Hepatitis 2016-2021. [cited 31 December 2020]. Geneva, Switzerland: World Health Organization [Internet]. Available from: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1

2 **Messina JP**, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015; **61**: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]

3 **Petruzziello A**, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol* 2016; **22**: 7824-7840 [PMID: 27678366 DOI: 10.3748/wjg.v22.i34.7824]

4 **Petruzziello A**, Loquercio G, Sabatino R, Balaban DV, Ullah Khan N, Piccirillo M, Rodrigo L, di Capua L, Guzzo A, Labonia F, Botti G. Prevalence of Hepatitis C virus genotypes in nine selected European countries: A systematic review. *J Clin Lab Anal* 2019; **33**: e22876 [PMID: 30843304 DOI: 10.1002/jcla.22876]

5 **Alberti A**, Lacoin L, Morais E, Lefevre C, Abogunrin S, Iheanacho I. Literature review of the distribution of hepatitis C virus genotypes across Europe. *J Med Virol* 2016; **88**: 2157-2169 [PMID: 27171396 DOI: 10.1002/jmv.24573]

6 **Dalgard O**, Weiland O, Noraberg G, Karlsen L, Heggelund L, Färkkilâ M, Balslev U, Belard E, Øvrehus A, Skalshøi Kjær M, Krarup H, Thorup Røge B, Hallager S, Madsen LG, Lund Laursen A, Lagging M, Weis N. Sofosbuvir based treatment of chronic hepatitis C genotype 3 infections-A Scandinavian real-life study. *PLoS One* 2017; **12**: e0179764 [PMID: 28704381 DOI: 10.1371/journal.pone.0179764]

7 **Flisiak R**, Pogorzelska J, Berak H, Horban A, Orłowska I, Simon K, Tuchendler E, Madej G, Piekarska A, Jabłkowski M, Deroń Z, Mazur W, Kaczmarczyk M, Janczewska E, Pisula A, Smykał J, Nowak K, Matukiewicz M, Halota W, Wernik J, Sikorska K, Mozer-Lisewska I, Rozpłochowski B, Garlicki A, Tomasiewicz K, Krzowska-Firych J, Baka-Ćwierz B, Kryczka W, Zarębska-Michaluk D, Olszok I, Boroń-Kaczmarska A, Sobala-Szczygieł B, Szlauer B, Korcz-Ondrzejek B, Sieklucki J, Pleśniak R, Ruszała A, Postawa-Kłosińska B, Citko J, Lachowicz-Wawrzyniak A, Musialik J, Jezierska E, Dobracki W, Dobracka B, Hałubiec J, Krygier R, Strokowska A, Chomczyk W, Witczak-Malinowska K. Prevalence of HCV genotypes in Poland - the EpiTer study. *Clin Exp Hepatol* 2016; **2**: 144-148 [PMID: 28856279 DOI: 10.5114/ceh.2016.63871]

8 **Palladino C**, Ezeonwumelu IJ, Marcelino R, Briz V, Moranguinho I, Serejo F, Velosa JF, Marinho RT, Borrego P, Taveira N. Epidemic history of hepatitis C virus genotypes and subtypes in Portugal. *Sci Rep* 2018; **8**: 12266 [PMID: 30116054 DOI: 10.1038/s41598-018-30528-0]

9 **Brady Z**, Stoykova Z. Hepatitis C virus genotype analysis in patients with chronic hepatitis in North Eastern Bulgaria. *J Drug Assess* 2019; **8**: 146-149 [PMID: 31552145 DOI: 10.1080/21556660.2019.1654484]

10 **Gervain J**. [Analysis of hepatitis C virus type and subtype distribution in Hungary]. *Orv Hetil* 2018; **159**: 2-8 [PMID: 29847988 DOI: 10.1556/650.2018.31177]

11 **Björnsson E**, Angulo P. Hepatitis C and steatosis. *Arch Med Res* 2007; **38**: 621-627 [PMID: 17613353 DOI: 10.1016/j.arcmed.2006.09.001]

12 **Adinolfi LE**, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364 [PMID: 11391523 DOI: 10.1053/jhep.2001.24432]

13 **Lonardo A**, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* 2004; **126**: 586-597 [PMID: 14762795 DOI: 10.1053/j.gastro.2003.11.020]

14 **Mihm S**, Fayyazi A, Hartmann H, Ramadori G. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997; **25**: 735-739 [PMID: 9049227 DOI: 10.1002/hep.510250340]

15 **Abid K**, Pazienza V, de Gottardi A, Rubbia-Brandt L, Conne B, Pugnale P, Rossi C, Mangia A, Negro F. An *in vitro* model of hepatitis C virus genotype 3a-associated triglycerides accumulation. *J Hepatol* 2005; **42**: 744-751 [PMID: 15826725 DOI: 10.1016/j.jhep.2004.12.034]

16 **Rubbia-Brandt L**, Quadri R, Abid K, Giostra E, Malé PJ, Mentha G, Spahr L, Zarski JP, Borisch B, Hadengue A, Negro F. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000; **33**: 106-115 [PMID: 10905593 DOI: 10.1016/s0168-8278(00)80166-x]

17 **d'Avigdor WMH**, Budzinska MA, Lee M, Lam R, Kench J, Stapelberg M, McLennan SV, Farrell G, George J, McCaughan GW, Tu T, Shackel NA. Virus Genotype-Dependent Transcriptional Alterations in Lipid Metabolism and Inflammation Pathways in the Hepatitis C Virus-infected Liver. *Sci Rep* 2019; **9**: 10596 [PMID: 31332246 DOI: 10.1038/s41598-019-46664-0]

18 **Negro F**. Mechanisms and significance of liver steatosis in hepatitis C virus infection. *World J Gastroenterol* 2006; **12**: 6756-6765 [PMID: 17106922 DOI: 10.3748/wjg.v12.i42.6756]

19 **Asselah T**, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; **55**: 123-130 [PMID: 16344578 DOI: 10.1136/gut.2005.069757]

20 **Fartoux L**, Poujol-Robert A, Guéchot J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005; **54**: 1003-1008 [PMID: 15951550 DOI: 10.1136/gut.2004.050302]

21 **Mirandola S**, Realdon S, Iqbal J, Gerotto M, Dal Pero F, Bortoletto G, Marcolongo M, Vario A, Datz C, Hussain MM, Alberti A. Liver microsomal triglyceride transfer protein is involved in hepatitis C liver steatosis. *Gastroenterology* 2006; **130**: 1661-1669 [PMID: 16697730 DOI: 10.1053/j.gastro.2006.02.035]

