O desafio do genótipo 3

Priscila Nader

Por que discutir genótipos?

- HCV → 185 milhões pessoas no mundo
- HCV-3 → 2º mais prevalente
- 54,3 milhões de pessoas infectadas (30.1%)
- Índia, Paquistão, Grécia, Polônia
- Associação com uso de drogas endovenosas

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Global Distribution and Prevalence of Hepatitis C Virus Genotypes

Jane P. Messina,[1] Isla Humphreys,[2] Abraham Flaxman,[3] Anthony Brown,[2] Graham S. Cooke,[4*] Oliver G. Pybus,[5*] and Eleanor Barnes[2*]

Table 2. Global and Regional Estimates of HCV Seroprevalence Attributable to Each Genotype

	Genotype 1		Genotype 2		Genotype 3		Genotype 4		Genotype 5		Genotype 6		Regional HCV
WHO GBD Region	N (thousands)	%	N (thousands)	%	N (thousands)	%	N (thousands)	%	N (thousands)	%	N (thousands)	%	Seroprevalence Totals* (thousands)
Andean Latin America	1,003	90.9	17	1.5	83	7.6	0	0.0	0	0.0	0	0.0	1,103
Australasia	388	54.2	34	4.7	280	39.2	9	1.3	0	0.0	3	0.5	715
Caribbean	450	92.6	15	3.2	17	3.5	4	0.8	0	0.0	0	0.0	486
Central Asia	2,100	66.6	148	4.7	906	28.7	0	0.0	0	0.0	0	0.0	3,155
Central Europe	1,548	89.2	1	0.1	164	9.4	22	1.3	0	0.0	0	0.0	1,736
Central Latin America	2,796	71.7	754	19.3	330	8.5	16	0.4	2	0.0	0	0.0	3,899
Central sub-Saharan Africa	37	1.7	17	0.8	0	0.0	2,145	97.6	0	0.0	0	0.0	2,198
East Asia	32,082	58.0	8,444	15.3	5,762	10.4	40	0.1	0	0.0	8,982	16.2	55,311
Eastern Europe	4,023	65.1	270	4.4	1,881	30.4	6	0.1	0	0.0	0	0.0	6,181
Eastern sub-Saharan Africa	1,187	37.3	294	9.2	288	9.1	978	30.7	436	13.7	0	0.0	3,183
High-income Asia Pacific	1,926	74.9	629	24.5	15	0.6	0	0.0	0	0.0	0	0.0	2,571
High-income North America	3,595	75.8	567	12.0	492	10.4	55	1.2	6	0.1	26	0.6	4,742
North Africa and Middle East	3,808	27.3	115	0.8	884	6.3	9,118	65.3	47	0.3	0	0.0	13,971
South Asia	12,889	23.2	1,333	2.4	39,706	71.6	1,413	2.5	80	0.1	55	0.1	55,475
Southeast Asia	4,910	57.0	1,572	18.2	1,331	15.4	77	0.9	0	0.0	729	8.5	8,619
Southern Latin America	876	87.0	58	5.7	65	6.5	5	0.5	4	0.4	0	0.0	1,008
Southern sub-Saharan Africa	399	26.5	18	1.2	107	7.1	98	6.5	887	58.8	0	0.0	1,508
Tropical Latin America	1,802	69.3	89	3.4	699	26.9	7	0.3	3	0.1	0	0.0	2,600
Western Europe	3,169	59.0	583	10.8	1,332	24.8	262	4.9	26	0.5	2	0.0	5,374
Western sub-Saharan Africa	4,427	65.7	1,550	23.0	0	0.0	761	11.3	5	0.1	0	0.0	6,743
Totals (excludes Oceania)	*83,413.4*	*46.2*	*16,509.0*	*9.1*	*54,345.0*	*30.1*	*15,014.5*	*8.3*	*1,496.3*	*0.8*	*9,798.6*	*5.4*	*180,576.8*

*Regional HCV seroprevalence data from Hanafiah et al.[2]

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Jane P. Messina,[1] Isla Humphreys,[2] Abraham Flaxman,[3] Anthony Brown,[2] Graham S. Cooke,[4*] Oliver G. Pybus,[5*] and Eleanor Barnes[2*]

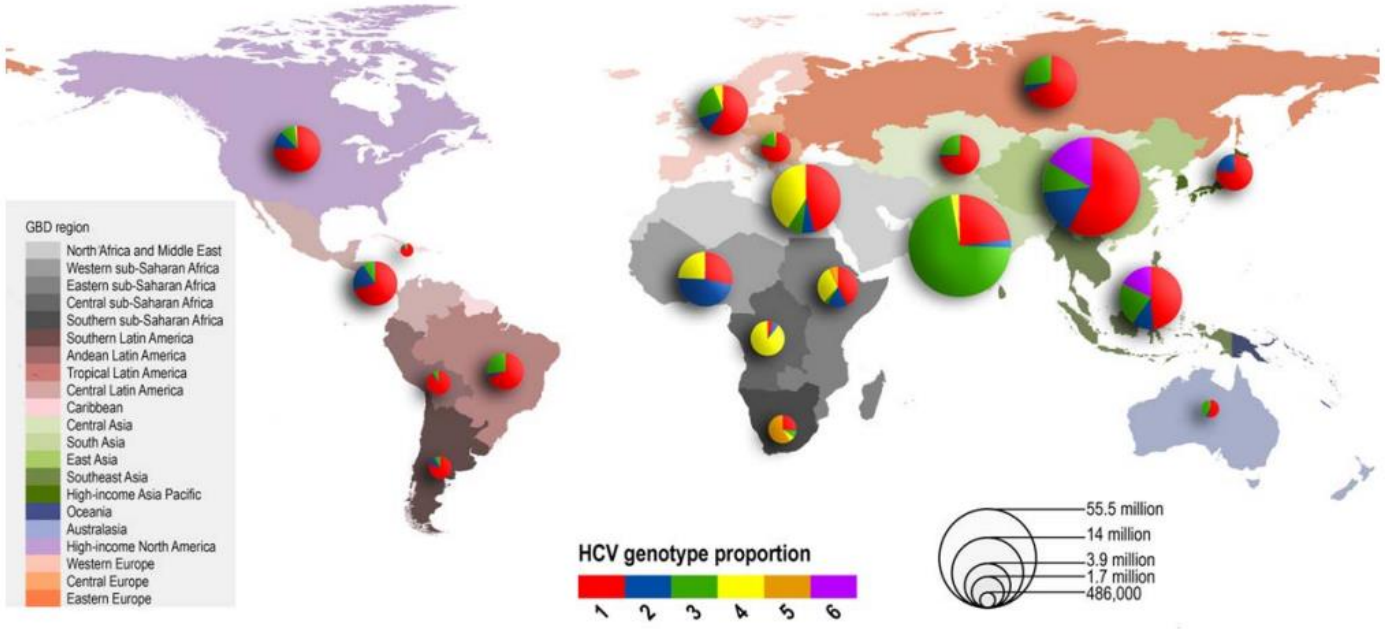

Fig. 1. Relative prevalence of each HCV genotype by GBD region. Size of pie charts is proportional to the number of seroprevalent cases as estimated by Hanafiah et al.[2]

O genótipo viral pode influenciar o curso natural na hepatite C?

