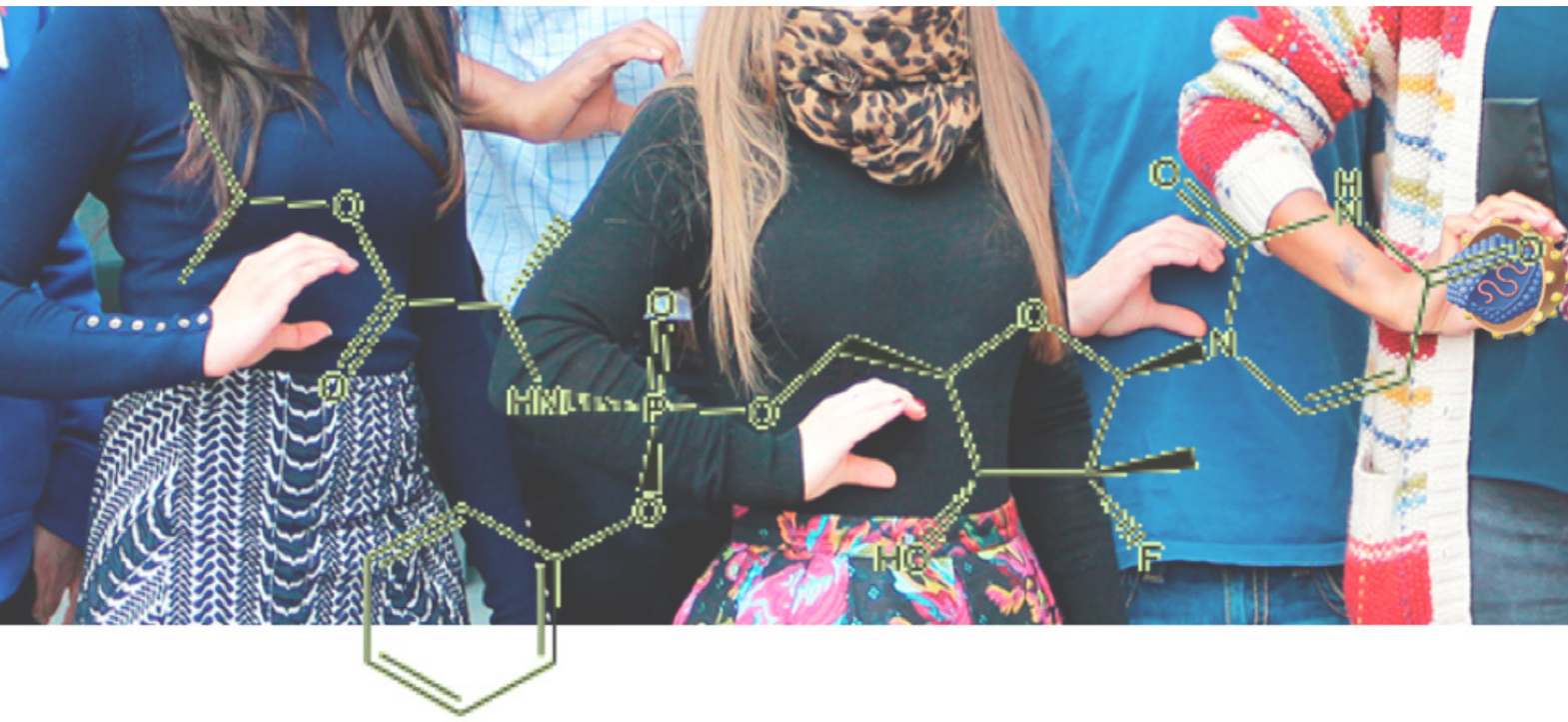

Andreia Filipa Pintor Gi

Sofosbuvir: the hepatitis C patients' hope

Monografia realizada no âmbito da unidade Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pela Professora Doutora Paula Cristina Santos Luxo Maia e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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UNIVERSIDADE DE COIMBRA

Eu, Andreia Filipa Pintor Gi, estudante do Mestrado Integrado em Ciências Farmacêuticas, com o nº 2011146796, declaro assumir toda a responsabilidade pelo conteúdo da Monografia apresentada à Faculdade de Farmácia da Universidade de Coimbra, no âmbito da unidade de Estágio Curricular.

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Coimbra, 15 de julho de 2016.

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Abbreviations

HCV – Hepatitis C virus

SVR – Sustained Virologic Response

SOF – Sofosbuvir

HCC – Hepatocellular carcinoma

PegIFN – Peginterferon

IFN – Interferon

DAA – Direct-acting Antiviral Agent

RBV – Ribavirin

LLOQ – Lower Limit of Quantification

HIV – Human Immunodeficiency Virus

HAART – Highly Active Anti-Retroviral Therapy

ART – Anti-Retroviral Therapy

pTVR – post-Transplant Virologic Response

CPT – Child-Pugh-Turcotte

MELD – Model for End-Stage Liver Disease

Abstract

Hepatitis C virus infection is a substantial health problem on a global scale. (1) It is estimated that approximately 185 million people live with hepatitis C worldwide, with 350,000–500,000 patients dying each year from liver disease associated with hepatitis C. (2) However, something is about to change.

In the latest years, there has been a shift in treatment paradigm due to the discovery and approval of agents that target specific proteins crucial for hepatitis C virus replication. (3) At the center of this revolution is the new NS5B polymerase inhibitor, sofosbuvir (Sovaldi®) - a novel direct-acting antiviral agent, with pan-genotypic activity and high barrier to viral resistance. (4)

In Portugal, as in many other countries, sustainability has been the buzzword across all stakeholders. Nevertheless, sofosbuvir has demonstrated a favorable cost-effectiveness profile (5) and its exceptional cures rates have already helped establish the concept that chronic hepatitis C virus infection can be cured in most, if not all, affected individuals.

This review summarizes the clinical potential of sofosbuvir and its important role in hepatitis C antiviral therapy, discussing key results and future directions. Its aim is to highlight the significance of a future free from hepatitis C.

