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Contents

Three issues per month Volume 7 Number 15 July 28, 2015

EDITORIAL

REVIEW

MINIREVIEWS

World Journal of Hepatology
Volume 7 Number 15 July 28, 2015

Contents

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EDITORIAL

3.0 Tesla magnetic resonance imaging: A new standard in liver imaging?

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Abstract

An ever-increasing number of 3.0 Tesla (T) magnets are installed worldwide. Moving from the standard of 1.5 T to higher field strength implies a number of potential advantage and drawbacks, requiring careful optimization of imaging protocols or implementation of novel hardware components. Clinical practice and literature review suggest that state-of-the-art 3.0 T is equivalent to 1.5 T in the assessment of focal liver lesions and diffuse liver disease. Therefore, further technical improvements are needed in order to fully exploit the potential of higher field strength.

Key words: Magnetic resonance imaging; Liver; 1.5 Tesla; 3.0 Tesla; Magnetic field strength

Core tip: The editorial focuses on potential advantages and drawbacks related to the use of 3.0 Tesla (T) magnets in liver imaging. Current clinical applications are discussed, with special emphasis on the comparison with 1.5 T. If careful optimization is performed, state-of-the-art 3.0 T is equivalent to 1.5 T. Further technical improvements are needed in order to fully exploit the potential of higher field strength.

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MOVING TOWARDS 3.0 TESLA?

Because of limited availability and costs, magnetic resonance imaging (MRI) of the liver is usually performed as a problem-solving tool after inconclusive prior ultrasound and/or computed tomography (CT). However, MRI is, *per se*, the imaging modality of choice for the detection and characterization of focal liver lesions[1], owing to superior contrast resolution and the "all-in-one" information provided by hepatospecific contrast agents such as gadobenate dimeglumine (Gd-BOPTA) and gadoxetic acid (Gd-EOB-DTPA). Less defined is the role of MRI in assessing diffuse liver disease, as exemplified

by current, intensive research on different techniques aimed to quantify fibrosis, steatosis or iron overload[2].

1.5 Tesla (T) systems still represent the technical standard for abdominal MRI[3]. Nonetheless, the use of ultra-high field strength is a major focus in liver imaging, given the ever-increasing number of new 3.0 T magnets installed worldwide for research and clinical practice. One might wonder whether 3.0 T might become the new standard, as occurred in the past when moving from lower field strength to 1.5 T. In theory, 3.0 T magnets have the capability to provide better image quality as the base for improved diagnostic performance. This is because doubling the field strength (almost) doubles signal-to-noise ratio[4], that is the quantity of signal made available from the patient in order to build MRI images. Exceeding signal can be converted into better image detail (higher spatial resolution) and/or faster acquisition (higher temporal resolution), as well as more efficient fat suppression and better lesion conspicuity because of improved lesion-to-liver contrast after gadolinium administration[5]. Both conventional imaging and functional techniques such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced MRI and spectroscopy may benefit from the above changes.

CHALLENGES RELATED TO 3.0 T

Despite theoretical promises, the available evidence shows some disappointing results when comparing 3.0 T *vs* 1.5 T, especially for T2-weighted imaging. For example, two studies[6,7] on patients with chronic liver disease showed that radiologists perceive equal or lower image quality at higher field strength. The explanation for such a discrepancy is that the transition from 1.5 T to 3.0 T harbours technical challenges at serious risk of impairing the gain in signal-to-noise ratio. Major concerns in liver imaging are related to three factors[5]. First, changes in tissue relaxation times affect image contrast, at a larger degree on T1-weighted Spoiled Gradient Echo images. This can make the detection of focal lesions, fibrosis or steatosis more challenging at 3.0 T[8]. Second, the radiofrequency (RF) power deposition to the patient significantly increases, especially for Turbo Spin Echo (TSE)-designed T2-weighted sequence using a large number of RF pulses to generate image contrast. RF power deposition represents the energy administered to the patient to obtain signal back, and is measured as specific absorption rate (SAR). Unfortunately, strategies to reduce 3.0 T-related increase in SAR frequently occur at the expense of the gain in signal. Third, image quality can be degraded by the so called standing wave artefact, resulting from inhomogeneous RF deposition due to interactions between RF waves and the patients' body[5]. Standing wave artefact consists of zones of gross signal drop affecting T2-weighted images at a serious extent[9], usually in correspondence of the left liver lobe (Figure 1). Despite there is no definite correlation with body mass index or body fat content, the artefact prevails in larger patients, being characteristically exacerbated by the presence of ascites[5,8,9].