Hepatitis C Virus Genotype 3 Is Cytopathic to Hepatocytes: Reversal of Hepatic Steatosis After Sustained Therapeutic Response

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On the basis of cross-sectional studies, it has been proposed that hepatic steatosis is a cytopathic effect of hepatitis C virus (HCV) genotype 3 but not genotype 1 infections. We tested this hypothesis by examining whether antiviral treatment altered hepatic steatosis in chronic hepatitis C. In 28 patients with genotype 1 and 34 with genotype 3 HCV, we determined the severity of steatosis in pre- and posttreatment liver biopsies using computer-assisted morphometric image analysis as well as conventional semiquantitative scoring. Before treatment, hepatic steatosis was present in 16 (57%) patients infected with HCV genotype 1 and 21 (62%) of those with genotype 3. Sustained viral response (SVR) was achieved in 9 (32%) patients with genotype 1 and 22 (65%) with genotype 3. In neither group were there significant changes in body weight or alcohol consumption between pre- and posttreatment biopsies. In patients with HCV genotype 1, there was no change in hepatic steatosis after treatment, irrespective of the treatment response. Among those infected with genotype 3, SVR significantly reduced steatosis ($P < .001$), but there was no change in steatosis among those without a SVR. By logistic regression analysis, SVR was the only variable predictive of improvement in hepatic steatosis (OR = 36, 95% CI = 2.7-481, $P = .007$). In conclusion, these data provide strong support for a direct causal association between HCV genotype 3 infection and hepatic steatosis. (HEPATOLOGY 2002;36:1266-1272.)

LIVER

Steatosis affects chronic hepatitis C progression in a genotype specific way

L Rubbia-Brandt, P Fabris, S Paganin, G Leandro, P-J Male, E Giostra, A Carlotto, L Bozzola, A Smedile, F Negro

Gut 2004;**53**:406–412. doi: 10.1136/gut.2003.018770

See end of article for authors' affiliations

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Accepted for publication 17 July 2003

Background and aims: Liver steatosis is frequent in chronic hepatitis C, particularly in patients infected with hepatitis C virus (HCV) genotype 3. The aim of this study was to determine the relationship between steatosis and fibrosis in chronic hepatitis C as a function of viral genotype.

Methods: A multivariable logistic regression analysis was carried out in 755 chronic hepatitis C patients (mean body mass index (BMI) 24.11 kg/m^2; 178 with genotype 3), consecutively admitted to three referral hospitals. Liver histology showed steatosis in 315 and fibrosis in 605 patients, of whom 187 had cirrhosis (78 compensated and 109 decompensated).

Results: Steatosis was independently associated with fibrosis ($p<0.001$), genotype 3 ($p<0.001$), BMI ($p<0.001$), ongoing alcohol abuse ($p<0.001$), and age ($p=0.001$). Fibrosis was associated with the Metavir activity score ($p<0.001$), age ($p<0.001$), steatosis ($p=0.001$), past alcohol abuse for >5 years ($p=0.015$), and BMI ($p=0.034$). When regression analysis was repeated on patients divided according to viral genotype (that is, 3 *v* non-3) to identify type specific risk factors, steatosis was associated with ongoing alcohol abuse ($p<0.001$) and age ($p=0.01$) only in non-3 genotype infected patients and with Metavir activity ($p=0.044$) only in genotype 3 infected patients. Similarly, fibrosis was associated with steatosis only in genotype 3 infected individuals ($p=0.018$), and with past alcohol abuse ($p=0.003$) and (marginally) diabetes ($p=0.078$) only in non-3 genotype infected patients.

Conclusions: Steatosis influences chronic hepatitis C progression in a genotype specific way. Patients infected with genotype 3 and histologically confirmed steatosis should not be deferred from effective antiviral therapy.

RECENT ADVANCES IN CLINICAL PRACTICE

STEATOSIS IN CHRONIC HEPATITIS C: WHY DOES IT REALLY MATTER?

T Asselah, L Rubbia-Brandt, P Marcellin, F Negro

Gut 2006;**55**:123–130. doi: 10.1136/gut.2005.069757

Table 1 Frequency and distribution of steatosis in patients with chronic hepatitis C

		Patients with steatosis (n (%))			Distribution of steatosis (n (%))	
Author, year	**Patients (n)**	**Overall**	**Genotype 3**	**Other**	**Mild (<30%)**	**Marked (>30%)**
Mihm 1997[10]	85	73 (86)	ND	ND	60 (82)	13 (18)
Czaja 1998[11]	60	31 (52)	ND	ND	31 (100)	0 (0)
Hourigan 1999[12]	148	91 (61)	14/17 (78)	14/23 (61)	61 (67)	30 (33)
Rubbia-Brandt 2000[13]	70	28 (40)	16/24 (67)	12/46 (26)	18 (65)	10 (35)
Adinolfi 2001[14]	180	86 (48)	20/26 (77)	66/154 (43)	44 (51)	42 (49)
Serfaty 2001[15]	100	ND	ND	ND	88 (88)	12 (12)
Monto 2002[16]	297	171 (58)	ND	ND	146 (85)	25 (15)
Westin 2002[17]	98	41 (42)	22/25 (88)	11/45 (24)	25 (61)	16 (39)
Hui 2002[18]	124	90 (73)	33/43 (77)	50/71 (70)	55 (61)	35 (39)
Castéra 2003[19]	96	51 (54)	15/20 (75)	36/76 (47)	42 (82)	9 (18)
Poynard 2003[20]	1428	935 (65)	175/210 (83)	760/1218 (62)	836 (89)	99 (11)
Asselah 2003[21]	290	135 (46)	36/58 (63)	97/232 (42)	91 (68)	44 (32)
Rubbia-Brandt 2004[22]	755	315 (42)	109/178 (61)	206/577 (36)	206 (65)	109 (35)
Patton 2004[23]	574	277 (48)	61/84 (91)	216/490 (44)	187 (68)	90 (32)
Total	4305	2324 (55)	501/685 (73)	1468/2932 (50)	1890 (78)	531 (22)

ND, not done.