Keywords: Hepatitis C virus, sofosbuvir, direct-acting antivirals, sustained virologic response, cure.

Resumo

A infecção pelo vírus da hepatite C é um problema de saúde significativo à escala global. (1) Estima-se que vivam com hepatite C aproximadamente 185 milhões de pessoas em todo mundo, morrendo 350,000-500,000 doentes por ano devido a doença hepática associada à hepatite C. (2) Mas algo está prestes a mudar.

Nos últimos anos, tem havido uma alteração do paradigma do tratamento com a descoberta e aprovação de agentes que têm como alvo proteínas específicas, cruciais para a replicação do vírus da hepatite C. (3) No centro desta revolução, encontra-se o novo inibidor da polimerase NS5B, o sofosbuvir (Sovaldi®) - um novo agente antiviral de acção directa, com actividade pan-genotípica e uma elevada barreira à resistência viral. (4)

Em Portugal, como em muitos outros países, a sustentabilidade tem sido a palavra de ordem de todos os intervenientes no processo. No entanto, o sofosbuvir tem demonstrado um perfil favorável de custo-efectividade (5) e as suas taxas de cura excepcionais ajudaram já a estabelecer o conceito de que a hepatite C crónica pode ser curada na maioria, se não em todos, os indivíduos infectados.

Esta monografia resume o potencial clínico do sofosbuvir e o seu importante papel na terapia antiviral para a hepatite C, discutindo os principais resultados e as direcções futuras. O seu objectivo é destacar a importância de um futuro livre da hepatite C.

Palavras-chave: vírus da Hepatite C, sofosbuvir, antivíricos de acção directa, resposta virológica sustentada, cura.

Introduction

The Hepatitis C virus (HCV) is a small-enveloped virus of the *Flaviridae* family and genus *Hepacivirus*, (6) with a single-stranded positive RNA molecule of approximately 9.6 kb. (7) Prior to the discovery of the viral agent, HCV was mainly transmitted via blood products. Since then, injection drug use has arisen as the major mode of transmission in developed countries. (2)

The diagnosis of hepatitis C consists in two standard blood tests. The first one is an antibody test that confirms exposure to hepatitis C; while the second one is a RNA test that searches for the genome of HCV in the blood, checking whether or not there is an active infection. (8)

The main problem is that the majority of HCV-infected individuals are unaware of their infection, mostly due to the absence of symptoms during the disease. (9) In fact, following exposure to HCV, only a minority of patients clears the acute infection, whereas 80% persist with life-long chronic viremia. (10)

The goal of treatment in all infected individuals, regardless of which of the six major genotypes are present, remains the achievement of a sustained virologic response (SVR) in which circulating HCV RNA is undetectable (with the use of a highly sensitive assay) following treatment. When a SVR is achieved, there is a 99% chance that the hepatitis C infection is cured. (8,11)

Sofosbuvir (SOF) has demonstrated impressively high SVR rates in HCV-infected patients, (12,13) representing an enormous improvement over the prior standard of care. Consequently, it is expected that SOF could become an effective, safe and well-tolerated regimen with a potential for wide applicability.

The clinical problem

Chronic HCV infection is a serious, progressive, and potentially life-threatening disease. (14,15) If left untreated, over time it can cause liver damage or failure due to the development of cirrhosis. This liver complication can lead patients at substantial risk of decompensated disease and hepatocellular carcinoma (HCC), (16) which impose a considerable burden on affected people, healthcare systems and society. (8,17) However, recent advances in the field of HCV infection have increased the hope for cure.

The new regimens for HCV mean a breakthrough novelty in the history of anti-HCV treatment. Previous treatments for HCV were often long and difficult. Many lasted from 24 to 48 weeks and showed suboptimal efficacy in viral response with a range of commonly occurring significant side effects, which impaired therapeutic compliance. (18,19)

As a 12- or 24-week all-oral therapy taken once daily, along with its favorable safety profile, (13) SOF has dramatically simplified the HCV treatment and thus, optimized quality of life during therapy.

Sofosbuvir

SOF was developed to meet an urgent medical need for shorter, simpler, safer and more effective HCV treatment regimens that reduced or eliminated the need for peginterferon (PegIFN). Actually, new treatment options were particularly important for patients who had failed prior HCV therapy, who had cirrhosis, or who were either intolerant to or had contraindications to interferon (IFN). (15)

SOF became the first all-oral treatment for HCV genotypes 2 and 3 and it is the first and only direct-acting antiviral agent (DAA) to be approved as part of an IFN-free regimen for HCV treatment in pre-transplant patients with HCC within Milan criteria. HCV/HIV-1 co-infected patients have also been shown to benefit from this revolutionary treatment. (13)

Mechanism of action

The understanding of the HCV genome and life cycle is crucial to the development of new DAAs.

HCV genome encodes for a long polyprotein of 3011 amino acids which is cleaved by cellular and viral proteases to yield three structural proteins (core, E1, and E2) and seven non-structural proteins (NS1/p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). (20–22) What makes NS5B polymerase such an attractive target is its importance for viral RNA replication, and the fact that its catalytic site is highly conserved across the different HCV genotypes. (23) These characteristics targeted by SOF account for its pan-genotypic activity and high barrier to resistance.

After oral administration, this competitive nucleotide inhibitor of HCV NS5B polymerase remains largely intact in transit through the gastrointestinal system and it is efficiently taken

up by hepatocytes where it becomes phosphorylated to a pharmacologically active uridine triphosphate form (GS-461203). (14) Then, it is incorporated as a substrate by NS5B polymerase and causes premature HCV RNA strand termination, (13,24) blocking the virus multiplication.

This mechanism of action allows treatment in patients across all HCV genotypes, with minimal risk for the emergence of viral resistance (and its potential clinical consequences). (15) Furthermore, since there are no human enzymes that exhibit structural similarities to NS5B protein, this prodrug is highly specific for HCV treatment and has fewer side effects. (25)

Potential for cure

Since the HCV genome is not integrated into the host genome, and infected hepatocytes are cleared within several days or weeks, (26) if viral replication is suppressed, it is possible to eradicate liver HCV infection. (27) The intention is to limit the progression of liver disease, in order to prevent complications such as cirrhosis and cancer.