How to overcome technical limitations? In a study by von Falkenhausen *et al*[10], image quality at 3.0 T was found equivalent to 1.5 T using comparable acquisition parameters, emphasizing that the implementation of standard 1.5 T MRI protocols on 3.0 T magnets requires careful optimization and/or new technical solutions to exploit the potential of higher field-strength. While problems in T1 contrast and SAR are faced by implementing proper sequence design[11,12], standing wave artefacts should be more consistently prevented by intervening on the magnet hardware[13], that is by implementing more than one conventional RF source in order to independently correct phase and amplitude of the RF pulses for patient-induced B1-inhomogeneity. Studies using new-generation 3.0 T systems with dual-source parallel RF transmission[9,13,14] showed significant qualitative and quantitative image improvement for TSE-based T2-weighted imaging, which is the real "Achilles heel" of liver MRI at 3.0 T. Results with and without hardware implementation are conflicting in terms of better lesions detectability[9,14]. However, dual-source systems are reasonably the best state-of-the-art solution to minimize standing wave effect in obese individuals and/or patients with ascites, in whom lesions can be missed because of degraded image quality.

ADVANTAGES OF USING 3.0 T

On the bright side, 3.0 T was proven to provide superior post-gadolinium image quality using 1.5 T-equivalent volumetric fat-saturated Gradient-Echo T1-weighted imaging[7,12]. This is in accordance with the experience in many centers using 3.0 T, including our Institution (Figure 2). Lee *et al*[15] suggested that the quality of the dynamic study is further improved when replacing conventional fat suppression technique at 3.0 T (spectrally adiabatic inversion recovery) with the Dixon approach. These results have potential diagnostic impact in terms of better detection and characterization of smaller lesions, especially in late arterial phase or hepatobiliary phase[8].

One might wonder whether superior quality of post-contrast imaging is just a matter of the sequence used or rather the type and dose of contrast medium. Indeed, the T1 relaxation time of the liver *in vivo* increases of about 41% at 3.0 T compared to 1.5 T[5], translating into a theoretical increase in contrast differences using an equivalent dose of gadolinium-based contrast agents[16]. A study by Kim *et al*[17] supports this assumption. Comparing arterial late phases acquired in same individuals with the standard dose of gadoxetic acid (0.025 mmol/kg) and half dose of gadobenate dimeglumine (0.05 mmol/kg), the Authors found higher relative enhancement of the liver at 3.0 T rather than 1.5 T, for both contrast agents (19.4% *vs* 11.4% and 33.4% *vs* 18.9%, respectively). Alternatively, one can achieve adequate image contrast at 3.0 T using less contrast medium, as shown by de Campos *et al*[18] with a quarter dose of gadobenate dimeglumine (0.025 mmol/kg). Potential

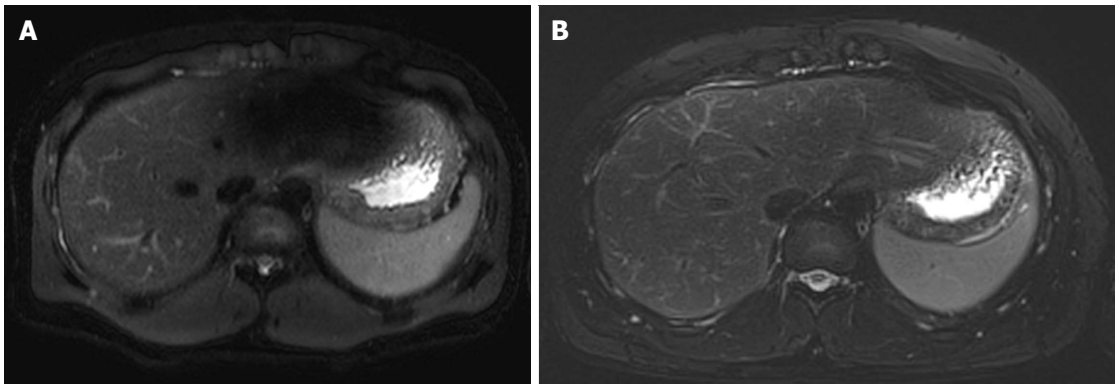

Figure 1 T2-weighted imaging with 3.0 Tesla. In the absence of dedicated technical solutions, T2-weighted images at 3.0 Tesla (T) (A) are at risk of typical artefacts (namely standing-wave artefacts) causing signal drop-out over the field of view, especially left liver lobe. Focal liver lesions might be masked accordingly. The artefact is not present at 1.5 T (B).