J Hepatol. 2009 Oct;51(4):655-66. doi: 10.1016/j.jhep.2009.05.016. Epub 2009 Jun 6.

Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C.

Bochud PY[1], 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.

⊕ Collaborators (23)

⊕ Author information

Abstract

BACKGROUND/AIMS: While several risk factors for the histological progression of chronic hepatitis C have been identified, the contribution of HCV genotypes to liver fibrosis evolution remains controversial. The aim of this study was to assess independent predictors for fibrosis progression.

METHODS: We identified 1189 patients from the Swiss Hepatitis C Cohort database with at least one biopsy prior to antiviral treatment and assessable date of infection. Stage-constant fibrosis progression rate was assessed using the ratio of fibrosis Metavir score to duration of infection. Stage-specific fibrosis progression rates were obtained using a Markov model. Risk factors were assessed by univariate and multivariate regression models.

RESULTS: Independent risk factors for accelerated stage-constant fibrosis progression (>0.083 fibrosis units/year) included male sex (OR=1.60, [95% CI 1.21-2.12], P<0.001), age at infection (OR=1.08, [1.06-1.09], P<0.001), histological activity (OR=2.03, [1.54-2.68], P<0.001) and genotype 3 (OR=1.89, [1.37-2.61], P<0.001). Slower progression rates were observed in patients infected by blood transfusion (P=0.02) and invasive procedures or needle stick (P=0.03), compared to those infected by intravenous drug use. Maximum likelihood estimates (95% CI) of stage-specific progression rates (fibrosis units/year) for genotype 3 versus the other genotypes were: F0-->F1: 0.126 (0.106-0.145) versus 0.091 (0.083-0.100), F1-->F2: 0.099 (0.080-0.117) versus 0.065 (0.058-0.073), F2-->F3: 0.077 (0.058-0.096) versus 0.068 (0.057-0.080) and F3-->F4: 0.171 (0.106-0.236) versus 0.112 (0.083-0.142, overall P<0.001).

CONCLUSIONS: This study shows a significant association of genotype 3 with accelerated fibrosis using both stage-constant and stage-specific estimates of fibrosis progression rates. This observation may have important consequences for the management of patients infected with this genotype.

Research Article

Hepatitis C Virus (HCV) Genotype 3 is Associated with Higher Grade of Liver Fibrosis in Hepatitis C Virus Infected Patients

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Abstract

In Chronic hepatitis C (CHC), one of the most important causes of chronic liver diseases, exact association of viral factors such as Genotype and viral load with fibrosis is not yet determined.

Objective: To investigate relationship between HCV genotypes, viral load, biochemical markers and degree of liver fibrosis in patients with chronic HCV infection.

Materials and Methods: Retrospective analysis of 887 HCV positive patients was done. Liver biopsy was done in 154 patients and degree of fibrosis was evaluated by modified ISHAK scoring system. HCV viral load was determined by COBAS TaqMan HCV test v2.0 (Roche Molecular System Inc, Branchburg, NJ, USA) and genotyping was performed by Linear Array HCV Genotyping Test (Roche Molecular System Inc, Branchburg, NJ, USA).

Result: The mean age of study population was 47.63 (±15.08) years and male: female ratio was 2.68:1. Overall mean HCV viral load was 6.26x105 (±12.52) IU/ml, mean ALT level 62.65 (±2.16) IU/ml, mean AST level 43.0 (±2.03) IU/ml and mean total bilirubin level 1.00 (±0.19) mg/dl. Genotype 3 (69.4%) was most common genotype followed by 1 (25.6%) and 4 (4.6%). The biochemical markers (ALT, AST and total bilirubin) were significantly higher in patients with genotype 3 as compared to genotype1 (p=0.036, 0.000 and 0.012 respectively). Of 154 patients, fibrosis score <3 was seen in 96 (62.5%) patients and ≥3 in the remaining 58 (37.5%) patients. Genotype 3 was significantly correlated with higher (≥3) fibrosis score (p=0.009).

Conclusion: Genotype 3 was found to be significantly associated with higher liver fibrosis which may have implications in clinical management of genotype 3 infected patients.

Keywords: Chronic hepatitis; Hepatitis C virus; Genotypes; Fibrosis

JOURNAL OF VIRAL HEPATITIS JVH

Journal of Viral Hepatitis, 2011, **18**, 745–759 doi:10.1111/j.1365-2893.2011.01481.x

REVIEW

Role of Hepatitis C virus genotype 3 in liver fibrosis progression – a systematic review and meta-analysis

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Clin Gastroenterol Hepatol. 2011 Aug;9(8):688-93. doi: 10.1016/j.cgh.2011.04.029. Epub 2011 May 13.

Steatosis is an independent predictor of relapse following rapid virologic response in patients with HCV genotype 3.

Shah SR[1], Patel K, Marcellin P, Foster GR, Manns M, Kottilil S, Healey L, Pulkstenis E, Subramanian GM, McHutchison JG, Sulkowski MS, Zeuzem S, Nelson DR.

⊕ **Author information**

Abstract

BACKGROUND & AIMS: It is recommended that patients with chronic hepatitis C virus (HCV) genotype 3 infections receive 24 weeks of treatment. A rapid virologic response (RVR; at week 4) predicts a sustained virologic response (SVR), although not all patients with an RVR achieve an SVR. We explored the relationships among hepatic steatosis, level of HCV RNA, relapse, and RVR in a phase 3 randomized controlled trial of 932 patients infected with HCV genotype 2 (n = 427) or 3 (n = 505) who received 24 weeks of therapy with interferon-α.

METHODS: In patients with an RVR (HCV RNA <43 IU/mL), the presence of an SVR was modeled using multivariate logistic regression as a function of age, sex, weight, body mass index, insulin resistance, steatosis, and levels of γ-glutamyl transpeptidase, alanine aminotransferase, liver fibrosis, and baseline HCV RNA.