Historically, SVR was defined as HCV RNA levels below a designated threshold of quantification 24 weeks after completion of treatment (SVR24). (28) However, more recent data shows that viral clearance 12 weeks post-treatment correlates closely to SVR24. (29) Therefore, an undetectable HCV RNA at 12 weeks after treatment (SVR12) is considered an appropriate primary efficacy endpoint (30) and translates into "cure" for nearly all patients. (8)

Clinical efficacy and safety

The approval of SOF was based on data obtained in five Phase 3 studies (NEUTRINO, FISSION, POSITRON, FUSION and VALENCE) in a total of 1568 treated subjects. (Table 1) Prominent features and strong points of these studies were: the enrollment of individuals intolerant, unwilling, or ineligible to IFN who are usually not selected by conventional trials on PegIFN plus ribavirin (RBV) and the substantial percentage of patients with liver cirrhosis. (14) There were also clinical studies in special populations: HCV/HIV co-infected patients, patients awaiting liver transplant and liver transplant recipients. (Table 2)

The primary endpoint to determine the HCV cure rate for all studies was SVR12, defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the end of

treatment. Note that Plasma HCV RNA values were measured during the clinical studies using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, and that the assay had a LLOQ of 25 IU/mL. (13)

Table1. Summary of sofosbuvir clinical studies.

Clinical study (Reference)	Design	HCV genotype (%)	Number of patients (% cirrhosis)	Treatment history	Regimen[a]	Overall SVR12
NEUTRINO (31)	Open-label, single-arm study	1 (89%) 4 (9%) 5 (0,2%) 6 (1,8%)	327 (17%)	Treatment-naïve	SOF+ PegIFN+ RBV 12 weeks	91%
FISSION (31)	Randomised, open-label, active-controlled study	2 (28%) 3 (72%)	499 (20%)	Treatment-naïve	SOF+RBV 12 weeks	67%
					PegIFN+ RBV 24 weeks	67%
POSITRON (32)	Randomised, double-blinded, placebo-controlled study	2 (51%) 3 (49%)	278 (16%)	Interferon intolerant with prior treatment (9%), ineligible (44%) or unwilling (47%)	SOF+RBV 12 weeks	78%
					Placebo 12 weeks	0%
FUSION (32)	Randomised, controlled, double-blinded study	2 (37%) 3 (63%)	201 (34%)	Treatment-experienced (75% relapsers and 25% non-responders)	SOF+RBV 12 weeks	50%
					SOF+RBV 16 weeks	71%
VALENCE (33)	Randomised, unblinded study	2 (22%) 3 (78%)	419 (21%)	Treatment-naïve or treatment-experienced (65% prior relapsers)	SOF+RBV 12 weeks (G2)	27%
					SOF+RBV 12 weeks (G3)	93 %
					SOF+RBV 24 weeks (G3)	84 %

a. All clinical studies used a fixed 400 mg daily dosage of SOF given with weight-based RBV (1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg). The NEUTRINO study also used 180 µg of PegIFN once weekly.

Abbreviations: HCV: hepatitis C virus; SVR: sustained virologic response; SOF: sofosbuvir; PegIFN: peginterferon; RBV: ribavirin; G2: genotype 2; G3: genotype 3.

Table 2. Summary of sofosbuvir clinical studies in special populations.

Clinical study (Reference)	Design	HCV genotype (%)	Number of patients (% cirrhosis)	Treatment history	Regimen	Overall SVR-12
PHOTON-1 (34)	Open-label, non-randomised, uncontrolled clinical study	1 (51%) 2 (22%) 3 (27%)	223 (< 20%)	HCV/HIV co-infected patients, treatment-naïve or treatment-experienced	SOF+RBV 12 weeks (G2/3, naïve)	75%
					SOF+RBV 24 weeks (G2/3, experienced)	93%
					SOF+RBV 24 weeks (G1, naïve)	76%
PHOTON-2 (35)	Open-label, non-randomised, uncontrolled clinical study	1 (41%) 2 (9%) 3 (39%) 4 (11%)	274 (20%)	HCV/HIV co-infected patients, treatment-naïve (G1-G4) or treatment-experienced (G2/3)	SOF+RBV 24 weeks (G1, naïve)	85%
					SOF+RBV 12 weeks (G2, naïve)	89%
					SOF+RBV 24 weeks (G3, naïve)	91%
					SOF+RBV 24 weeks (G4, naïve)	84%
					SOF+RBV 24 weeks (G2, experienced)	83%
					SOF+RBV 24 weeks (G3, experienced)	86%
Patients awaiting liver transplant (36)	Open-label, pilot clinical study	1 (74%) 2 (13%) 3 (11%) 4 (2%)	61	Treatment-naïve or treatment-experienced	SOF+RBV 48 weeks or until liver transplant (whichever occurred first)	49%
Liver transplant recipients (37)	Open-label, prospective, single-arm clinical study	1 (83%) 3 (15%) 4 (2%)	40 (40%)	Treatment-naïve or treatment-experienced	SOF+RBV 24 weeks	70%

Abbreviations: HCV: hepatitis C virus; SVR: sustained virologic response; SOF: sofosbuvir; RBV: ribavirin; G1: genotype 1; G2: genotype 2; G3: genotype 3; G4: genotype 4.

Clinical studies in subjects with genotype 1, 4, 5 and 6 chronic hepatitis C

Treatment-naïve subjects – NEUTRINO

The NEUTRINO study was designed to assess the treatment with SOF in combination with PegIFN and RBV in treatment-naïve subjects with genotype 1, 4, 5 or 6 chronic hepatitis C. (31)

Table 3. Response rates in NEUTRINO study. (13)

Response rates in NEUTRINO study	
	SOF+PegIFN+RBV 12 weeks (n = 327)
Overall SVR12	91% (296/327)
On-treatment virologic failure	0/327
Relapse[a]	9% (28/326)
Other[b]	1% (3/327)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g. lost to follow-up).