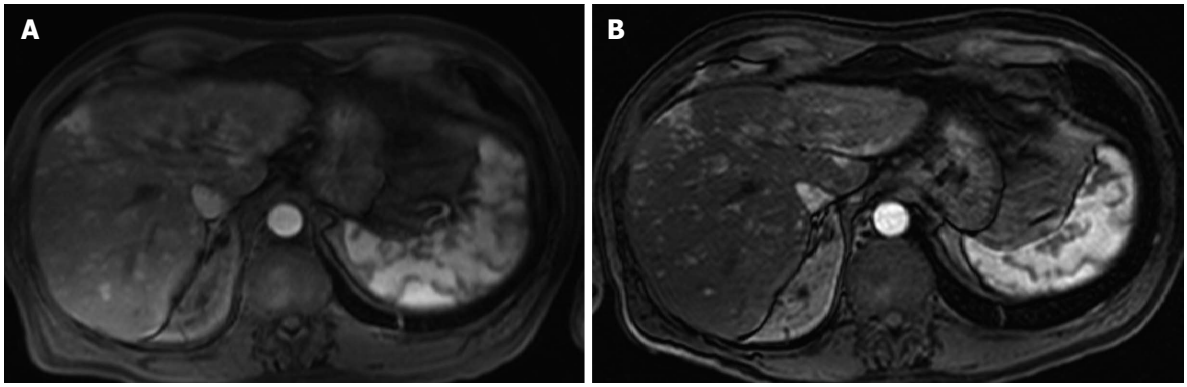

Figure 2 T1-weighted post-contrast imaging at 3.0 Tesla. Compared to 1.5 Tesla (T) (A), post-contrast images acquired on 3.0 T magnets (B) show sharper details, as exemplified in this patient with chronic liver disease showing multiple artero-portal shunts.

clinical consequences are better lesions detectability and reduction of the risk of nephrogenic systemic fibrosis in selected patients. However, image contrast after the administration of gadolinium chelates is a matter of complex interactions. Not surprisingly, studies *in vitro* and *in vivo*[16] are concordant in showing comparable contrast enhancement of the liver between 1.5 T and 3.0 T at equivalent concentrations, regardless of the dose. In summary, it is difficult to quantify the impact of contrast agent properties in determining superior image quality of 3.0 T contrast-enhanced studies.

DIAGNOSTIC PERFORMANCE OF 3.0 T SYSTEMS

The ever-increasing diffusion of magnets for everyday clinical practice, and rise in publications of radiological studies performed with 3.0 T suggest that higher field strength is at least equivalent to 1.5 T in diagnostic terms. Unfortunately, there is paucity of prospective works comparing 1.5 T and 3.0 T on an intraindividual basis. In a study on 35 patients who underwent both 1.5 T and 3.0 T with a superparamagnetic iron oxide contrast agent, Chang *et al*[19] showed equivalent accuracy in assessing malignant focal liver lesions, with lower image quality at higher field strength. Only a few papers focus on hepatocellular carcinoma (HCC) and colorectal cancer metastases. In a 3.0 T standing-alone study by Lee *et al*[15], the Authors found an overall accuracy in the detection of HCC with gadoxetic acid similar to 1.5 T (mean AUC 0.95). Interestingly, two different studies[20,21] compared the detection of HCC between 3.0 T MRI and triple-phase multidetector CT (MDCT), showing equivalent high accuracy, though MRI was able to detect more lesions on a per-patient basis (2.7 *vs* 2.3)[20] and performed better for smaller HCC ($\leqslant$ 1 cm in size)[21]. It is difficult to compare these results with those obtained in other studies with lower field strength, *e.g.*, by Akai *et al*[22], who showed a trend to a better performance of gadoxetic-acid-enhanced 1.5 T MRI *vs* 64-raw MDCT. Based on the experience in my Institution, 3.0 T MRI is at least equivalent to 1.5 T, being helpful in assessing cases in which the number of lesions is crucial to plan the treatment (*e.g.,* liver transplant), as well in the scenarios of lesion characterization and detection of recurrence. Concerning colorectal cancer metastases, 3.0 T showed excellent detection rates combining gadoxetic acid and DWI, with AUCs of 0.915-0.937 at ROC analysis[23]. Compared to MDCT, 3.0 T MRI showed better performance, though without statistical significance[24], especially in the detection of

smaller lesions, having the potential to change initial management plan in about one-third of patients[25]. Due to superior contrast resolution, 3.0 T MRI more clearly outperforms MDCT in the subset of patients with fatty liver infiltration (detection rate of 97% *vs* 72%)[26]. Indeed, fatty infiltration may impair detection of metastases on MDCT by diminishing the contrast between an hypodense lesion and the surrounding liver tissue[27]. Despite theoretical advantages of thinner slice thickness and improved lesion-to-liver contrast in the hepatobiliary phase at 3.0 T, it is still challenging to prove any superiority in detecting metastases compared to 1.5 T.