RESULTS: RVR, SVR, and relapse rates among patients with HCV genotype 3 were 79.6%, 79.2%, and 15.6%, respectively; corresponding rates among patients with HCV genotype 2 were 86.7%, 84.3%, and 10.1%. An RVR had high predictive value for an SVR in patients with HCV genotypes 2 (88.9%) and 3 (88.1%). The strongest independent predictors of relapse in patients with genotype 3 and an RVR were steatosis (odds ratio 3.0; P = .003) and HCV RNA ≥400,000 IU/mL (odds ratio 2.5; P = .04). Relapse rates in patients with steatosis were 17.4% and 20.9% for low and high baseline levels of HCV RNA, respectively; corresponding rates in those without steatosis were 2.5% and 8.8%.

CONCLUSIONS: Steatosis was associated with significantly higher rates of relapse, irrespective of viral load, in patients infected with HCV genotype 3 who had an RVR. Further studies are needed to determine if longer treatment durations are effective in patients with an RVR and these risk factors.

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HCV Genotype 3 Is Associated With an Increased Risk of Cirrhosis and Hepatocellular Cancer in a National Sample of U.S. Veterans With HCV

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Data show that viral genotype 1 may increase the risk of cirrhosis and hepatocellular carcinoma (HCC) compared to genotype 2 in patients with chronic hepatitis C virus (HCV) infection. However, the effect of HCV genotype 3 on cirrhosis and HCC risk is uncertain. We identified patients with active HCV infection, confirmed by positive polymerase chain reaction (PCR) and a known HCV genotype, from the VA HCV Clinical Case Registry between 2000 and 2009. We examined the effect of HCV genotype on the risk of cirrhosis and HCC in a Cox proportional hazards model adjusting for patients' age, period of service (World War I/II, Vietnam era, post-Vietnam era), race, gender, human immunodeficiency virus (HIV) infection, alcohol use, diabetes, body mass index, and antiviral treatment receipt. Of the 110,484 patients with active HCV viremia, 88,348 (79.9%) had genotype 1, 13,077 (11.8%) genotype 2, 8,337 (7.5%) genotype 3, and 1,082 (0.9%) patients had genotype 4 infection. Despite being younger, patients with genotype 3 had a higher risk of developing cirrhosis (unadjusted hazard ratio [HR] = 1.40, 95% confidence interval [CI] = 1.32-1.50) and HCC (unadjusted HR = 1.66, 95% CI = 1.48-1.85) than HCV genotype 1 patients. After adjustment for prespecified demographic, clinical, and antiviral treatment factors, the risk of cirrhosis and HCC was 31% (adjusted HR = 1.31, 95% CI = 1.22-1.39) and 80% (adjusted HR = 1.80, 95% CI = 1.61-2.03) higher in patients with genotype 3 compared to genotype 1 infected patients. *Conclusion*: HCV genotype 3 is associated with a significantly increased risk of developing cirrhosis and HCC compared to HCV genotype 1. This association is independent of patients' age, diabetes, body mass index, or antiviral treatment. (HEPATOLOGY 2014;60:98-105)

Genótipo 3

- Fator de risco independente na progressão para fibrose hepática
- Associação com esteatose hepática e progressão para fibrose
- Alteração no metabolismo lipídico/resistência a insulina
- Progressão para cirrose e HCC
- Efeito citopático direto do vírus

Como o genótipo 3 responde ao tratamento?

- ↑carga viral se relaciona com menor RVS
- 59% x 85% em pacientes com CV> 800000IU/ml

GASTROENTEROLOGY 2005;129:522–527

Peginterferon-α-2a (40KD) and Ribavirin for 16 or 24 Weeks in Patients With Genotype 2 or 3 Chronic Hepatitis C

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Background & Aims: Standard therapy of patients with chronic hepatitis C virus (HCV) infected with HCV genotype-2 or -3 is the combination of pegylated interferon-α and ribavirin for 24 weeks. Whether shorter treatment durations are possible for these patients without compromising sustained virologic response rates is unknown. *Methods:* Patients chronically infected with HCV-2 (n = 39), HCV-2/3 (n = 1), or HCV-3 (n = 113) were treated with peginterferon-α-2a (180 μg/wk) plus ribavirin 800–1200 mg/day. HCV RNA was quantitatively assessed after 4 weeks. Patients with a rapid virologic response (HCV RNA below 600 IU/mL) were randomized for a total treatment duration of 16 (group A) or 24 weeks (group B). All patients with HCV RNA ≥600 IU/mL at week 4 (group C) were treated for 24 weeks. End-of-treatment and sustained virologic response were assessed by qualitative RT-PCR (sensitivity 50 IU/mL). *Results:* Only 11 of 153 patients (7%) were allocated to group C. End-of-treatment and sustained virologic response rates were 94% and 82%, (group A), 85% and 80% (group B), and 73% and 36% (group C), respectively. In patients infected with genotype HCV-3 and high viral load (>800,000 IU/mL), a significant lower sustained virologic response rate was found than in patients infected with HCV-3 and a viral load lower or equal to 800,000 IU/mL (59% vs 85%, respectively; P = .003). *Conclusions:* In HCV-2 and -3 (low viral load)-infected patients who have a rapid virologic response, treatment for 16 weeks with peginterferon-α-2a and ribavirin is sufficient. In patients infected by HCV-3 (high viral load), longer treatment may be necessary.

Como o genotipo 3 responde ao tratamento?

- Fibrose hepática

(76% RVS) e cirrose (60% RVS)possuem efeito negativo na resposta ao tratamento com PEG-IFN + RBV

- curta duração da terapia associada a menor RVS

774 **BASELINE AND ON-TREATMENT FACTORS ASSOCIATED WITH HIGH RATES OF SUSTAINED VIROLOGICAL RESPONSE IN PATIENTS WITH AND WITHOUT CIRRHOSIS FOLLOWING TREATMENT WITH PEGINTERFERON ALFA-2A AND RIBAVIRIN**