Abbreviations: SOF: sofosbuvir; PegIFN: peginterferon; RBV: ribavirin; SVR: sustained virologic response.

Table 4. Response rates for selected subgroups. (13)

Response rates (SVR12) for selected subgroups in NEUTRINO	
	SOF+PegIFN+RBV 12 weeks (n = 327)
Genotype	
Genotype 1	90% (262/292)
Genotype 4, 5 or 6	97% (34/35)
Cirrhosis	
Absence	93% (253/273)
Presence	80% (43/54)
Race[a]	
Black	87% (47/54)
Non-Black	91% (249/273)

a. 79% of patients were white; 17% were black and 14% were hispanic or latino.

Abbreviations: SOF: sofosbuvir; PegIFN: peginterferon; RBV: ribavirin; SVR: sustained virologic response.

This study highlighted the efficacy of SOF plus PegIFN plus RBV for genotype 1 patients, including cirrhotic patients, who historically have had poor response rates to previous standard-of-care therapy. (4) Additionally, in this study, 27 out of 28 patients with HCV

genotype 4, the single subject with genotype 5 and all six subjects with genotype 6 HCV infection achieved SVR12. (Table 4)

After the beginning of treatment, all patients had rapid and substantial decreases in serum HCV RNA levels, with no significant differences in the rate or degree of decrease by HCV genotype, race, IL28B genotype, and presence or absence of cirrhosis.

Although, after the end of treatment, 9% had virus relapse, deep-sequencing analysis of samples collected at post-treatment visits showed no viral resistance to SOF. (Table 3)

The regimen was generally well tolerated and thus, treatment discontinuation due to adverse events was uncommon (only 2%). In fact, fatigue (59%), insomnia (41%) and headache (36%) were the most common side effects. (31)

Clinical studies in subjects with genotype 2 and 3 chronic hepatitis C

Treatment-naïve adults – FISSION

The FISSION study was designed to compare 12 weeks of treatment with SOF and RBV to 24 weeks of treatment with PegIFN and RBV in treatment-naïve subjects with genotype 2 or 3 chronic hepatitis C. (31)

Table 5. Response rates in FISSION study. (13)

Response rates in FISSION study		
	SOF+RBV 12 weeks (n = 256)[a]	**PegIFN+RBV 24 weeks (n = 243)**
Overall SVR12	67% (171/256)	67% (162/243)
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
On-treatment virologic failure	< 1% (1/256)	7% (18/243)
Relapse[b]	30% (76/252)	21% (46/217)
Other[c]	3% (8/256)	7% (17/243)

a. The efficacy analysis includes three subjects with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g. lost to follow-up).
Abbreviations: SOF: sofosbuvir; PegIFN: peginterferon; RBV: ribavirin; SVR: sustained virologic response.

Table 6. Response rates for subjects with cirrhosis at baseline by HCV genotype. (13)

SVR12 rates by cirrhosis and genotype in study FISSION				
	Genotype 2		Genotype 3	
	SOF+RBV 12 weeks (n = 73)[a]	PegIFN +RBV 24 weeks (n = 67)	SOF+RBV 12 weeks (n = 183)	PegIFN+RBV 24 weeks (n = 176)
Cirrhosis				
Absence	97% (59/61)	81% (44/54)	61% (89/145)	71% (99/139)
Presence	83% (10/12)	62% (8/13)	34% (13/38)	30% (11/37)

a. The efficacy analysis includes three subjects with recombinant genotype 2/1 HCV infection.

Abbreviations: SOF: sofosbuvir; PegIFN: peginterferon; RBV: ribavirin; SVR: sustained virologic response.

Notably, this study met the predefined non-inferiority criterion and showed that overall, a 12-week regimen of SOF plus weight-based RBV was as effective as the standard of care (24 weeks of PegIFN plus fixed-dose RBV). (Table 5)

Additionally, the incidence of adverse events was lower among patients receiving SOF and RBV than among those receiving PegIFN and RBV. Moreover, among patients receiving 12 weeks of SOF and RBV, 1% discontinued the study due to adverse events, compared with 11% among patients receiving 24 weeks of PegIFN and RBV. (31)

Although these results proved the efficacy of an IFN-free regimen for HCV genotype 2 infection, lower SVR rates were seen in HCV genotype 3 cirrhotics. In fact, in patients treated with SOF and RBV, the SVR12 rates were notably higher in patients with HCV genotype 2 versus those with HCV genotype 3. (Table 6) Thus, this study clearly established that 12 weeks of therapy with SOF plus RBV for HCV genotype 3 infection may not be appropriated.

Interferon intolerant, ineligible or unwilling adults – POSITRON

The POSITRON study was designed to evaluate 12 weeks of treatment with SOF plus RBV (n = 207) compared to placebo (n = 71) in patients with genotype 2 and 3 chronic hepatitis C in whom IFN was not an option. In other words, this clinical trial studied the use of SOF and RBV in patients with HCV genotype 2 or 3 who were ineligible for IFN-based therapy, had prior intolerance to IFN or who preferred not to be treated with IFN-based regimens. (32)

Table 7. Response rates in POSITRON study. (13)

Response rates in POSITRON study		
	SOF+RBV 12 weeks (n = 207)	**Placebo 12 weeks (n = 71)**
Overall SVR12	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
On-treatment virologic failure	0/207	97% (69/71)
Relapse[a]	20% (42/205)	0/0
Other[b]	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g. lost to follow-up).

Abbreviations: SOF: sofosbuvir; RBV: ribavirin; SVR: sustained virologic response.

Table 8. Response rates by genotype for cirrhosis and interferon category. (13)

SVR12 rates for selected subgroups by genotype in POSITRON		
	SOF+RBV 12 weeks	
	Genotype 2 (n = 109)	**Genotype 3 (n = 98)**
Cirrhosis		
Absence	92% (85/92)	68% (57/84)
Presence	94% (16/17)	21% (3/14)
Interferon category		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Abbreviations: SOF: sofosbuvir; RBV: ribavirin; SVR: sustained virologic response.