A few studies deal with the role of 3.0 T in diffuse liver disease. Promising results have been obtained in different scenarios, including the use of DWI in staging liver fibrosis in patients with nonalcoholic fatty liver disease[28], iron quantification[29], or the assessment of liver function with relative-contrast enhancement of liver parenchyma on the hepatobiliary phase after gadoxetic acid administration[30]. Because of the increase of spectral resolution, 3.0 T has the potential to better differentiate between hepatic metabolites, thus providing robust magnetic resonance spectroscopy (MRS) for the assessment of chronic liver disease, *e.g.*, by measuring hepatic fat content[31]. Several pilot studies[31,32] show that liver MRS is feasible. Nonetheless, this technique is still in its infancy and requires further optimization and validation. Research on diffuse liver diseases is particularly intense in the setting of DWI, a popular technique exploiting normal and pathological water Brownian motion within the liver under the form of both signal intensity and apparent diffusion coefficients (ADC)[33]. DWI is expected to benefit from increased signal-to-noise ratio in terms of better image quality and more robust estimation of the ADC. Available results are somewhat disappointing, suggesting that ADC quantification is equivalent compared to 1.5 T, thought at the expense of lower image quality[34]. Thus, optimization of DWI at 3.0 T is still a matter of research[35,36].

CONCLUSION

In conclusion, optimization of 3.0 T liver protocols is still in progress, both in terms of sequence design and hardware upgrade. Using comparable imaging technique, T2-weighted sequnce provide images of worse quality than 1.5 T, unless new magnets with dual-source RF transmission are used. On the bright side, dynamic study after contrast injection is qualitatively and quantitatively better at 3.0 T. Such an equilibrium translates into similar diagnostic accuracy compared to the reference of 1.5 T, as shown by an increasing amount of evidence from literature. Concerning clinical practice, our experience shows that liver imaging is routinely feasible at 3.0 T, unless patients show conditions such as obesity and/or ascites that may significantly degrade T2-weighted imaging. 3.0 T should be avoided in these subjects. In the remaining cases, 3.0 T is a reliable alternative to 1.5 T, especially in those patients in whom improved dynamic study is expected to provide "key" information, such as detection and characterization of hypervascular lesions (*e.g.,* HCC).

In summary, if the new standard in liver imaging should be undoubtedly better than the older one, state-of-the-art 3.0 T is far from representing it. However, ongoing technical improvements are expected to exploit all the potential advantages inherent to higher field strength, suggesting that 3.0 T candidates for the new standard in liver imaging in the next future.

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EDITORIAL

Selection tool alpha-fetoprotein for patients waiting for liver transplantation: How to easily manage a fractal algorithm

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Abstract

Alpha-fetoprotein (AFP) behavior in patients with hepatocellular carcinoma (HCC) waiting for liver transplant (LT) represents a perfect biological example of a fractal model in which its progressive modification and possible future prediction of its values are very hard to capture. As a consequence, AFP represents a useful but poorly manageable tool to increase the ability to better select HCC patients waiting for LT. Trying to find a "fil-rouge" in the recent literature, no definitive answers can be done to several open questions: (1) the best AFP value to adopt; (2) the best cut-off measurement; and (3) the best way to comfortably capture the effective, time-related, fluctuations of this biological marker. More, structured and prospective, studies using serial determination of AFP values within and without the context of locoregional therapies are needed in order to find the "ideal" (static and dynamic) cut-off values allowing to respond to all the still open questions in this field of transplant oncology.

Key words: Alpha-fetoprotein; Hepatocellular cancer; Milan criteria; Recurrence; Drop-out

Core tip: Alpha-fetoprotein (AFP) behavior in patients with hepatocellular carcinoma waiting for liver transplant (LT) represents a perfect example of a fractal model. Consequently, AFP represents a useful but poorly manageable selection tool for patients waiting for LT. Looking at the recent literature, we can assume that: (1) last AFP value seem to be the best values to adopt; (2) different cut-offs may be adopted in the two different scenarios of Milan Criteria (MC) IN and MC OUT status; (3) AFP cut-off of 1000 ng/mL represent

a good compromise for MC-IN patients; and (4) no definitive conclusion has been reached in relation to MC-OUT patients.

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CHAOS THEORY AND BIOLOGICAL SCIENCES

Chaos is the science of surprise, of nonlinearity and of unpredictability, teaching us to expect the unexpected. Sciences are connected with predictable events such as chemical reactions, electricity, gravity, whilst the chaos theory concerns with non-linear processes such as weather, stock market and biological modifications. These last phenomena are typically described by fractal mathematics, a field of study created with the intent to capture the infinite complexity of nature (Figure 1).

The behavior of alpha-fetoprotein (AFP) in patients having hepatocellular carcinoma (HCC) awaiting for liver transplant (LT) represents a perfect biological example of a fractal model in which its progressive modification and possible future prediction of its values are very hard to capture[1].