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Background: Although patients with HCV and advanced fibrosis/cirrhosis show low SVR rates, data showing which subsets of patients may respond better are required. We therefore determined the predictive values of baseline and on-treatment factors associated with SVR in patients with advanced fibrosis/cirrhosis using data from three large phase III studies of PEG-IFNα-2a (40KD) plus ribavirin (RBV).
Methods: Patients were classified by liver staging (Non-cirrhotic: Metavir ⩽2, Knodell ⩽2, Ishak ⩽3; Cirrhotic (including advanced fibrosis): Metavir 3+4, Knodell 3+4, Ishak 4+5+6): Genotype (G) 1/4 patients were randomized to PEG-IFNα-2a 180 μg/week plus RBV 1000/1200 mg/day for 48 weeks and G2/3 patients were randomized to PEG-IFNα-2a 180 μg/week plus RBV 800 mg/day for 24 or 16 weeks.
Results: Overall, SVR rates in G1/4 patients were 59.5% (n = 242) in non-cirrhotics and 44.4% (n = 99) in cirrhotics (P = 0.0111). SVR rates in G2/3 patients treated for 24 weeks were 76.0% (N = 629) and 59.8% (N = 189) in non-cirrhotics and cirrhotics, respectively (p < 0.0001). G2/3 patients receiving 16 weeks of therapy achieved SVR rates of 66.9% (N = 538) in non-cirrhotics and 48.2% (N = 191) in cirrhotics (p < 0.0001). The difference in SVR between G2/3 cirrhotic patients treated for 16 weeks vs. 24 weeks was significant in favor of the longer treatment duration (p = 0.0231). Cirrhotics with younger age (<40 years), low baseline HCV RNA (<400,000 IU/mL), and maximum exposure to PEG-IFNα-2a and RBV (⩾80% target) achieved higher SVR rates (49–85%) in each population. SVR rates were high (70–95%) for all patients with an RVR (<50 IU/mL at week 4) in each population. Degree of fibrosis/cirrhosis severity did not influence the rates of treatment completion or discontinuation due to adverse effects. Across all genotypes, cirrhotics received slightly lower cumulative PEG-IFN exposure (vs. non-cirrhotic) and G1/4 patients with fibrosis/cirrhosis received lower cumulative RBV exposure (vs. non-cirrhotic).
Conclusions: Despite patients with fibrosis/cirrhosis having lower rates of SVR in comparison to patients with milder liver disease, high SVR rates can be achieved in younger subjects, with low viral loads, who showed RVR and who maintained high exposure to both PEG and RBV. The results also suggest that G2/3 patients with cirrhosis should not be treated with abbreviated therapy.

Desafios no tratamento

• Até 2011 – relativa eficácia de tratamento com PEG-INF/RBV por 24 semanas →70 a 80% SVR

Best Pract Res Clin Gastroenterol. 2012 Aug;26(4):413-27. doi: 10.1016/j.bpg.2012.09.004.

The role of viral and host genetics in natural history and treatment of chronic HCV infection.

Doyle JS[1], Hellard ME, Thompson AJ.

• De 2011 a 2013→DAA

•2011 – 1º geração de inibidores de protease (telaprevir e boceprevir)

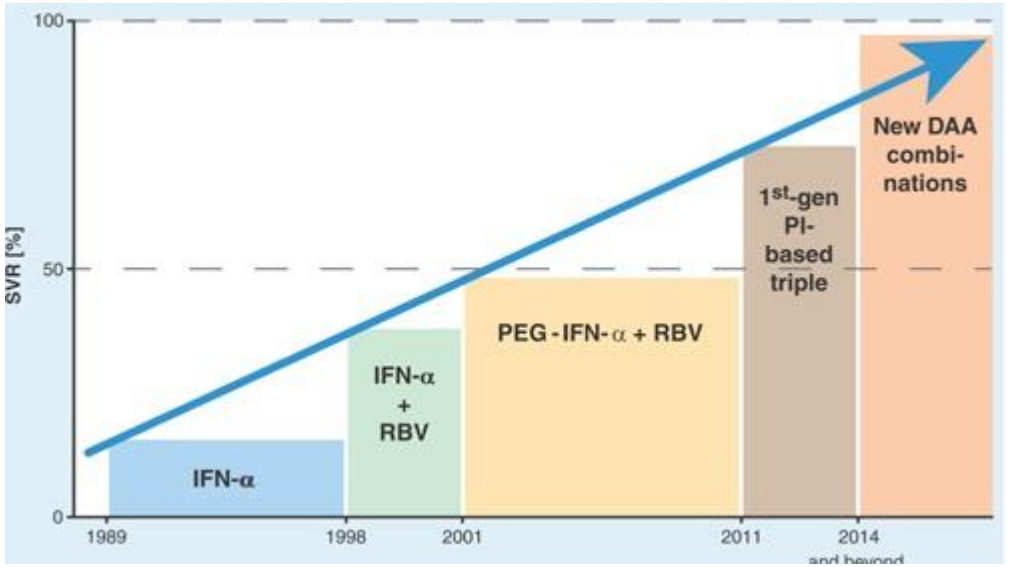
• Ação limitada contra genótipo 3

• 2013 → novos DAAs

• Sofosbuvir (SOF)

• Simeprevir

• Daclastavir (DCV)



ORIGINAL ARTICLE

Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3

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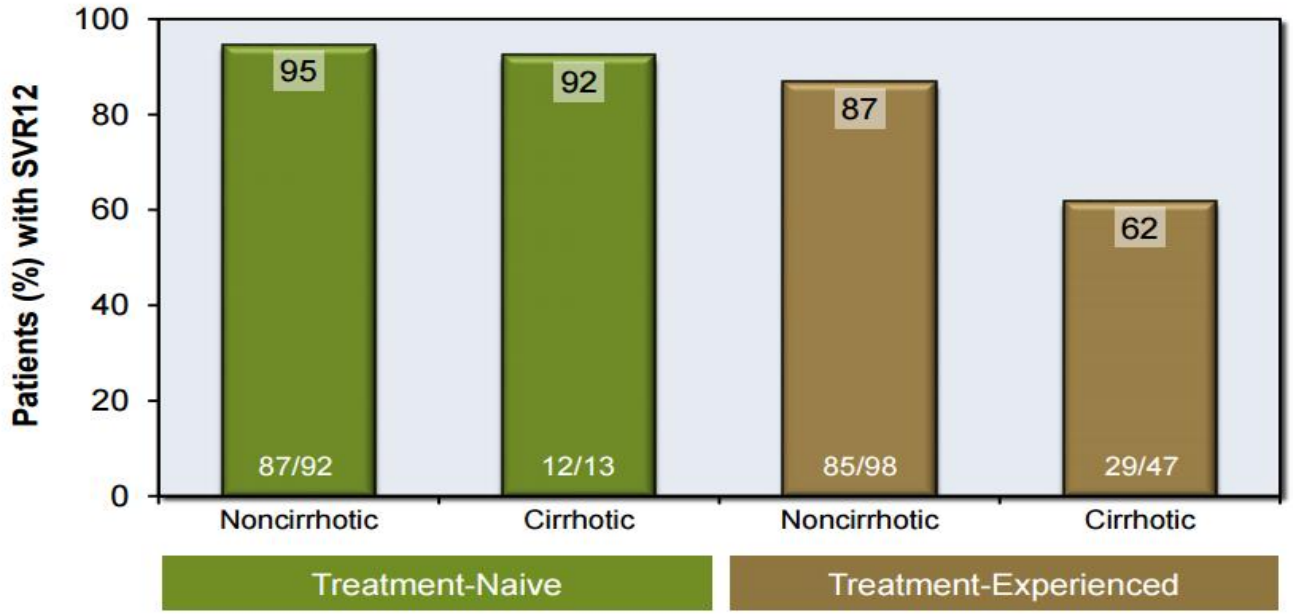
N Engl J Med 2014; 370:1993-2001 | May 22, 2014 | DOI: 10.1056/NEJMoa1316145