SOF and RBV treatment produced a rapid decline in circulating HCV RNA levels and its efficacy was higher among patients with HCV genotype 2 infection and those without cirrhosis. (Table 8)

No patient receiving SOF and RBV had virologic breakthrough during treatment. Among the 42 patients who relapsed after the end of treatment, deep sequencing analysis of samples collected at time of relapse showed no resistance-associated variants. (Table 7)

Treatment discontinuation due to adverse events was rare, with 2% of patients who received SOF and RBV discontinuing treatment, compared with 4% who received placebo. (32) Thus, POSITRON results showed SOF's optimal tolerability and low side effects.

Previously treated adults – FUSION

The FUSION study was designed to evaluate 12 or 16 weeks of treatment with SOF and RBV in subjects who did not achieve SVR with prior IFN-based treatment (relapsers and non-responders). (32)

Table 9. Response rates in FUSION study. (13)

Response rates in FUSION study		
	SOF+RBV 12 weeks (n = 103)[a]	**SOF+RBV 16 weeks (n = 98)**[a]
Overall SVR12	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
On-treatment virologic failure	0/103	0/98
Relapse[b]	48% (49/103)	29% (28/98)
Other[c]	3% (3/103)	0/98

a. The efficacy analysis includes six subjects with recombinant genotype 2/1 HCV infection.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g. lost to follow-up).
Abbreviations: SOF: sofosbuvir; RBV: ribavirin; SVR: sustained virologic response.

Table 10. Response rates by genotype for cirrhosis and response to prior HCV treatment. (13)

SVR12 rates for selected subgroups by genotype in study FUSION				
	Genotype 2		**Genotype 3**	
	SOF+RBV 12 weeks (n = 39)	**SOF+RBV 16 weeks (n = 35)**	**SOF+RBV 12 weeks (n = 64)**	**SOF+RBV 16 weeks (n = 63)**
Cirrhosis				
Absence	90% (26/29)	92% (24/26)	37% (14/38)	63% (25/40)
Presence	60% (6/10)	78% (7/9)	19% (5/26)	61% (14/23)
Response to prior HCV treatment				
Relapser	86% (25/29)	89% (24/27)	31% (15/49)	65% (30/46)
Non-responder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

Abbreviations: SVR: sustained virologic response; SOF: sofosbuvir; RBV: ribavirin; HCV: hepatitis C virus.

This study demonstrated that patients with HCV genotype 2 infection can be treated effectively with 12 weeks of treatment with SOF and RBV; while patients with genotype 3 infection, particularly those who have cirrhosis and who have not had a response to prior treatment, appear to benefit from a longer duration of therapy. (Table 10)

No patient receiving SOF and RBV experienced on-treatment viral breakthrough or non-response. Among the 77 patients who relapsed after the end of treatment, deep sequencing analysis of samples collected at time of relapse revealed no resistance-associated variants. (Table 9)

The overall safety profile was identical between patients receiving 16 weeks of therapy and those receiving 12 weeks of therapy. Fatigue, headache, nausea, and insomnia were the most commonly reported adverse events in both study arms. A patient in the 12-week arm discontinued treatment due to an adverse event; on the contrary, no patients discontinued treatment owing to an adverse event in the 16-week group. (32)

Treatment-naïve and previously treated adults – VALENCE

The VALENCE study was designed to evaluate SOF in combination with weight-based RBV for the treatment of HCV genotype 2 or 3 infection in treatment-naïve subjects or subjects who did not achieve SVR with prior IFN-based treatment, including subjects with compensated cirrhosis. The study was designed as a direct comparison of SOF and RBV versus placebo for 12 weeks. However, when results from the FUSION study suggested that extended treatment could benefit HCV genotype 3 patients, the VALENCE protocol was redefined as a descriptive study to characterize SVR rates in patients with HCV genotype 2 infection who were treated for 12 weeks (*n* = 73) and HCV genotype 3 in patients with treated for 24 weeks (*n* = 250), with no hypothesis testing. Note that, at the time of the amendment, 11 HCV genotype 3 infected individuals had already completed treatment with SOF and RBV for 12 weeks. (33) (Table 11)

Table 11. Response rates in VALENCE study. (13)

Response rates in VALENCE study			
	Genotype 2 SOF+RBV 12 weeks (n = 73)	**Genotype 3 SOF+RBV 12 weeks (n = 11)**	**Genotype 3 SOF+RBV 24 weeks (n = 250)**
Overall SVR12	93% (68/73)	27% (3/11)	84% (210/250)
On-treatment virologic failure	0% (0/73)	0% (0/11)	0.4% (1/250)
Relapse[a]	7% (5/73)	55% (6/11)	14% (34/249)
Other[b]	0% (0/73)	18% (2/11)	2% (5/250)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g. lost to follow-up).

Abbreviations: SVR: sustained virologic response; SOF: sofosbuvir; RBV: ribavirin.

Table 12. Response rates by genotype for cirrhosis and exposure to prior HCV treatment. (13)

SVR12 rates for selected subgroups by genotype in study VALENCE		
	Genotype 2 SOF+RBV 12 weeks (n = 73)	**Genotype 3 SOF+RBV 24 weeks (n = 250)**
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
Treatment-experienced	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)

Abbreviations: SVR: sustained virologic response; SOF: sofosbuvir; RBV: ribavirin.

Previous trials left on the table the low SVR12 rate in patients infected with HCV genotype 3 treated with SOF and RBV for 12 - 16 weeks. This important issue was addressed in the VALENCE trial, which showed that, in HCV genotype 3 patients, the prolongation of therapy with SOF plus RBV up to 24 weeks increases the SVR12 rates to 93% and 77% in treatment-naive and treatment experienced individuals, respectively. (Table 12)

In fact, treatment with SOF and RBV resulted in a rapid decrease in HCV RNA levels. By week 4, 99% of patients receiving SOF and RBV had an HCV RNA level <LLOQ. No patients receiving placebo achieved an HCV RNA level <LLOQ at any time point in the study (and so, placebo recipients are not included in the tables).