AFP AND ITS PREDICTION OF HCC RECURRENCE: ROLE OF STATIC VALUES

During the last years, a growing number of studies has been focused on the predictive role of AFP for the diagnosis of tumor recurrence after LT[2]. AFP has been strongly connected with HCC biological behavior, commonly connecting its values with the grade of differentiation as well as the vascular invasiveness of the tumor[3].

As a confirmation of this renewed interest in relation to the role of AFP, the recently published EASL-EORTC guidelines suggest to investigate AFP modification as a clinical selection parameter of patients waiting for LT[4]. However, several questions still remain unsolved in relation to the clinical use of AFP measurements in daily practice, as clearly stated in a recent focused editorial[5]. Among them: (1) the best static value to adopt; (2) the best cut-off measurement; and (3) the best way to comfortably capture the effective, time-related, fluctuations of this biological marker.

Many authors focused on the last pre-transplant value of AFP as the best predictor of recurrence; the threshold level of 400 ng/mL was most frequently advanced.

A large United States experience including 6817 HCC patients listed for LT showed that patients having AFP values superior to 400 ng/mL at the moment of waiting-list inscription and then downstaged (using locoregional therapies) to AFP values $\leqslant$ 400 ng/mL immediately before LT showed better intent-to-treat survivals respect to the cases in which their values could not be reduced (3-year survivals: 81% *vs* 48%; $P < 0.001$); these downstaged patients had results comparable results to those patients having stable AFP values $\leqslant$ 400 ng/mL (74%; $P = 0.14$). In contrast to AFP at the moment of waiting-list inscription or to modifications of AFP, only last pre-transplant AFP independently predicted survival ($P < 0.001$)[6]. Another United States study proposed the combination total tumor volume inferior to 115 cm^3 and AFP inferior to 400 ng/mL and as a better tool for selecting patients with HCC, showing, 3 years after transplant, survivals inferior to 50% in patients exceeding this cut-off[7]. The Hangzhou group proposed in a study containing 195 patients to combine one of the two following items in order to obtain good tumor free survival rates: total HCC diameter inferior or equal to 8 cm; total HCC diameter superior to 8 cm contemporaneously having pathologic grade Ⅰ-Ⅱ and pre-LT AFP $\leqslant$ 400 ng/mL[8]. An Italian study showed that the combination of morphological and biological parameters (*e.g.*, total tumor diameter > 8 cm and AFP > 400 ng/mL) conferred scarce survivals: patients having the last AFP value > 400 ng/mL had an eight-times incremented risk of tumor recurrence after transplantation[9].

A monocentric Belgian study similarly identified the last AFP determination > 400 ng/mL as the most important independent predictor for tumor recurrence after LT (HR = 4.86; $P = 0.01$)[10]. The United Network for Organ Sharing region 6 experience showed that peak AFP value > 400 and AFP at LT > 400 ng/mL were connected with poor outcomes post-LT in patients previously treated with loco-regional treatment (LRT)[11].

Despite many analyses underlined the role of the last AFP measure > 400 ng/mL before LT as a predictive tool, several, greatly differing, cut-off values (100, 200, 210, 300, 1000 ng/mL) have been put forward in the recent literature. The unfollowing paragraph gives an overview of all these different findings published during the period 2009-2014.

A United States study including 101 patients showed that AFP > 100 ng/mL (OR = 5.0, $P = 0.006$) and tumor size (OR = 4.1, $P = 0.013$) were correlated with microvascular invasion and post-LT recurrence[12]. Another Polish study including 121 HCC patients confirmed the validity of 100 ng/mL as cut-off value in predicting the risk of post-LT recurrence in patients meeting San Francisco criteria or up-to-seven criteria[13]. An Egyptian study identified AFP value > 200 ng/mL as a predictive tool for HCC recurrence in 170 living donor LT (LDLT)[14]. An Italian study reported that a AFP cut-off measure of 210 ng/mL, significantly influenced 5-year survivals (23.3% *vs* 76.2%; $P < 0.0001$)[15]. A Japanese analysis of 167 LDLT patients identified a threshold measure of 300 ng/mL as predictor of HCC recurrence and poor prognosis[16]. Finally some studies identified