Sofosbuvir and Ribavirin for HCV GT 2 or 3
VALENCE: Results for GT 3

VALENCE: GT 3 SVR12, by Treatment Experience & Liver Disease



Source: Zeuzem S, et al. N Engl J Med. 2014;370:1993-2001.

Hepatitis web study

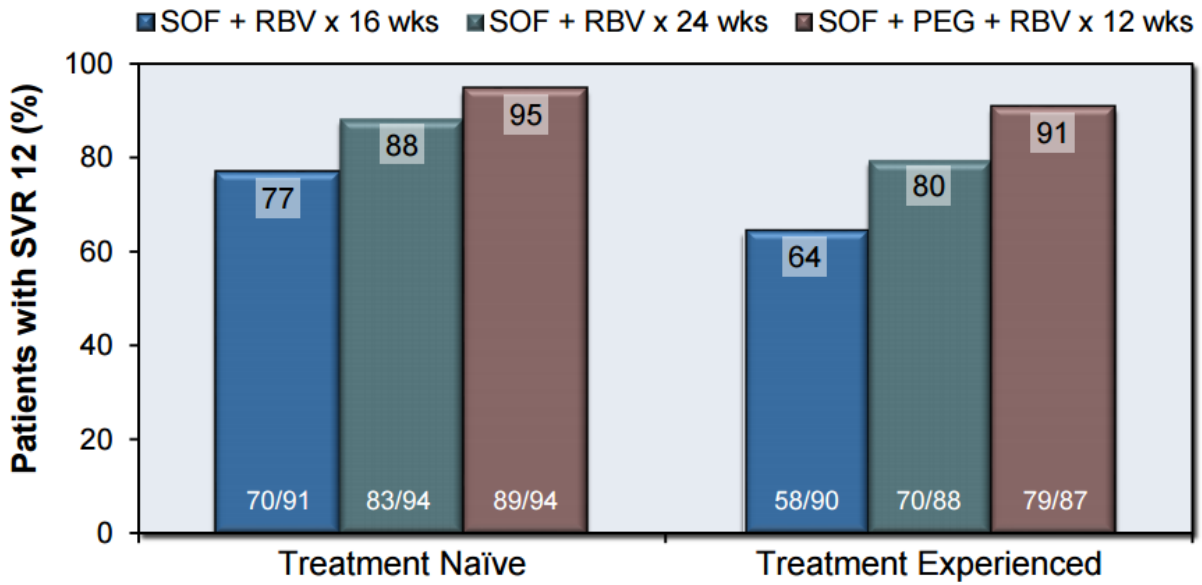
Gastroenterology. 2015 Nov;149(6):1462-70. doi: 10.1053/j.gastro.2015.07.043. Epub 2015 Aug 4.

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.

Foster GR[1], Pianko S[2], Brown A[3], Forton D[4], Nahass RG[5], George J[6], Barnes E[7], Brainard DM[8], Massetto B[8], Lin M[8], Han B[8], McHutchison JG[8], Subramanian GM[8], Cooper C[9], Agarwal K[10]; BOSON Study Group.

Sofosbuvir + Ribavirin +/- Peginterferon for HCV GT 2 or 3 BOSON: Results

Genotype 3: SVR12 by Regimen and Treatment History



Source: Foster GR, et al. 50th EASL. 2015. Abstract L05.

Hepatitis web study

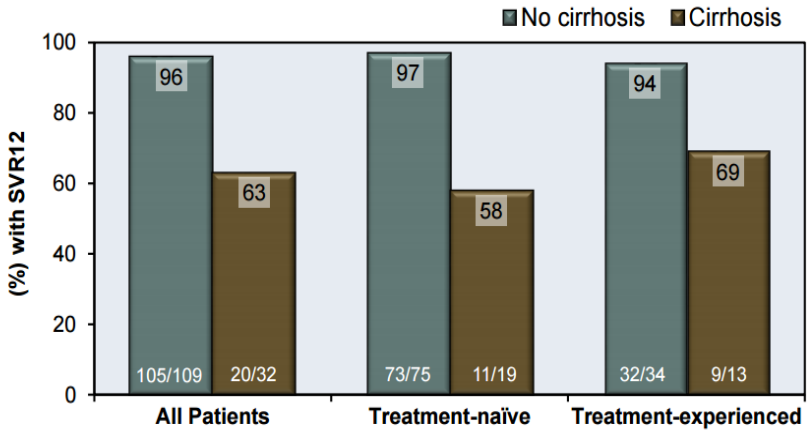
All-Oral 12-Week Treatment With Daclatasvir Plus Sofosbuvir in Patients With Hepatitis C Virus Genotype 3 Infection: ALLY-3 Phase III Study

David R. Nelson,[1] James N. Cooper,[2] Jacob P. Lalezari,[3] Eric Lawitz,[4] Paul J. Pockros,[5] Norman Gitlin,[6] Bradley F. Freilich,[7] Ziad H. Younes,[8] William Harlan,[9] Reem Ghalib,[10] Godson Oguchi,[11] Paul J. Thuluvath,[12] Grisell Ortiz-Lasanta,[13] Mordechai Rabinovitz,[14] David Bernstein,[15] Michael Bennett,[16] Trevor Hawkins,[17] Natarajan Ravendhran,[18] Aasim M. Sheikh,[19] Peter Varunok,[20] Kris V. Kowdley,[21] Delphine Hennicken,[22] Fiona McPhee,[23] Khurram Rana,[23] and Eric A. Hughes,[24] on behalf of the ALLY-3 Study Team