In HCV genotype 3 infected patients who experienced virologic failure, the SOF treatment–emergent variants V321A and L159F were detected in two and six patients, respectively. Still, during *in vitro* testing, neither mutation was found to confer phenotypic resistance to SOF.

Premature discontinuation of treatment owing to adverse events was uncommon across all study groups. However, diarrhea and irritability were seen more frequently in patients in the 24-week treatment group than in the 12-week treatment group. (33)

Clinical efficacy and safety in special populations

HCV/HIV co-infected patients – PHOTON-1

Patients with HCV/HIV co-infection are at risk for accelerated liver disease progression, and thus, it is imperative to treat the HCV infection. Since successful HCV eradication in this subgroup is associated with lower mortality, (38) this study was designed to examine the efficacy, safety and tolerability of 12 or 24 weeks of treatment with SOF and RBV in subjects with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1.

Genotype 2 and 3 subjects were either treatment-naïve or experienced, whereas genotype 1 subjects were naïve to prior treatment. A 24-week treatment course was given to all patients with HCV genotype 1 and to treatment-experienced patients with HCV genotype 2 or 3; while treatment-naive patients with HCV genotype 2 or 3 received a 12-week treatment course. Patients in the trial were required to be either on stable antiretroviral therapy with an undetectable HIV RNA level and $CD4^+$ cell count greater than 200 cells/mm^3, or if not on antiretroviral therapy, they must have $CD4^+$ cell count greater than 500 cells/mm^3. (34)

Table 13. Response rates by genotype and exposure to prior HCV treatment. (13)

Response rates in study PHOTON-1			
	Genotype 2/3 treatment-naïve SOF+RBV 12 weeks (n = 68)	**Genotype 2/3 treatment-experienced SOF+RBV 24 weeks (n = 28)**	**Genotype 1 treatment-naïve SOF+RBV 24 weeks (n = 114)**
Overall SVR12	75% (51/68)	93% (26/28)	76% (87/114)
On-treatment virologic failure	1% (1/68)	0/28	1% (1/114)
Relapse[a]	18% (12/67)	7% (2/28)	22% (25/113)
Other[b]	6% (4/68)	0/28	1% (1/114)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Abbreviations: SVR: sustained virologic response; SOF: sofosbuvir; RBV: ribavirin.

Table 14. Response rates by genotype for cirrhosis. (13)

SVR12 rates for selected subgroups by genotype in study PHOTON-1				
	HCV genotype 2		HCV genotype 3	
	SOF+RBV 12 weeks Treatment-naïve (n = 26)	SOF+RBV 24 weeks Treatment-experienced (n = 15)	SOF+RBV 12 weeks Treatment-naïve (n = 42)	SOF+RBV 24 weeks Treatment-experienced (n = 13)
Overall SVR12	88% (23/26)	93% (14/15)	67% (28/42)	92% (12/13)
No cirrhosis	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Cirrhosis	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

Abbreviations: SVR: sustained virologic response; HCV: hepatitis C virus; SOF: sofosbuvir; RBV: ribavirin.

This study demonstrated the first evidence that HIV coinfection may not produce an unfavorable treatment effect with the use of IFN-free treatment. (Table 13) The fact that SOF metabolism is independent of cytochrome P450 explains why it has less drug-drug interaction with the contemporary Highly Active Anti-Retroviral Therapy (HAART) regimens. It is important to note that 95% of patients in the PHOTON-1 trial were on antiretroviral regimens during the trial, and HIV treatment was not adversely affected by treatment with SOF and RBV. (29) Current guidelines recommend the use of SOF-containing regimens in this patient population. (13)

In addition, no significant changes in HIV RNA levels were observed in patients not receiving HIV therapy at baseline. Two of the patients, taking Anti-Retroviral Therapy (ART) with suppressed HIV viremia at study entry, experienced HIV viral breakthrough. One of the patients had an increase in HIV RNA level due to documented non-adherence to ART; the other patient showed resuppressed HIV RNA level without altering the ART regimen. A decrease in absolute lymphocyte and $CD4^+$ T cell numbers was observed in patients during the study; however, the $CD4^+$ T cell percentage did not change throughout study treatment, and absolute $CD4^+$ T cell counts returned to baseline by post-treatment week 12. (34)

Thus, this study showed that patients coinfected with HIV can achieve high SVR rates with the all-oral regimen of SOF and RBV. It also demonstrated the clear benefit of extending treatment with SOF plus RBV from 12 to 24 weeks in patients with genotype 3 HCV infection. (Table 14)

HCV/HIV co-infected patients – PHOTON-2

Although IFN-based regimens are still an option for HIV-infected patients coinfected with HCV, their significant toxic effects and drug interactions with antiretroviral therapy limit

their use. (39) Therefore, the PHOTON-2 study was designed to assess the efficacy and safety of an IFN-free, all-oral regimen of SOF plus RBV in this patient population.

Patients in this trial were either not on antirretroviral therapy with a $CD4^+$ cell count greater than 500 cells/mm^3 or were on stable antiretroviral therapy with an undetectable HIV RNA level and $CD4^+$ cell count greater than 200 cells/mm^3. Among those enrolled, 81% of the patients were HCV treatment naïve, the mean $CD4^+$ cell count was 588 cells/mm^3 and 97% were on antiretroviral therapy (tenofovir-emtricitabine plus one of the following: efavirenz, atazanavir plus ritonavir, darunavir plus ritonavir, rilpivirine, or raltegravir). Note that a 24-week treatment course was given to all patients, except treatment-naïve patients with HCV genotype 2, who received a 12-week regimen. (35)

Table 15. Response rates in PHOTON-2 study.