22 **de Gottardi A**, Pazienza V, Pugnale P, Bruttin F, Rubbia-Brandt L, Juge-Aubry CE, Meier CA, Hadengue A, Negro F. Peroxisome proliferator-activated receptor-alpha and -gamma mRNA levels are reduced in chronic hepatitis C with steatosis and genotype 3 infection. *Aliment Pharmacol Ther* 2006; **23**: 107-114 [PMID: 16393287 DOI: 10.1111/j.1365-2036.2006.02729.x]

23 **Jackel-Cram C**, Qiao L, Xiang Z, Brownlie R, Zhou Y, Babiuk L, Liu Q. Hepatitis C virus genotype-3a core protein enhances sterol regulatory element-binding protein-1 activity through the phosphoinositide 3-kinase-Akt-2 pathway. *J Gen Virol* 2010; **91**: 1388-1395 [PMID: 20130133 DOI: 10.1099/vir.0.017418-0]

24 **Castéra L**, Hézode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, Dhumeaux D. Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. *Gut* 2004; **53**: 420-424 [PMID: 14960527 DOI: 10.1136/gut.2002.009936]

25 **Kumar D**, Farrell GC, Fung C, George J. Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response. *Hepatology* 2002; **36**: 1266-1272 [PMID: 12395339 DOI: 10.1053/jhep.2002.36370]

26 **Bochud PY**, Cai T, Overbeck K, Bochud M, Dufour JF, Müllhaupt B, Borovicka J, Heim M, Moradpour D, Cerny A, Malinverni R, Francioli P, Negro F; Swiss Hepatitis C Cohort Study Group. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J Hepatol* 2009; **51**: 655-666 [PMID: 19665246 DOI: 10.1016/j.jhep.2009.05.016]

27 **Westin J**, Nordlinder H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; **37**: 837-842 [PMID: 12445426 DOI: 10.1016/s0168-8278(02)00299-4]

28 **Rubbia-Brandt L**, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, Carlotto A, Bozzola L, Smedile A, Negro F. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004; **53**: 406-412 [PMID: 14960525 DOI: 10.1136/gut.2003.018770]

29 **Probst A**, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. *J Viral Hepat* 2011; **18**: 745-759 [PMID: 21992794 DOI: 10.1111/j.1365-2893.2011.01481.x]

30 **Larsen C**, Bousquet V, Delarocque-Astagneau E, Pioche C, Roudot-Thoraval F; HCV Surveillance Steering Committee; HCV Surveillance Group, Desenclos JC. Hepatitis C virus genotype 3 and the risk of severe liver disease in a large population of drug users in France. *J Med Virol* 2010; **82**: 1647-1654 [PMID: 20827760 DOI: 10.1002/jmv.21850]

31 **McMahon BJ**, Bruden D, Bruce MG, Livingston S, Christensen C, Homan C, Hennessy TW, Williams J, Sullivan D, Rosen HR, Gretch D. Adverse outcomes in Alaska natives who recovered from or have chronic hepatitis C infection. *Gastroenterology* 2010; **138**: 922-31.e1 [PMID: 19909749 DOI: 10.1053/j.gastro.2009.10.056]

32 **McCombs J**, Matsuda T, Tonnu-Mihara I, Saab S, Hines P, L'italien G, Juday T, Yuan Y. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. *JAMA Intern Med* 2014; **174**: 204-212 [PMID: 24193887 DOI: 10.1001/jamainternmed.2013.12505]

33 **Kanwal F**, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology* 2014; **60**: 98-105 [PMID: 24615981 DOI: 10.1002/hep.27095]

34 **Nkontchou G**, Ziol M, Aout M, Lhabadie M, Baazia Y, Mahmoudi A, Roulot D, Ganne-Carrie N, Grando-Lemaire V, Trinchet JC, Gordien E, Vicaut E, Baghad I, Beaugrand M. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. *J Viral Hepat* 2011; **18**: e516-e522 [PMID: 21914071 DOI: 10.1111/j.1365-2893.2011.01441.x]

35 **Lee SS**, Kim CY, Kim BR, Cha RR, Kim WS, Kim JJ, Lee JM, Kim HJ, Ha CY, Kim HJ, Kim TH, Jung WT, Lee OJ. Hepatitis C virus genotype 3 was associated with the development of hepatocellular carcinoma in Korea. *J Viral Hepat* 2019; **26**: 459-465 [PMID: 30516858 DOI: 10.1111/jvh.13047]

36 **Bruno S**, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007; **46**: 1350-1356 [PMID: 17680653 DOI: 10.1002/hep.21826]

37 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]

38 **Mangia A**, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 wk in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609-2617 [PMID: 15972867 DOI: 10.1056/NEJMoa042608]

39 **Mecenate F**, Pellicelli AM, Barbaro G, Romano M, Barlattani A, Mazzoni E, Bonaventura ME, Nosotti L, Arcuri P, Picardi A, Barbarini G, D'Ambrosio C, Paffetti A, Andreoli A, Soccorsi F; Club Epatologi Ospedalieri (CLEO) Group. Short *vs* standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. *BMC Gastroenterol* 2010; **10**: 21 [PMID: 20170514 DOI: 10.1186/1471-230X-10-21]

40 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]

41 **Zarębska-Michaluk D**, Lebensztejn D, Chrapek M, Paluch K, Stępień P, Kryczka W. Predictors of sustained virological response in patients with hepatitis C virus genotype 3 infection. *Clin Exp Hepatol* 2016; **2**: 117-124 [PMID: 28856274 DOI: 10.5114/ceh.2016.62526]

42 **Dalgard O**, Bjøro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, Reichard O, Myrvang B, Sundelöf B, Ritland S, Hellum K, Frydén A, Florholmen J, Verbaan H; North-C Group. Pegylated interferon alfa and ribavirin for 14 *vs* 24 wk in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008; **47**: 35-42 [PMID: 17975791 DOI: 10.1002/hep.21975]

43 **Shiffman ML**, Suter F, Bacon BR, Nelson D, Harley H, Solá R, Shafran SD, Barange K, Lin A, Soman A, Zeuzem S; ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 wk in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**: 124-134 [PMID: 17625124 DOI: 10.1056/NEJMoa066403]

44 **von Wagner M**, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Häussinger D, Herrmann E, Zeuzem S. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 wk in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; **129**: 522-527 [PMID: 16083709 DOI: 10.1016/j.gastro.2005.05.008]

45 **Andriulli A**, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Meta-analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. *Aliment Pharmacol Ther* 2008; **28**: 397-404 [PMID: 18549461 DOI: 10.1111/j.1365-2036.2008.03763.x]

46 **Powis J**, Peltekian KM, Lee SS, Sherman M, Bain VG, Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM; Canadian Pegasys Study Group. Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3. *J Viral Hepat* 2008; **15**: 52-57 [PMID: 18088245 DOI: 10.1111/j.1365-2893.2007.00889.x]