Treatment options for patients with hepatitis C virus (HCV) genotype 3 infection are limited, with the currently approved all-oral regimens requiring 24-week treatment and the addition of ribavirin (RBV). This phase III study (ALLY-3; ClinicalTrials.gov: NCT02032901) evaluated the 12-week regimen of daclatasvir (DCV; pangenotypic nonstructural protein [NS]5A inhibitor) plus sofosbuvir (SOF; pangenotypic NS5B inhibitor) in patients infected with genotype 3. Patients were either treatment naïve (n = 101) or treatment experienced (n = 51) and received DCV 60 mg plus SOF 400 mg once-daily for 12 weeks. Coprimary endpoints were the proportions of treatment-naïve and treatment-experienced patients achieving a sustained virological response (SVR) at post-treatment week 12 (SVR12). SVR12 rates were 90% (91 of 101) and 86% (44 of 51) in treatment-naïve and treatment-experienced patients, respectively; no virological breakthrough was observed, and ≥99% of patients had a virological response (VR) at the end of treatment. SVR12 rates were higher in patients without cirrhosis (96%; 105 of 109) than in those with cirrhosis (63%; 20 of 32). Five of seven patients who previously failed treatment with an SOF-containing regimen and 2 of 2 who previously failed treatment with an alisporivir-containing regimen achieved SVR12. Baseline characteristics, including gender, age, HCV-RNA levels, and *interleukin-28B* genotype, did not impact virological outcome. DCV plus SOF was well tolerated; there were no adverse events (AEs) leading to discontinuation and only 1 serious AE on-treatment, which was unrelated to study medications. The few treatment-emergent grade 3/4 laboratory abnormalities that were observed were transient. *Conclusion:* A 12-week regimen of DCV plus SOF achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3–infected patients with cirrhosis is underway. (Hepatology 2015;61:1127-1135)

Daclatasvir + Sofosbuvir for HCV GT 3
ALLY-3 Trial: Results

ALLY-3: SVR12, by Cirrhosis Status



Note:11 had missing or inconclusive findings for cirrhosis and not included in denominators

Source: Nelson DR, et al. Hepatology 2015;61:1127-35.

Hepatitis web study

Protocolo clínico

13.4.3 Genótipo 3

Quadro 11 – Tratamento da Hepatite C - Genótipo 3

Genótipo 3	Regime terapêutico	Tempo
PR autorizado	Sofosbuvir + PR	12 semanas
PR contraindicado	Sofosbuvir + daclatasvir	12 semanas

Fonte: DDAHV/SVS/MS.

* O acréscimo de ribavirina ao regime terapêutico poderá ser realizado para pacientes experimentados ou portadores de cirrose hepática, a fim de aumentar a taxa de RVS. A posologia recomendada para esse antiviral é de 11mg/kg/dia. Pode-se utilizar, como regra, a administração de 1 g para pacientes com peso inferior a 75kg e 1,25g para pacientes com peso superior a 75kg.

Novo tratamento

- Estender tratamento para 24 semanas em pacientes cirróticos
- Tratamento baseado em PEG-IFN

Genótipo 3	Regime terapêutico	Tempo
Com ou sem cirrose Child A	*Sofosbuvir + alfapeguinterferona*	*12 semanas*
PEG-IFN contra-indicado sem cirrose	*Sofosbuvir + daclatasvir+/- ribavirina*	*12 semanas*
PEG-IFN contra-indicado com cirrose	*Sofosbuvir + daclatasvir+/- ribavirina*	*24 semanas*

1. (David R. Nelson, 2015);2. (American Association for the Study of Liver Diseases, 2016); 3. (The European Association for the Study of the Liver, 2016) 4. (Foster GR & Group., 2015).

SEPTEMBER 2016

EASL | JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016

SUMMARY

European Association for the Study of the Liver

- SOF + DCV por 12 semanas em pacientes virgens de tratamento não cirróticos
- SOF + DCV + RBV por 12 semanas em pacientes não experimentados não cirróticos
- pacientes cirróticos → SOF + DCV + RBV por 24 semanas

Genotype 3, Option 2: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 3 can be treated with a combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**A1**).
- Treatment-naïve patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- If no NS5A resistance testing is performed, treatment-experienced patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis with the NS5A RAS Y93H detectable at baseline should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RASs Y93H at baseline should receive the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**C1**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (**C1**).

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

- Pacientes virgens de tratamento sem cirrose :
- SOF+ DCV por 12 semanas → 97% RVS
- SOF + velpastavir por 12 semanas → 98% RVS

- Pacientes virgens de tratamento com cirrose :
- SOF + velpastavir por 12 semanas →

93% RVS **(ASTRAL -3)**

- SOF+ DCV por 24 semanas com ou sem RBV → 86% RVS
- é recomendado a extensão da terapia em cirróticos (58% de RVS com 12 semanas de terapia)

Genotype 3 Treatment-Naïve Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who do not have cirrhosis.**
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretoviral therapy.