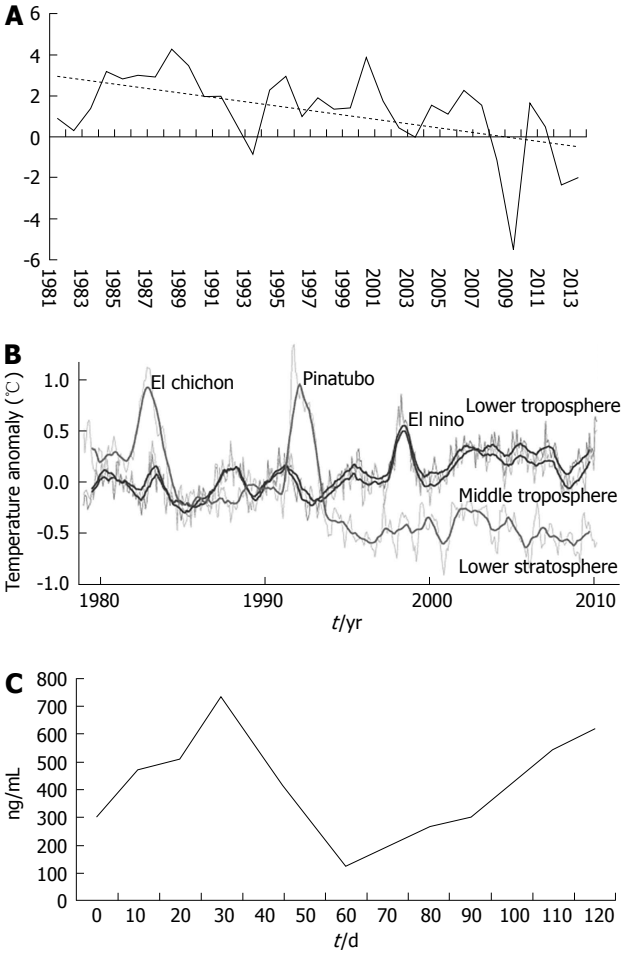

Figure 1 Some examples of systems with chaotic behaviour. A: Annual gross domestic product (GDP) growth of Italy in the last 35 years (%) (from: http://thenextrecession.wordpress.com/2013/08/05/greece-still-bust-spain-depressed-italy-paralysed/); B: Atmospheric temperature from 1979 to 2010, determined by NASA satellites (from: http://earthobservatory.nasa.gov/Features/GlobalWarming/images/msu_1978-2010.png); C: Hypothetical patients' alpha-fetoprotein fluctuation during his waiting list period before liver transplantation.

the value of 1000 ng/mL as significant.

The Seoul National University study including 63 LDLT patients proposed a score based on the following three different variables: (1) tumor size: ⩽ 3, 3.1-5, 5.1-6.5, ⩾ 6.5 cm; (2) tumor number: 1, 2-3, 4-5, ⩾ 6 nodules; and (3) AFP: ⩽ 20, 20.1-200, 200.1-1000, > 1000 ng/mL. According to the proposed score, an excellent stratification in relation to recurrence rates and patient survival could be achieved[17]. Another Chinese study in 303 patients similarly found AFP > 1000 ng/mL together with microvascular invasion and tumor size > 6.5 cm as risk factors for fatal recurrence after LT. Interestingly, dead due to tumor recurrence within one year after LT was 85.7% when all three risk factors were present, 37.8% when two factors, 13.6% when one factor and 6.7% when no risk factor were present[18].

A multicentric analysis from France (n = 435 cases) created a mathematical model based on the number of HCC lesions, tumor size and last AFP value. Interestingly, the authors found two different cut-off values in relation

Table 1 Recent articles focused on alpha-fetoprotein static values

Ref.	Year	*n*	Country	Cut-off value (ng/mL)
McHugh *et al*[12]	2010	101	United States	100
Grąt *et al*[13]	2014	121	Poland	100
Abdel-Wahab *et al*[14]	2013	170 (LDLT)	Egypt	200
Lai *et al*[15]	2011	153	Italy	210
Harimoto *et al*[16]	2013	167 (LDLT)	Japan	300
Merani *et al*[6]	2011	6817	United States	400
Toso *et al*[7]	2009	6478	United States	400
Zheng *et al*[8]	2008	195	China	400
Lai *et al*[9]	2012	158	Italy	400
Ciccarelli *et al*[10]	2012	137	Belgium	400
Wong *et al*[11]	2013	211	United States	400
Yang *et al*[17]	2007	63 (LDLT)	South Korea	1000
Zou *et al*[18]	2008	303	China	1000
Duvoux *et al*[19]	2012	435	France	1000
Hameed *et al*[20]	2014	211	United States	1000

LDLT: Living donor liver transplantation.

to the Milan Criteria (MC) status. When MC status was exceeded, patients experienced high or low 5-year recurrence rates when AFP measures were < 100 or > 1000 ng/mL (47.6% and 14.4%, respectively; P < 0.006). When patients meeting MC had AFP levels > 1000 ng/mL, showed high-risk for recurrence (37.1%; P < 0.001)[19]. An analysis from United States including 211 patients similarly showed that patients meeting MC with last pre-LT AFP > 1000 ng/mL showed a higher number of recurrences 5 years after transplant. An AFP level > 1000 ng/mL strongly predicted vascular invasion (OR = 6.8, P = 0.006), the most important risk factor for recurrence. Five-year recurrence-free survivals were 80.3% and 52.7% for patients meeting or exceeding the AFP threshold measure of 1000 ng/mL (P = 0.026), respectively. Application of the AFP > 1000 ng/mL as a cut-off was connected with the exclusion of 4.7% of cases from the opportunity to be transplanted and with the reduction of 20% of tumor recurrence[20]. All the reported studies are reassumed in Table 1.