47 **Hadziyannis SJ**, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676 DOI: 10.7326/0003-4819-140-5-200403020-00010]

48 **Shoeb D**, Dearden J, Weatherall A, Bargery C, Moreea S, Alam S, White E, Vila X, Freshwater D, Ryder S, Mills PR, Alexander GJ, Forton D, Foster GR. Extended duration therapy with pegylated interferon and ribavirin for patients with genotype 3 hepatitis C and advanced fibrosis: final results from the STEPS trial. *J Hepatol* 2014; **60**: 699-705 [PMID: 24291239 DOI: 10.1016/j.jhep.2013.11.011]

49 **Jacobson IM**, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, Becker S, Wakil AE, Pound D, Godofsky E, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhopadhyay P, Griffel LH, Brass CA; WIN-R Study Group. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007; **46**: 971-981 [PMID: 17894303 DOI: 10.1002/hep.21932]

50 **Manzano-Robleda Mdel C**, Ornelas-Arroyo V, Barrientos-Gutiérrez T, Méndez-Sánchez N, Uribe M, Chávez-Tapia NC. Boceprevir and telaprevir for chronic genotype 1 hepatitis C virus infection. A systematic review and meta-analysis. *Ann Hepatol* 2015; **14**: 46-57 [PMID: 25536641 DOI: 10.1016/S1665-2681(19)30800-2]

51 **Janczewska E**, Flisiak R, Zarebska-Michaluk D, Kozielewicz D, Berak H, Dobracka B, Librant-Suska M, Lojewski W, Jurczyk K, Musialik J, Postawa-Klosińska B, Wroblewski J, Augustyniak K, Dudziak M, Olszok I, Ruszala A, Pisula A, Lapinski T, Kryczka W, Horban A, Dobracki W. Effect of Peginterferon or Ribavirin Dosing on Efficacy of Therapy With Telaprevir in Treatment-Experienced Patients With Chronic Hepatitis C and Advanced Liver Fibrosis: A Multicenter Cohort Study. *Medicine (Baltimore)* 2015; **94**: e1411 [PMID: 26402801 DOI: 10.1097/MD.0000000000001411]

52 **European Association for Study of Liver**. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]

53 **Foster GR**, Hézode C, Bronowicki JP, Carosi G, Weiland O, Verlinden L, van Heeswijk R, van Baelen B, Picchio G, Beumont M. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology* 2011; **141**: 881-889.e1 [PMID: 21699786 DOI: 10.1053/j.gastro.2011.05.046]

54 **Lenz O**, Vijgen L, Berke JM, Cummings MD, Fevery B, Peeters M, De Smedt G, Moreno C, Picchio G. Virologic response and characterisation of HCV genotype 2-6 in patients receiving TMC435 monotherapy (study TMC435-C202). *J Hepatol* 2013; **58**: 445-451 [PMID: 23142061 DOI: 10.1016/j.jhep.2012.10.028]

55 **Dore GJ**, Lawitz E, Hézode C, Shafran SD, Ramji A, Tatum HA, Taliani G, Tran A, Brunetto MR, Zaltron S, Strasser SI, Weis N, Ghesquiere W, Lee SS, Larrey D, Pol S, Harley H, George J, Fung SK, de Lédinghen V, Hagens P, McPhee F, Hernandez D, Cohen D, Cooney E, Noviello S, Hughes EA. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. *Gastroenterology* 2015; **148**: 355-366.e1 [PMID: 25311593 DOI: 10.1053/j.gastro.2014.10.007]

56 **Lawitz E**, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir with peginterferon-ribavirin for 12 wk in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology* 2015; **61**: 769-775 [PMID: 25322962 DOI: 10.1002/hep.27567]

57 **Lawitz E**, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, Bernstein DE, Dejesus E, Freilich B, Nelson DR, Dieterich DT, Jacobson IM, Jensen D, Abrams GA, Darling JM, Rodriguez-Torres M, Reddy KR, Sulkowski MS, Bzowej NH, Hyland RH, Mo H, Lin M, Mader M, Hindes R, Albanis E, Symonds WT, Berrey MM, Muir A. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; **13**: 401-408 [PMID: 23499158 DOI: 10.1016/S1473-3099(13)70033-1]

58 **Foster GR**, Pianko S, Brown A, Forton D, Nahass RG, George J, Barnes E, Brainard DM, Massetto B, Lin M, Han B, McHutchison JG, Subramanian GM, Cooper C, Agarwal K; BOSON Study Group. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology* 2015; **149**: 1462-1470 [PMID: 26248087 DOI: 10.1053/j.gastro.2015.07.043]

59 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34-44 [PMID: 23281974 DOI: 10.1056/NEJMoa1208953]

60 **Ioannou GN**, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI, Su F, Berry K. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. *Gastroenterology* 2016; **151**: 457-471.e5 [PMID: 27267053 DOI: 10.1053/j.gastro.2016.05.049]

61 **Zarębska-Michaluk D**, Flisiak R, Jaroszewicz J, Janczewska E, Czauż-Andrzejuk A, Berak H, Horban A, Staniaszek A, Gietka A, Tudrujek M, Tomasiewicz K, Dybowska D, Halota W, Piekarska A, Sitko M, Garlicki A, Orłowska I, Simon K, Belica-Wdowik T, Baka-Ćwierz B, Mazur W, Białkowska J, Socha Ł, Wawrzynowicz-Syczewska M, Laurans Ł, Deroń Z, Lorenc B, Dobracka B, Tronina O, Pawłowska M. Is Interferon-Based Treatment of Viral Hepatitis C Genotype 3 Infection Still of Value in the Era of Direct-Acting Antivirals? *J Interferon Cytokine Res* 2018; **38**: 93-100 [PMID: 29443655 DOI: 10.1089/jir.2017.0113]

62 **Cornberg M**, Petersen J, Schober A, Mauss S, Böker KH, Link R, Günther R, Serfert Y, Pfeiffer-Vornkahl H, Manns MP, Sarrazin C, Hüppe D, Berg T, Niederau C. Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection. *Aliment Pharmacol Ther* 2017; **45**: 688-700 [PMID: 28078723 DOI: 10.1111/apt.13925]

63 **European Association for Study of Liver**. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015; **63**: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]

64 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

65 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R; VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

66 **AASLD/IDSA HCV Guidance Panel**. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; **62**: 932-954 [PMID: 26111063 DOI: 10.1002/hep.27950]