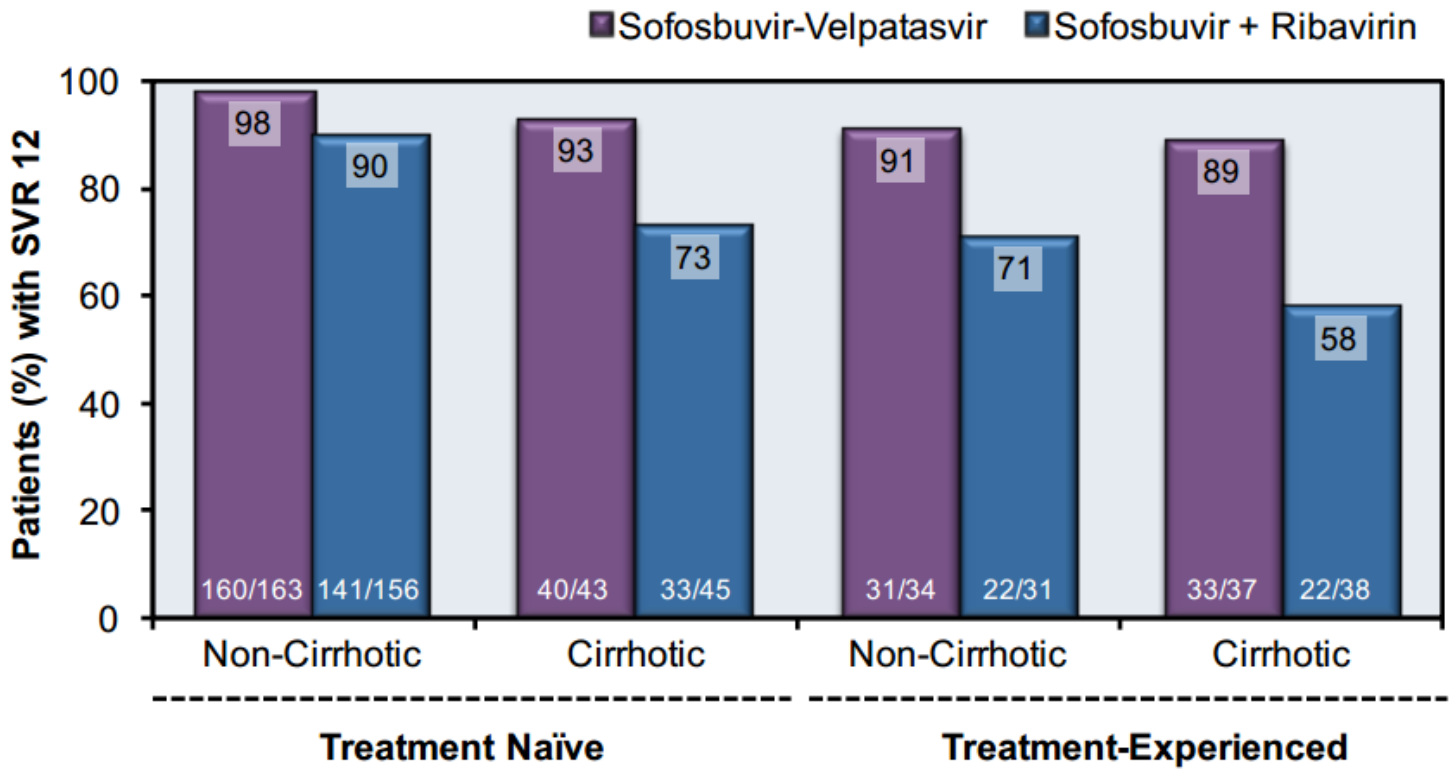
Genotype 3 Treatment-Naïve Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.[1]**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based ribavirin is a Recommended regimen for treatment-naïve patients with HCV genotype 3 infection who have compensated cirrhosis.[1]**
  Rating: Class IIa, Level B

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Results

ASTRAL-3: SVR12 Results by Cirrhosis & Treatment Experience



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

Hepatitis web study

AASLD
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• Pacientes previamente tratados com PEG-INF/ RBV não cirróticos:

• DCV + SOF por 12 semanas → 94% RVS

• SOF + velpastavir por 12 semanas → 95% RVS

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients Without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.¶**
  Rating: Class I, Level A

- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed¶.**
  Rating: Class I, Level A

• Pacientes previamente tratados com PEG-INF/ RBV cirróticos:

•SOF + velpastavir + RBV por 12 semanas → 89% RVS

•DCV + SOF + RBV por 24 semanas → 88% RVS com 12 semanas e 89% RVS com 16 semanas ; recomendado extensão da terapia para 24 semanas

Genotype 3 PEG-IFN/Ribavirin Treatment-Experienced Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

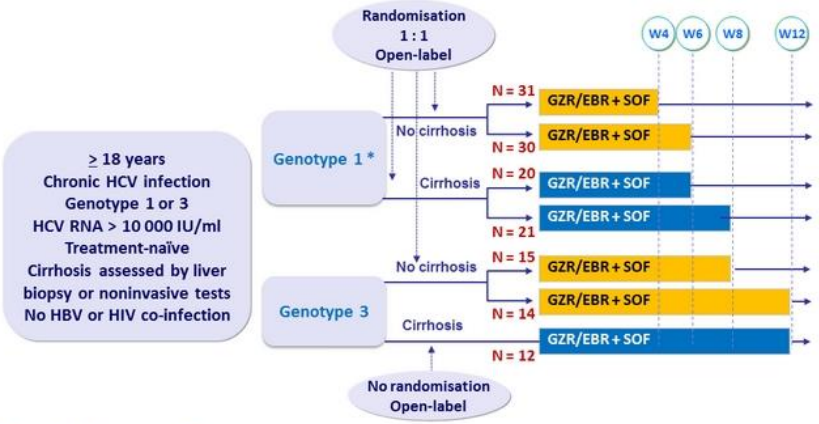
- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.**
  Rating: Class I, Level B

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.**
  Rating: Class IIa, Level B

C-SWIFT Study: elbasvir/grazoprevir + SOF in genotypes 1 or 3, with or without cirrhosis

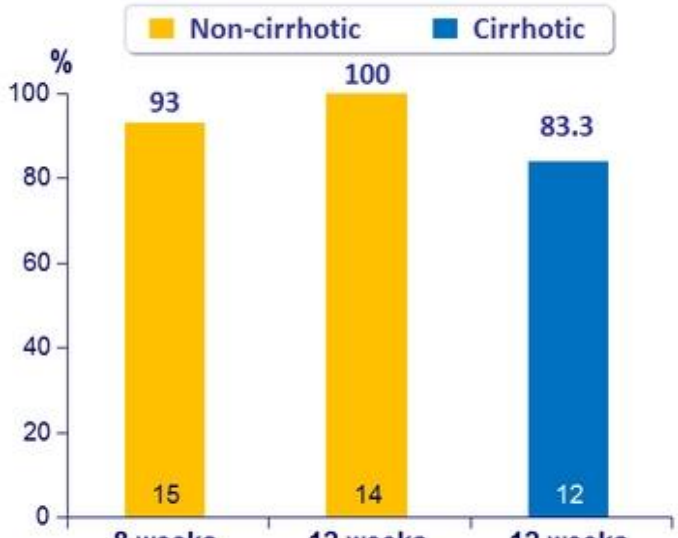
Lawitz E. Hepatology 2017;65:439-50

Design



* Randomisation stratified on genotype (1a vs non-1a)

SVR$_{12}$ (HCV RNA < 15 IU/ml), mITT, Genotype 3



	8 weeks	12 weeks	12 weeks
Breakthrough	0	0	0
Relapse	1	0	1
Early discontinuation	0	0	1

OBRIGADA À TODOS!