FROM STATIC TO DYNAMIC

A fascinating way for trying to better define AFP with the intent to completely capture its selective role in HCC patients is to investigate its dynamic behavior more than its static values. During the waiting list period many conditions can indeed occur, some of them being directly connected to the history of the tumor such as progression or need for LRT. Consequently, these conditions may play an important role in conditioning AFP fluctuations. Starting from this statement, different equations able to define AFP modification have been proposed. The San Francisco transplant center underlined the recent implementation in their inclusion policy for LT to include patients with AFP levels > 1000 ng/mL only if LRT enabled to decrease this level beneath 500 ng/mL[21].

A Canadian study including 48 patients showed by

Table 2 Recent articles focused on alpha-fetoprotein dynamic values

Ref.	Year	*n*	Country	Cut-off value (ng/mL per month)
Han *et al*[22]	2007	48	Canada	50
Vibert *et al*[23]	2010	153	France	15
Dumitra *et al*[24]	2013	92	Canada	0.1[1]
Lai *et al*[25]	2013	422	Europe[2]	15

[1]ng/mL per day; [2]Austria, Belgium, Germany, Italy.

multivariate analysis that preoperative slope of AFP was the unique independent tool able to predict tumor recurrence. Receiver operating characteristic analysis showed that the best discriminant cut-off value was 50 ng/mL per month (sensitivity: 36%; specificity: 97%). Cases having a pre-LT AFP slope > 50 ng/mL per month experienced a much worse one-year recurrence-free survival rate (40% *vs* 90%, $P < 0.001$)[22].

The Paris Paul Brousse experience including 153 patients transplanted during the period 1985-2005 revealed that patients exceeding the cut-off value of 15 ng/mL per month had lower five-year overall (54% *vs* 77%) and recurrence-free survival rates (47% *vs* 74%). At multivariate analysis, progression of AFP > 15 ng/mL per month and presence of more than three nodules at LT were poor prognostic factors[23].

Another study from Canada based on 92 patients transplanted during the period 1992-2010 showed that patients with an AFP slope exceeding 0.1 ng/mL per day had an increased risk of recurrence. Such slope was able to strongly predict post-LT recurrence, and microvascular invasion[24].

Finally, the European multicenter experience (EURHECALT study) performed on 306 patients meeting and 116 exceeding MC showed that mRECIST progression during waiting time and AFP slope > 15 ng/mL per month were the sole predictors of tumor recurrence and post-LT death[25]. All the reported studies are reassumed in Table 2.

It should be underlined that in all these mentioned studies, AFP slope was calculated using only two data points. Vibert *et al*[23] adopted the value obtained from the difference between the lowest and highest measured divided by the lapse of time passed between the two measurements; our group (Lai *et al*[25]) adopted the measures at the moment of waiting-list inscription and at moment of LT. Both methods insufficiently show the real behavior of AFP changes overtime because they are not able to completely capture the AFP oscillations during the time.

Until now, neither "dynamic" *vs* "static" values nor the proposed cut-off value of AFP slope (15 or 50 ng/mL per month, 0.1 ng/mL per day) have been validated.

CONSIDERATION FOR AN INTEGRATED MODEL

Several questions are thus still open in relation to the possible adoption of AFP as a refinement selector of patients with HCC awaiting for transplant. The, growing, recent literature focused on the prognostic role of AFP in relation to tumoral features, recurrence and overall patient survival, did not yet identify the best way to integrating this marker into the morphologic tumor behavior. It is however clear that besides the fundamental starting point, namely tumor morphology (based on MC), biologic tumor behaviour must obtain a valid place within the construction of every LT selection model. In a fascinating editorial, Marsh stressed that biological features, typically considered the "king" among all prognostic variables in oncology, have not enough space in the "Metroticket" paradigm (the longer the distance the higher the price; the more the tumor is advanced, the higher is the risk of recurrence) proposed by Marsh *et al*[3] and Mazzaferro *et al*[26]. Lai *et al*[27] reported that biology is like a dwarf on the shoulder of a giant (the MC), but thanks to this "privileged position", the dwarf is able to see further, this means to identify risk factors and so to refine selection criteria for LT[27]. Despite these "visionary" statements, AFP appears not to be a manageable variable. Firstly, AFP may increase due to tumor-unrelated events such as viral- and toxic- (due to LRT or medication) related events; secondly, this marker frequently is not secreted by the tumor, explaining its poor sensitivity and specificity in the diagnostic process of HCC. As a consequence, all high AFP values are not equal to aggressive tumors and not all the low-value are equal to good-prognosis HCC. Moreover, the chaotic fluctuations of AFP make it difficult to find the best variable/equation able to capture them and finally, no definitive answer has been found to identify the best cut-off value to adopt.