67 **Wehmeyer MH**, Ingiliz P, Christensen S, Hueppe D, Lutz T, Simon KG, Schewe K, Boesecke C, Baumgarten A, Busch H, Rockstroh J, Schmutz G, Kimhofer T, Berger F, Mauss S, Schulze Zur Wiesch J. Real-world effectiveness of sofosbuvir-based treatment regimens for chronic hepatitis C genotype 3 infection: Results from the multicenter German hepatitis C cohort (GECCO-03). *J Med Virol* 2018; **90**: 304-312 [PMID: 28710853 DOI: 10.1002/jmv.24903]

68 **Feld JJ**, Maan R, Zeuzem S, Kuo A, Nelson DR, Di Bisceglie AM, Manns MP, Sherman K, Frazier LM, Sterling R, Mailliard M, Schmidt M, Akushevich L, Vainorius M, Fried MW. Effectiveness and Safety of Sofosbuvir-Based Regimens for Chronic HCV Genotype 3 Infection: Results of the HCV-TARGET Study. *Clin Infect Dis* 2016; **63**: 776-783 [PMID: 27325691 DOI: 10.1093/cid/ciw387]

69 **Nelson DR**, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; **61**: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726]

70 **Leroy V**, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, Pol S, Stuart K, Tse E, McPhee F, Bhore R, Jimenez-Exposito MJ, Thompson AJ. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; **63**: 1430-1441 [PMID: 26822022 DOI: 10.1002/hep.28473]

71 **Poordad F**, Shiffman ML, Ghesquiere W, Wong A, Huhn GD, Wong F, Ramji A, Shafran SD, McPhee F, Yang R, Noviello S, Linaberry M; ALLY-3C study team. Daclatasvir and sofosbuvir with ribavirin for 24 wk in chronic hepatitis C genotype-3-infected patients with cirrhosis: a Phase III study (ALLY-3C). *Antivir Ther* 2019; **24**: 35-44 [PMID: 30382942 DOI: 10.3851/IMP3278]

72 **European Association for the Study of the Liver**. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017; **66**: 153-194 [PMID: 27667367 DOI: 10.1016/j.jhep.2016.09.001]

73 **American Association for the Study of Liver Diseases and Infectious Diseases Society of America**. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated: July 6, 2016. Changes made September 16, 2016. [cited 31 December 2020]. In: AASLD and IDSA [Internet]. Available from: http://www.hcvguidelines.org

74 **Omata M**, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, Lesmana CR, Sollano J, Kumar M, Jindal A, Sharma BC, Hamid SS, Dokmeci AK, Mamun-Al-Mahtab, McCaughan GW, Wasim J, Crawford DH, Kao JH, Yokosuka O, Lau GK, Sarin SK. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatol Int* 2016; **10**: 702-726 [PMID: 27130427 DOI: 10.1007/s12072-016-9717-6]

75 **Macken L**, Gelson W, Priest M, Abouda G, Barclay S, Fraser A, Healy B, Irving W, Verma S. Efficacy of direct-acting antivirals: UK real-world data from a well-characterised predominantly cirrhotic HCV cohort. *J Med Virol* 2019; **91**: 1979-1988 [PMID: 31329295 DOI: 10.1002/jmv.25552]

76 **Hézode C**, Lebray P, De Ledinghen V, Zoulim F, Di Martino V, Boyer N, Larrey D, Botta-Fridlund D, Silvain C, Fontaine H, D'Alteroche L, Leroy V, Bourliere M, Hubert-Fouchard I, Guyader D, Rosa I, Nguyen-Khac E, Fedchuk L, Akremi R, Bennai Y, Filipovics A, Zhao Y, Bronowicki JP. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. *Liver Int* 2017; **37**: 1314-1324 [PMID: 28177199 DOI: 10.1111/liv.13383]

77 **Soria A**, Fava M, Bernasconi DP, Lapadula G, Colella E, Valsecchi MG, Migliorino GM, D'Ambrosio R, Landonio S, Schiavini M, Spinetti A, Carriero C, Degasperi E, Cologni G, Gatti F, Viganò P, Hasson H, Uberti-Foppa C, Pasulo L, Baiguera C, Rossotti R, Vinci M, Puoti M, Giorgini A, Menzaghi B, Lombardi A, Pan A, Aghemo A, Grossi PA, Boldizzoni R, Colombo S, Viganò M, Rumi MG, Del Poggio P, Valenti L, Giglio O, De Bona A, d'Arminio Monforte A, Colombo A, Spinelli O, Pigozzi MG, Molteni C, Bonfanti P, Terreni N, Perini P, Capretti A, Bella D, Liani C, Polo S, Aimo G, Pagnucco L, Bhoori S, Centenaro R, Graffeo M, Ciaccio A, Dionigi E, Lazzaroni S, Carderi I, Di Marco M, Rizzardini G, Noventa F, Lampertico P, Fagiuoli S. Comparison of three therapeutic regimens for genotype-3 hepatitis C virus infection in a large real-life multicentre cohort. *Liver Int* 2020; **40**: 769-777 [PMID: 31970845 DOI: 10.1111/liv.14386]

78 **European Association for the Study of the Liver**, Clinical Practice Guidelines Panel: Chair, EASL Governing Board representative, Panel members. EASL recommendations on treatment of hepatitis C: Final update of the series☆. *J Hepatol* 2020; **73**: 1170-1218 [PMID: 32956768 DOI: 10.1016/j.jhep.2020.08.018]

79 **Ghany MG**, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology* 2020; **71**: 686-721 [PMID: 31816111 DOI: 10.1002/hep.31060]

80 **Foster GR**, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med* 2015; **373**: 2608-2617 [PMID: 26575258 DOI: 10.1056/NEJMoa1512612]

81 **Esteban R**, Pineda JA, Calleja JL, Casado M, Rodríguez M, Turnes J, Morano Amado LE, Morillas RM, Forns X, Pascasio Acevedo JM, Andrade RJ, Rivero A, Carrión JA, Lens S, Riveiro-Barciela M, McNabb B, Zhang G, Camus G, Stamm LM, Brainard DM, Subramanian GM, Buti M. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis. *Gastroenterology* 2018; **155**: 1120-1127.e4 [PMID: 29958855 DOI: 10.1053/j.gastro.2018.06.042]

82 **European Medicines Agency**. Epclusa: Summary of Product Characteristics 2020. [cited 31 December 2020]. In: European Medicines Agency [Internet]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/epclusa#product-information-section

83 **Wong YJ**, Thurairajah PH, Kumar R, Tan J, Fock KM, Law NM, Li W, Kwek A, Tan YB, Koh J, Lee ZC, Kumar LS, Teo EK, Ang TL. Efficacy and safety of sofosbuvir/velpatasvir in a real-world chronic hepatitis C genotype 3 cohort. *J Gastroenterol Hepatol* 2020 [PMID: 33217040 DOI: 10.1111/jgh.15324]