Response rates in PHOTON-2 study						
	Treatment-naïve				**Treatment-experienced**	
	HCV genotype 1-4				**HCV genotype 2/3**	
	Genotype 1 SOF+RBV 24 weeks (n = 112)	Genotype 2 SOF+RBV 12 weeks (n = 19)	Genotype 3 SOF+RBV 24 weeks (n = 57)	Genotype 4 SOF+RBV 24 weeks (n = 31)	Genotype 2 SOF+RBV 24 weeks (n = 6)	Genotype 3 SOF+RBV 24 weeks (n = 49)
Overall SVR12	85% (95/112)	89% (17/19)	91% (52/57)	84% (26/31)	83% (5/6)	86% (42/49)

Abbreviations: SVR: sustained virologic response; HCV: hepatitis C virus; SOF: sofosbuvir; RBV: ribavirin.

This study demonstrated that patients, treatment-naïve or treatment-experienced, coinfected with HIV can achieve high SVR rates with the all-oral regimen of SOF and RBV. Even subjects with genotype 3 chronic hepatitis C co-infected with HIV can benefit from this treatment option. (Table 15)

Note that only six (2%) patients discontinued treatment because of adverse events and although four (1%) patients, receiving antiretroviral treatment had a transient HIV viral breakthrough, none required changes in antiretroviral regimen. (35)

Patients awaiting liver transplant

Recurrence of HCV following liver transplantation is the most common cause of graft loss and patient mortality in HCV-infected liver transplant recipients. (40) Antiviral treatment before transplantation can prevent HCV recurrence afterward, but IFN-based regimens are

poorly tolerated and frequently associated with life-threatening infections and decompensation. (41) So, this study was designed to evaluate the safety and efficacy of SOF and RBV administered pre-transplant to prevent post-transplant HCV recurrence. The primary endpoint of the study was post-transplant virologic response, defined as non-quantifiable HCV RNA 12 weeks post-transplant (pTVR). Eligibility was restricted to patients with HCV RNA $\geq 10^4$ IU/mL, Child-Pugh-Turcotte (CPT) score ≤ 7 and Model for End-Stage Liver Disease (MELD) score ≤ 17. Patients were excluded if they had decompensated liver disease.

HCV infected subjects, regardless of genotype, with HCC meeting the MILAN criteria received 400 mg of SOF and 1000-1200 mg of RBV daily for a maximum of 24 weeks, subsequently amended to 48 weeks, or until the time of liver transplantation (whichever occurred first).

Of the 92 patients screened, 63 were enrolled in the study; but only 61 received at least one dose of SOF and RBV. Of these 61 patients, 46 underwent a transplantation and 15 discontinued the study before transplantation (due to viral relapse, progressive disease, non-response, viral-breakthrough, death or removal from the transplant list). Of the 46 patients who underwent transplantation, 43 had HCV-RNA level less than the LLOQ at the time of transplantation. Of these 43 patients, 30 (70%) achieved pTVR, meaning HCV-RNA level was undetectable at post-transplant week 12. Of the 13 patients, who did not achieve pTVR, 10 had confirmed HCV recurrence and three died immediately after transplant. The rate of discontinuation due to adverse events was low, and most observed events were those frequently associated with RBV therapy - fatigue, anemia, headache, and nausea. (36)

Taking into account that this antiviral therapy before liver transplantation prevented the HCV recurrence afterward in 70% of patients, this study demonstrated that SOF and RBV administered pre-transplant can reduce the rate of post-transplant HCV recurrence.

Liver transplant recipients

An ideal therapy for post-transplantation HCV infection would have high efficacy, good tolerability, lack of interaction with commonly administered immunosuppressive agents, and absence of potentiating allograft rejection. (42) This study was designed to evaluate the safety and efficacy of 24 weeks of treatment with SOF and RBV in liver transplant recipients with chronic hepatitis C. The primary efficacy endpoint was SVR12, defined as HCV RNA below the LLOQ (25 IU/mL) 12 weeks after stopping treatment.

Eligible patients had HCV RNA ≥10^4 IU/mL at screening and documented evidence of chronic HCV infection pre-transplantation (any genotype included). Note that liver transplantation was required to have taken place from 6 to 150 months before screening and elegibility was also restricted to patients with CPT score ≤ 7 and MELD score ≤ 17. Patients were excluded if they had decompensated liver disease.

The starting dose of RBV was 400 mg given in a divided daily dose. If subjects maintained haemoglobin levels ≥12 g/dL, RBV dose was increased at weeks 2, 4, and up to every 4 weeks until the appropriate weight-based dose was reached (1000 mg daily in subjects <75 kg; 1200 mg daily in subjects ≥75 kg). The median RBV dose was 600 mg - 800 mg daily at weeks 4-24.

In this study, 40 patients were enrolled, 35 of whom had previously failed IFN-based treatment. Of the 40 subjects, 28 (70%) achieved SVR12: 22/33 (73%) with HCV genotype 1 infection, 6/6 (100%) with HCV genotype 3 infection, and 0/1 (0%) with HCV genotype 4 infection. Furthermore, all subjects who achieved SVR12 achieved SVR24 and SVR48. (37)

Additionally, there were no graft losses, organ rejection or deaths. No drug–drug interactions were noted between SOF and the immunosuppressants. Headache, fatigue, arthralgias and diarrhea were the most common side effects seen in more than 20% of subjects. (29)

Thus, this study encouraged the use of SOF plus RBV in the post-liver transplantation setting.

Posology and method of administration

This prescription medicine should be initiated and monitored by a physician experienced in the management of patients with chronic hepatitis C.

The recommended dose is one 400 mg tablet, taken orally, once daily. Monotherapy is not recommended and so, SOF should be taken as part of a combination therapy. (Table 16)

Table 16. Recommended current indications of SOF in clinical practice. (13)

Patient population[a]	Treatment	Duration
Patients with genotype 1, 4, 5 or 6 chronic hepatitis C	SOF + RBV + PegIFN	12 weeks[b,c]
	SOF + RBV Only for patients ineligible or intolerant to PegIFN	24 weeks
Patients with genotype 2 chronic hepatitis C	SOF + RBV	12 weeks[c]
Patients with genotype 3 chronic hepatitis C	SOF + RBV + PegIFN	12 weeks[c]
	SOF + RBV	24 weeks
Patients with chronic hepatitis C awaiting liver transplantation	SOF + RBV	Until liver transplantation

a. Includes patients co-infected with HIV.

b. For previously treated patients with HCV genotype 1 infection, there is no data regarding the combination of SOF, RBV and PegIFN.

c. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to PegIFN and RBV therapy).