84 **Belperio PS**, Shahoumian TA, Loomis TP, Mole LA, Backus LI. Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3. *J Hepatol* 2019; **70**: 15-23 [PMID: 30266283 DOI: 10.1016/j.jhep.2018.09.018]

85 **Flisiak R**, Zarębska-Michaluk D, Jaroszewicz J, Lorenc B, Klapaczyński J, Tudrujek-Zdunek M, Sitko M, Mazur W, Janczewska E, Pabjan P, Dybowska D, Buczyńska I, Czauż-Andrzejuk A, Belica-Wdowik T, Berak H, Krygier R, Piasecki M, Dobracka B, Citko J, Piekarska A, Socha Ł, Deroń Z, Tronina O, Laurans Ł, Białkowska J, Tomasiewicz K, Halota W, Simon K, Pawłowska M. Changes in patient profile, treatment effectiveness, and safety during 4 years of access to interferon-free therapy for hepatitis C virus infection. *Pol Arch Intern Med* 2020; **130**: 163-172 [PMID: 32031541 DOI: 10.20452/pamw.15181]

86 **von Felden J**, Vermehren J, Ingiliz P, Mauss S, Lutz T, Simon KG, Busch HW, Baumgarten A, Schewe K, Hueppe D, Boesecke C, Rockstroh JK, Daeumer M, Luebke N, Timm J, Schulze Zur Wiesch J, Sarrazin C, Christensen S. High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection. *Aliment Pharmacol Ther* 2018; **47**: 1288-1295 [PMID: 29536554 DOI: 10.1111/apt.14592]

87 **Wilton J**, Wong S, Yu A, Ramji A, Cook D, Butt ZA, Alvarez M, Binka M, Darvishian M, Jeong D, Bartlett SR, Pearce ME, Adu PA, Yoshida EM, Krajden M, Janjua NZ. Real-world Effectiveness of Sofosbuvir/Velpatasvir for Treatment of Chronic Hepatitis C in British Columbia, Canada: A Population-Based Cohort Study. *Open Forum Infect Dis* 2020; **7**: ofaa055 [PMID: 32154326 DOI: 10.1093/ofid/ofaa055]

88 **European Medicines Agency**. EMA/332999/2020. Maviret: Procedural steps taken and scientific information after the authorization. [cited 31 December 2020]. In: European Medicines Agency [Internet]. Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/maviret-epar-procedural-steps-taken-scientific-information-after-authorisation\_en.pdf

89 **Puoti M**, Foster GR, Wang S, Mutimer D, Gane E, Moreno C, Chang TT, Lee SS, Marinho R, Dufour JF, Pol S, Hezode C, Gordon SC, Strasser SI, Thuluvath PJ, Zhang Z, Lovell S, Pilot-Matias T, Mensa FJ. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis. *J Hepatol* 2018; **69**: 293-300 [PMID: 29551706 DOI: 10.1016/j.jhep.2018.03.007]

90 **Brown RS Jr**, Buti M, Rodrigues L, Chulanov V, Chuang WL, Aguilar H, Horváth G, Zuckerman E, Carrion BR, Rodriguez-Perez F, Urbánek P, Abergel A, Cohen E, Lovell SS, Schnell G, Lin CW, Zha J, Wang S, Trinh R, Mensa FJ, Burroughs M, Felizarta F. Glecaprevir/pibrentasvir for 8 wk in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. *J Hepatol* 2020; **72**: 441-449 [PMID: 31682879 DOI: 10.1016/j.jhep.2019.10.020]

91 **Flamm S**, Mutimer D, Asatryan A, Wang S, Rockstroh J, Horsmans Y, Kwo PY, Weiland O, Villa E, Heo J, Gane E, Ryder SD, Welzel TM, Ruane PJ, Agarwal K, Ng TI, Xue Z, Lovell SS, Krishnan P, Kopecky-Bromberg S, Trinh R, Mensa FJ, Wyles DL. Glecaprevir/Pibrentasvir in patients with chronic HCV genotype 3 infection: An integrated phase 2/3 analysis. *J Viral Hepat* 2019; **26**: 337-349 [PMID: 30421537 DOI: 10.1111/jvh.13038]

92 **Zeuzem S**, Foster GR, Wang S, Asatryan A, Gane E, Feld JJ, Asselah T, Bourlière M, Ruane PJ, Wedemeyer H, Pol S, Flisiak R, Poordad F, Chuang WL, Stedman CA, Flamm S, Kwo P, Dore GJ, Sepulveda-Arzola G, Roberts SK, Soto-Malave R, Kaita K, Puoti M, Vierling J, Tam E, Vargas HE, Bruck R, Fuster F, Paik SW, Felizarta F, Kort J, Fu B, Liu R, Ng TI, Pilot-Matias T, Lin CW, Trinh R, Mensa FJ. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *N Engl J Med* 2018; **378**: 354-369 [PMID: 29365309 DOI: 10.1056/NEJMoa1702417]

93 **Kwo PY**, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, Felizarta F, Sulkowski MS, Gane E, Maliakkal B, Overcash JS, Gordon SC, Muir AJ, Aguilar H, Agarwal K, Dore GJ, Lin CW, Liu R, Lovell SS, Ng TI, Kort J, Mensa FJ. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol* 2017; **67**: 263-271 [PMID: 28412293 DOI: 10.1016/j.jhep.2017.03.039]

94 **Wyles D**, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY, Maliakkal B, Agarwal K, Hassanein T, Weilert F, Lee SS, Kort J, Lovell SS, Liu R, Lin CW, Pilot-Matias T, Krishnan P, Mensa FJ. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: A partially randomized phase 3 clinical trial. *Hepatology* 2018; **67**: 514-523 [PMID: 28926120 DOI: 10.1002/hep.29541]

95 **D'Ambrosio R**, Pasulo L, Puoti M, Vinci M, Schiavini M, Lazzaroni S, Soria A, Gatti F, Menzaghi B, Aghemo A, Capelli F, Rumi MG, Morini L, Giorgini A, Pigozzi MG, Rossini A, Maggiolo F, Pan A, Memoli M, Spinelli O, Del Poggio P, Saladino V, Spinetti A, De Bona A, Capretti A, Uberti-Foppa C, Bonfanti P, Terreni N, Menozzi F, Colombo AE, Giglio O, Centenaro R, Borghi M, Baiguera C, Picciotto V, Landonio S, Gori A, Magnani C, Noventa F, Paolucci S, Lampertico P, Fagiuoli S; NAVIGATORE-Lombardia Study Group. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. *J Hepatol* 2019; **70**: 379-387 [PMID: 30472321 DOI: 10.1016/j.jhep.2018.11.011]

96 **Zarębska-Michaluk D**, Jaroszewicz J, Pabjan P, Łapiński TW, Mazur W, Krygier R, Dybowska D, Halota W, Pawłowska M, Janczewska E, Buczyńska I, Simon K, Dobracka B, Citko J, Laurans Ł, Tudrujek-Zdunek M, Tomasiewicz K, Piekarska A, Sitko M, Białkowska-Warzecha J, Klapaczyński J, Sobala-Szczygieł B, Horban A, Berak H, Deroń Z, Lorenc B, Socha Ł, Tronina O, Flisiak R. Is an 8-week regimen of glecaprevir/pibrentasvir sufficient for all hepatitis C virus infected patients in the real-world experience? *J Gastroenterol Hepatol* 2020 [PMID: 33171526 DOI: 10.1111/jgh.15337]

97 **Berg T**, Naumann U, Stoehr A, Sick C, John C, Teuber G, Schiffelholz W, Mauss S, Lohmann K, König B, Pangerl A, Niederau C. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry. *Aliment Pharmacol Ther* 2019; **49**: 1052-1059 [PMID: 30874328 DOI: 10.1111/apt.15222]

98 **Persico M**, Aglitti A, Milella M, Coppola C, Messina V, Claar E, Gentile I, Sogari F, Pierri P, Surace LA, Morisco F, Tundo P, Brancaccio G, Serviddio G, Gatti P, Termite AP, Di Costanzo GG, Caroleo B, Cozzolongo R, Coppola N, Longo A, Fontanella L, Federico A, Rosato V, Terrenato I, Masarone M. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: The MISTRAL study. *Liver Int* 2019; **39**: 1852-1859 [PMID: 31175707 DOI: 10.1111/liv.14170]

99 **Lampertico P**, Carrión JA, Curry M, Turnes J, Cornberg M, Negro F, Brown A, Persico M, Wick N, Porcalla A, Pangerl A, Crown E, Larsen L, Yu Y, Wedemeyer H. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-analysis. *J Hepatol* 2020; **72**: 1112-1121 [PMID: 32061651 DOI: 10.1016/j.jhep.2020.01.025]

100 **Flamm SL**, Kort J, Marx SE, Strezewski J, Dylla DE, Bacon B, Curry MP, Tsai N, Wick N. Effectiveness of 8-Week Glecaprevir/Pibrentasvir for Treatment-Naïve, Compensated Cirrhotic Patients with Chronic Hepatitis C Infection. *Adv Ther* 2020; **37**: 2267-2274 [PMID: 32279176 DOI: 10.1007/s12325-020-01301-5]

101 **Lampertico P**, Mauss S, Persico M, Barclay ST, Marx S, Lohmann K, Bondin M, Zhang Z, Marra F, Belperio PS, Wedemeyer H, Flamm S. Real-World Clinical Practice Use of 8-Week Glecaprevir/Pibrentasvir in Treatment-Naïve Patients with Compensated Cirrhosis. *Adv Ther* 2020; **37**: 4033-4042 [PMID: 32754824 DOI: 10.1007/s12325-020-01449-0]

102 **Bourlière M**, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, Tran TT, Pianko S, Bansal MB, de Lédinghen V, Hyland RH, Stamm LM, Dvory-Sobol H, Svarovskaia E, Zhang J, Huang KC, Subramanian GM, Brainard DM, McHutchison JG, Verna EC, Buggisch P, Landis CS, Younes ZH, Curry MP, Strasser SI, Schiff ER, Reddy KR, Manns MP, Kowdley KV, Zeuzem S; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017; **376**: 2134-2146 [PMID: 28564569 DOI: 10.1056/NEJMoa1613512]

103 **Jacobson IM**, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, Borgia SM, Shafran SD, Workowski KA, Pearlman B, Hyland RH, Stamm LM, Svarovskaia E, Dvory-Sobol H, Zhu Y, Subramanian GM, Brainard DM, McHutchison JG, Bräu N, Berg T, Agarwal K, Bhandari BR, Davis M, Feld JJ, Dore GJ, Stedman CAM, Thompson AJ, Asselah T, Roberts SK, Foster GR. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. *Gastroenterology* 2017; **153**: 113-122 [PMID: 28390869 DOI: 10.1053/j.gastro.2017.03.047]

104 **Wyles D**, Weiland O, Yao B, Weilert F, Dufour JF, Gordon SC, Stoehr A, Brown A, Mauss S, Zhang Z, Pilot-Matias T, Rodrigues L Jr, Mensa FJ, Poordad F. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. *J Hepatol* 2019; **70**: 1019-1023 [PMID: 30857780 DOI: 10.1016/j.jhep.2019.01.031]

105 **Gane EJ**, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, Stedman CA. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 wk in patients with HCV genotype 3 or 6 infection. *Gastroenterology* 2015; **149**: 1454-1461.e1 [PMID: 26261007 DOI: 10.1053/j.gastro.2015.07.063]

106 **Pawlotsky JM**, Flisiak R, Sarin SK, Rasenack J, Piratvisuth T, Chuang WL, Peng CY, Foster GR, Shah S, Wedemeyer H, Hézode C, Zhang W, Wong KA, Li B, Avila C, Naoumov NV; VITAL-1 study team. Alisporivir plus ribavirin, interferon free or in combination with pegylated interferon, for hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2015; **62**: 1013-1023 [PMID: 26118427 DOI: 10.1002/hep.27960]

107 **Gane E**, Nahass R, Luketic V, Asante-Appiah E, Hwang P, Robertson M, Wahl J, Barr E, Haber B. Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naïve, noncirrhotic HCV genotype 3-infected patients. *J Viral Hepat* 2017; **24**: 895-899 [PMID: 28470815 DOI: 10.1111/jvh.12719]

108 **Lawitz E**, Gane E, Feld JJ, Buti M, Foster GR, Rabinovitz M, Burnevich E, Katchman H, Tomasiewicz K, Lahser F, Jackson B, Shaughnessy M, Klopfer S, Yeh WW, Robertson MN, Hanna GJ, Barr E, Platt HL; C-BREEZE-2 Study Investigators. Efficacy and safety of a two-drug direct-acting antiviral agent regimen ruzasvir 180 mg and uprifosbuvir 450 mg for 12 weeks in adults with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6. *J Viral Hepat* 2019; **26**: 1127-1138 [PMID: 31108015 DOI: 10.1111/jvh.13132]

109 **Lawitz E**, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M, Badri P, Campbell A, Rodrigues L Jr, Hu Y, Pilot-Matias T, Vilchez RA. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. *J Infect* 2015; **70**: 197-205 [PMID: 25246359 DOI: 10.1016/j.jinf.2014.09.008]