Abbreviations: SOF: sofosbuvir; RBV: ribavirin; PegIFN: peginterferon.

Adverse events

Treatment discontinuations owing to adverse events have been uncommon in the SOF-based IFN-free treatment regimens. (43)

The fact that SOF does not interact with liver cell enzymes including polymerases accounts for its negligible spectrum of systemic effects, a fact that supports its safety profile. (44) Actually, patients exposed to SOF-based regimens reported only unspecific side effects, which generally reflected untoward reactions of the concomitant use of PegIFN and RBV. The most common adverse drug reactions occurring in subjects receiving SOF and RBV are fatigue and headache. When this new DAA is used in combination with RBV and PegIFN, the most common adverse events further include nausea and insomnia. (8)

Note that the safety profile of SOF and RBV in HCV/HIV co-infected subjects, in HCV infected subjects prior to liver transplantation and in liver transplant recipients with chronic hepatitis C was similar to that observed in subjects treated with SOF and RBV in Phase 3 clinical studies. (13)

Drug-to-drug interactions

SOF is not metabolized by cytochrome P450 enzymes and thus, the major concern with drug-to-drug interactions exists with medications that affect P-glycoprotein and breast cancer resistance protein. (13) Consequently, the use of SOF with potent inducers of P-glycoprotein such as rifampicin or St John's Wort would likely decrease plasma levels of the parent drug and thus, its use is not recommended. (24) Furthermore, coadministration of SOF with anticonvulsants such as phenytoin, carbamazepine, phenobarbital, and oxcarbazepine; antimycobacterials such as rifabutin and rifapentine; and antiretrovirals such as tipranavir/ritonavir are also not recommended for similar reasons. (10)

The portuguese example

This year, the National Competent Authority INFARMED assured that all portuguese patients who needed the treatment would receive the drug. Remarkably, Portugal became one of the first countries to sign an agreement with the laboratory and SOF is now 100% state subsidized. Although there is some controversy due to its high costs, SOF's clinical impact has been immediate. Since it was made available, it has already cured 3005 chronic HCV infected-patients in Portugal, according to the National Competent Authority INFARMED on the 1st of July, 2016. So far, 7840 patients are currently undergoing treatment and only 122 patients who reached the end of the treatment were not cured. (45) Thus, we can say that, irrespective the price, SOF is an unbelievable accomplishment in the HCV treatment that has brought hope to many patients in need. In Portugal, its high cures rates (exceeding 96%) represent an impressive advance in the care of HCV-infected patients, acting as a wake-up call for all health stakeholders.

Discussion

Although the post-marketing phase always requires a careful evaluation of data from the "everyday" clinical practice experience, clinical trials have showed that SOF has several advantages over existing treatments for chronic HCV. In the first place, it can be taken with or without food, with most other medications, and requires no dose adjustments in most circumstances commonly encountered in clinical practice. (15) Furthermore, an overview of outcomes by therapeutic regimen and treatment duration demonstrates the high SVR12 rates (exceeding 90%) for patients infected with HCV genotypes 1, 4, 5, and 6 patients treated with SOF plus PegIFN and RBV as well as a favourable efficacy and safety profile for

HCV genotype 2 population. (46) SOF is also the first oral IFN-free regimen for patients coinfected with HCV and HIV, as well as the backbone of the first regimen available for patients awaiting liver transplantation. Certain patients with chronic hepatitis C, who have liver cancer and are awaiting a liver transplant, can take SOF plus RBV (for up to 48 weeks or until the time of liver transplantation) to prevent reinfection with hepatitis C after transplant. (36)

The length of treatment depends on the genotype of HCV causing the infection. For most patients, treatment will last for 12 weeks. For those with genotype 3, treatment will last for 24 weeks. Note that this HCV genotype has become the most difficult to treat, with higher associated risks of hepatic steatosis and HCC. (47)

Treatment decision should always be based on an assessment of the potential benefits and risks for the individual patient. Still, it was the benefit-risk balance of SOF-based regimens that lead to its rapid approval and incorporation in the recommendations of the international societies on treatment of HCV infection. (44,48)

Future directions

Given its superior efficacy, safety and tolerability across multiple patient cohorts, and minimal drug-to-drug interaction profile, SOF-based regimens signal a new era in the HCV treatment. Actually, the concept of a single daily dosage, associated with pan-genotypic activity and effectiveness across stages of liver disease, represents a tremendous advance in these patients' health-related quality of life.

However, clinicians need more detailed, accurate and timely information in order to choose the right regimen for individual patients. In addition, future studies will be needed to help them understand how to best treat special populations such as those with cirrhosis (whether compensated, decompensated or post-transplant), renal disease and previous kidney transplant or even those patients who need immunosuppression for other reasons. Also, improved treatment options for HCV genotype 3 are desirable.

Conclusion

Chronic hepatitis C has brought many challenges that were quickly overcome after the availability of SOF. The results of this short-duration therapy have shown that it is possible to minimize the spread of HCV and the morbidity and mortality associated with this infection.

Despite the financial controversy around its high costs, which has served as a major barrier for more widespread use, many stakeholders recognize now its long-term cost-benefits and the advantages of a future free from hepatitis C are manifest.

It is true that patients undergoing treatment need systematic monitoring before, during and after therapy, but this new DAA has offered them hope and re-awakening. It is the beginning of a new life that starts with SOF's ideal properties along with its excellent SVR rates. This new NS5B polymerase inhibitor can even shape the future of the patients with the most unfavourable baseline characteristics and that is why it is certainly the sharp end of the spear against hepatitis C.

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