110 **Shafran SD**, Shaw D, Charafeddine M, Agarwal K, Foster GR, Abunimeh M, Pilot-Matias T, Pothacamury RK, Fu B, Cohen E, Cohen DE, Gane E. Efficacy and safety results of patients with HCV genotype 2 or 3 infection treated with ombitasvir/paritaprevir/ritonavir and sofosbuvir with or without ribavirin (QUARTZ II-III). *J Viral Hepat* 2018; **25**: 118-125 [PMID: 28833938 DOI: 10.1111/jvh.12782]

111 **Lawitz E**, Poordad F, Gutierrez JA, Wells JT, Landaverde CE, Evans B, Howe A, Huang HC, Li JJ, Hwang P, Dutko FJ, Robertson M, Wahl J, Barr E, Haber B. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. *Hepatology* 2017; **65**: 439-450 [PMID: 27770561 DOI: 10.1002/hep.28877]

112 **Foster GR**, Agarwal K, Cramp ME, Moreea S, Barclay S, Collier J, Brown AS, Ryder SD, Ustianowski A, Forton DM, Fox R, Gordon F, Rosenberg WM, Mutimer DJ, Du J, Gilbert CL, Asante-Appiah E, Wahl J, Robertson MN, Barr E, Haber B. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. *Hepatology* 2018; **67**: 2113-2126 [PMID: 29473975 DOI: 10.1002/hep.29852]

113 **Lawitz E**, Buti M, Vierling JM, Almasio PL, Bruno S, Ruane PJ, Hassanein TI, Muellhaupt B, Pearlman B, Jancoriene L, Gao W, Huang HC, Shepherd A, Tannenbaum B, Fernsler D, Li JJ, Grandhi A, Liu H, Su FH, Wan S, Dutko FJ, Nguyen BT, Wahl J, Robertson MN, Barr E, Yeh WW, Plank RM, Butterton JR, Yoshida EM. Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin in participants with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection (C-CREST-1 and C-CREST-2, part B): two randomised, phase 2, open-label trials. *Lancet Gastroenterol Hepatol* 2017; **2**: 814-823 [PMID: 28802814 DOI: 10.1016/S2468-1253(17)30163-2]

114 **Gane EJ**, Schwabe C, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, Brainard DM, McHutchison JG, Stedman CA. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-Naïve or Previously Treated Patients With Hepatitis C Virus Genotype 1 or 3 Infections. *Gastroenterology* 2016; **151**: 448-456.e1 [PMID: 27240903 DOI: 10.1053/j.gastro.2016.05.021]

115 **Gane EJ**, Kowdley KV, Pound D, Stedman CA, Davis M, Etzkorn K, Gordon SC, Bernstein D, Everson G, Rodriguez-Torres M, Tsai N, Khalid O, Yang JC, Lu S, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Tong M, Chung RT, Beavers K, Poulos JE, Kwo PY, Nguyen MH. Efficacy of Sofosbuvir, Velpatasvir, and GS-9857 in Patients With Hepatitis C Virus Genotype 2, 3, 4, or 6 Infections in an Open-Label, Phase 2 Trial. *Gastroenterology* 2016; **151**: 902-909 [PMID: 27486033 DOI: 10.1053/j.gastro.2016.07.038]

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**Table 1 Efficacy of interferon-free regimens in genotype 3 patients in clinical trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Phase** | **Number of GT3 participants** | **Regimen** | **Treatment duration** | **SVR** |
| **Noncirrhotics** | **Cirrhotics** |
| **Treatment-naive (%)** | **Treatment-experienced (%)** | **Treatment-naive (%)** | **Treatment-experienced (%)** |
| Lawitz *et al*[40], FISSION | 3 | 173 | SOF + RBV | 12 wk | 61 | - | 34 | - |
| Jacobson *et al*[64], POSITRON | 3 | 98 | SOF + RBV | 12 wk | 68 | - | 21 | - |
| Jacobson *et al*[64], FUSION | 3 | 127 | SOF + RBV | 12 wk | - | 37 | - | 19 |
| 16 wk | - | 63 | - | 61 |
| Foster *et al*[58], BOSON | 3 | 363 | SOF + RBV | 16 wk | 83 | 76 | 57 | 47 |
| 24 wk | 90 | 82 | 82 | 77 |
| Zeuzem *et al*[65], VALENCE | 3 | 250 | SOF + RBV | 24 wk | 95 | 87 | 92 | 62 |
| Nelson *et al*[69], ALLY-3 | 3 | 152 | SOF + DCV | 12 wk | 97 | 94 | 58 | 69 |
| Leroy *et al*[70], ALLY-3+ | 3 | 50 | SOF + DCV + RBV | 12 wk | 100 | 100 | 50 (1/2) | 93 |
| 16 wk | 100 | 100 | 100 | 86 |
| Poordad *et al*[71], ALLY-3C | 3 | 78 | SOF + DCV + RBV | 24 wk | - | - | 93 | 79 |
| Esteban *et al*[81], [NCT02781558](http://clinicaltrials.gov/show/NCT02781558) | 2 | 204 | SOF/VEL | 12 wk | - | - | 91 |
| SOF/VE + RBV | 12 wk | - | - | 96 |
| Foster *et al*[80], ASTRAL-3 | 3 | 552 | SOF + RBV | 24 wk | 90 | 73 | 71 | 58 |
| SOF/VEL | 12 wk | 98 | 93 | 91 | 89 |
| Bourlière *et al*[102], POLARIS-1 | 3 | 78 | SOF/VEL+ VOX | 12 wk | - | 1001 | - | 931 |
| Jacobson *et al*[103], POLARIS-2 | 3 | 181 | SOF/VEL | 12 wk | 97 | - | - |
| SOF/VEL+ VOX | 8 wk | 99 | - | - |
| Jacobson *et al*[103], POLARIS-3 | 3 | 219 | SOF/VEL | 12 wk | - | - | 99 | 91 |
| SOF/VEL+ VOX | 8 wk | - | - | 96 | 97 |
| Bourlière *et al*[102], POLARIS-4 | 3 | 106 | SOF/VEL | 12 wk | - | 852 | - | 85%2 |
| SOF/VEL+ VOX | 12 wk | - | 962 | - | 962 |
| Gane *et al*[114], LEPTON | 2 | 41 | SOF/VEL+ VOX | 6 wk | - | - | 83 | - |
| 8 wk | - |  | 100 | 100 |
| Gane *et al*[115], NCT02378961 | 2 | 74 | SOF/VEL+ VOX | 6 wk | 100 | - | - | - |
| 8 wk | - | - | 94 | - |
| 12 wk | - | 100 | - | 94 |
| Zeuzem *et al*[92], ENDURANCE-3 | 3 | 505 | GLE/PIB | 8 wk | 95 | - | - | - |
| 12 wk | 95 | - | - | - |
| SOF + DCV | 12 wk | 97 | - | - | - |
| Kwo *et al*[93], SURVEYOR-II (part 2) | 3 | 53 | GLE/PIB | 8 wk | 97 | - | - | - |
| 12 wk | - | 92 | - | - |
| Wyles *et al*[94], SURVEYOR-II (part 3) | 3 | 131 | GLE/PIB | 12 wk | - | 91 | 98 | - |
| 16 wk | - | 95 | - | 96 |
| Brown *et al*[90], EXPEDITION-8 | 3 | 124 | GLE/PIB | 8 wk | - | - | 98 | - |
| Wyles *et al*[104], MAGELLAN-3 | 3 | 14 | GEL/PIB+ SOF + RBV | 16 wk | - | 100 | - | 100 |
| Gane *et al*[105], ELECTRON-2 | 2 | 101 | SOF/LDV | 12 wk | 64 | - | - | - |
| SOF/LDV + RBV | 12 wk | 100 | 89 | - | 73 |
| Pawlotsky *et al*[106], VITAL-1 | 2 | 181 | ALV | 24 wk | 76 | - | - | - |
| ALV + RBV | 24 wk | 93 | - | - | - |
| Lawitz *et al*[109], NAVIGATOR | 2 | 21 | OBV/PTV/r | 12 wk | 40 | - | - | - |
| OBV/PTV/r + RBV | 12 wk | 9 | - | - | - |
| Shafran *et al*[110], QUARTZ II-III | 2 | 51 | OBV/PTV/r + SOF | 12 wk | 98 | - | - | - |
| OBV/PTV/r + SOF + RBV | 12 wk | 91 | - | 100 | - |
| Gane *et al*[107], C-WORTHY (part D) | 2 | 41 | GZR/EBR + RBV | 12 wk | 45 | - | - | - |
| 18 wk | 57 | - | - | - |
| Lawitz *et al*[111], C-SWIFT | 2 | 41 | GZR/EBR + SOF | 8 wk | 93 | - | - | - |
| 12 wk | 100 | - | 91 | - |
| Foster *et al*[112], C-ISLE | 2 | 100 | GZR/EBR + SOF | 8 wk | - | - | 91 | - |
| 12 wk | - | - | 96 | 1003 |
| 16 wk | - | - | - | 94 |
| Lawitz *et al*[113], C-CREST-1 and -2 | 2 | 337 | GZR + EBR + UPR ± RBV | 8 wk | 95 |
| 12 wk | 97 |
| 16 wk | 96 |
| Lawitz *et al*[108], C-BREEZE-2 | 2 | 61 | RZR + UPR | 12 wk | 80 | 68 |

1NS5A-inhibitor-experienced.

2No detailed information on the response rate in patients with and without liver cirrhosis.

3Recommended by American Association for the Study of Liver Diseases/Infectious Diseases Society of America as an alternative option for pegylated interferon + ribavirin-experienced patients with compensated liver cirrhosis. SVR: Sustained virologic response; GT: Genotype; SOF: Sofosbuvir; RVB: Ribavirin; DCV: Daclatasvir; VEL: Velpatasvir; VOX: Voxilaprevir; GLE: Glecaprevir; PIB: Pibrentasvir; LDV: Ledipasvir; ALV: Alisporivir; OBV: Ombitasvir; PTV/r: Paritaprevir boosted by ritonavir; GZR: Grazoprevir; EBR: Elbasvir; UPR: Uprifosbuvir; RBV: Ribavirin; RZR: Ruzasvir.

**Table 2 European Association for the Study of the Liver and** **American Association for the Study of Liver Diseases/Infectious Diseases Society of America current recommendations on the treatment of genotype 3-infected patients**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Recommendations** | **Genotype/subtype** | **Cirrhosis status** | **Prior treatment experience** | **SOF/VEL** | **GLE/PIB** | **SOF/VEL/VOX** | **GZR/EBR + SOF** |
| European Association for the Study of the Liver[78] | GT3 | No cirrhosis | Treatment-naïve | 12 wk | 8 wk | - | - |
| Treatment-experienced | 12 wk | - | - |
| Compensated cirrhosis | Treatment-naïve | 12 wk with RBV1 | 8-12 wk2 | 12 wk | - |
| Treatment-experienced | 16 wk | - |
| Decompensated cirrhosis | Treatment-naïve and experienced | 12 wk with RBV or 24 wk | - | - | - |
| GT3, subtype b, g or any other subtype naturally harbouring one or several NS5A RASs3 | No cirrhosis | Treatment-naïve | Unknown | Unknown | 12 wk | - |
| Treatment-experienced | - |
| Compensated cirrhosis | Treatment-naïve | - |
| Treatment-experienced | - |
| AASLD/IDSA (Ghany *et al*[79]) | GT3 | No cirrhosis | Treatment-naïve | 12 wk | 8 wk | - | - |
| Treatment-experienced | 12 wk | 16 wk4 | 12 wk4 | - |
| SOF + RBV ± PEGIFN-experienced | - | 16 wk | 12 wk | - |
| DAA-experienced5 | - | - | 12 wk, + RBV for NS5A failures | - |
| Compensated cirrhosis | Treatment-naïve | 12 wk, + RBV for 12 wk4 | 8 wk | 12 wk4 | - |
| PEGIFN + RBV-experienced | + RBV for 12 wk4 | 16 wk | 12 wk | 12 wk4 |
| SOF + RBV ± PEGIFN-experienced | - | 16 wk | 12 wk | - |
| DAA-experienced5 | - | - | 12 wk, + RBV for NS5A failures | - |
| Decompensated cirrhosis | Treatment-naïve and experienced | 12 wk with RBV or 24 wk | - | - | - |

1If resistance testing is performed, only patients with the nonstructural protein 5A Y93H resistance-associated substitutions at baseline should be treated with sofosbuvir/velpatasvir plus ribavirin or with sofosbuvir/velpatasvir/voxilaprevir, whereas patients without the Y93H resistance-associated substitutions should be treated with sofosbuvir/velpatasvir alone.

2In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 wk, but more data are needed to consolidate this recommendation.

3As determined by sequence analysis of the nonstructural protein 5A region by means of population sequencing or deep sequencing (cutoff 15%).

4Alternative regimen.

5Including nonstructural protein 5A inhibitors except glecaprevir/pibrentasvir failures. NS5A: Nonstructural protein 5A; SOF: Sofosbuvir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir; VOX: Voxilaprevir; GZR: Grazoprevir; EBR: Elbasvir; EASL: European Association for the Study of the Liver; GT: Genotype; RBV: Ribavirin; PEGIFN: Pegylated interferon; DAA: Direct-acting antivirals; AASLD/IDSA: American Association for the Study of Liver Diseases/Infectious Diseases Society of America.



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