Trying to find a "fil-rouge" in the recent literature, we assume that: (1) last AFP value or AFP slope seem to be the best values to adopt; (2) different cut-offs may be adopted in the two different scenarios of MC-IN and MC-OUT, adopting lower values in this latter context; (3) the possible use of 1000 ng/mL as cut-off for MC-IN patients seems to represent a good compromise between the necessity to exclude high-risk patients from LT and the desire to give the transplant opportunity to the highest number of patients; (4) the latter considerations can be potentially extended also to University California San Francisco criteria, eventually adopting a more stringent AFP parameter (necessity of post-LRT AFP reduction from 1000 to 500 ng/mL? eventually a lower value?); (5) no definitive conclusion has been reached in relation to the best cut-off value to adopt in case of MC-OUT patients (400 ng/mL or less?) and finally (6), no definitive cut-off has been investigated in relation to AFP slope in the two different published scenarios, so more studies are required (Table 3).

CONCLUSION

AFP represents a useful but poorly manageable tool to

Table 3 Proposal for the integration of alpha-fetoprotein values and morphological tumor criteria into the selection process for liver transplantation in hepatocellular carcinoma cirrhotic patients

Criteria	No. of lesions	Maximum diameter (cm)	Last AFP value (ng/mL)	AFP slope (ng/mL per month)
MC	1	5	1000	15, 50, higher?
	2-3	3	1000	15, 50, higher?
UCSFC	1	5.1-6.5	1000?	50 or higher?
			1000 → 500? lower?	
	2-3	3.1-4.5 (total sum 8)	1000?	50 or higher?
			1000 → 500? lower?	
Out of conventional criteria			400? lower?	50 or higher?

AFP: Alpha-fetoprotein; MC: Milan Criteria; UCSFC: University of California San Francisco Criteria.

increase the ability to better select HCC patients waiting for LT. More, structured and prospective, studies using serial determination of AFP values within and without the context of locoregional therapies are needed in order to find the "ideal" (static and dynamic) cut-off values allowing to respond to all the still open questions in this field of transplant oncology.

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EDITORIAL

Cross talk of the immune system in the adipose tissue and the liver in non-alcoholic steatohepatitis: Pathology and beyond

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Abstract

Non-alcoholic steatohepatitis (NASH) is considered to be the hepatic manifestation of the metabolic syndrome, thus has a tight correlation with systemic metabolic impairment. The complex mechanisms underlying the pathogenesis of NASH involve different organs and systems that cross talk together contributing to the onset of NASH. A crucial role is played by inflammatory mediators, especially those deriving from the adipose tissue and the liver, which are involved in the cascade of inflammation, fibrosis and eventually tumorigenesis. In this setting cytokines and adipokines as well as immunity are emerging drivers of the key features of NASH. The immune system participates in this process with disturbances of the cells constituting both the innate and the adaptive immune systems that have been reported in different organs, such as in the liver and in the adipose tissue, in clinical and preclinical studies. The role of the immune system in NASH is increasingly studied, not only because of its contribution to the pathogenetic mechanisms of NASH but also because of the new potential therapeutic options it offers in this setting. Indeed, novel treatments acting on the immune system could offer new options in the management of NASH and the correlated clinical consequences.

Key words: Non-alcoholic steatohepatitis; Immune system; Adipokines; Inflammation; Fibrosis

Core tip: Non-alcoholic steatohepatitis (NASH) is considered to be the hepatic manifestation of the metabolic syndrome, thus has a tight correlation with systemic metabolic impairment. The complex mechanisms underlying the pathogenesis of NASH involve different organs, including liver, adipose tissue and immune system, which cross talk together contributing to the onset of NASH. Increasing interest has been aroused by the role of the immune system in NASH, not only because of its

contribution to the pathogenetic mechanisms of NASH but also considering the new potential therapeutic options in this setting.

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INTRODUCTION

The increasing burden of non-alcoholic fatty liver disease (NAFLD) is a major health concern. The NAFLD worldwide prevalence shows an upward trend over time and has reached "pandemic" proportions. In the general population it is estimated to be 20%-30% in Western countries and 5%-18% in Asia and is associated with an increased prevalence of obesity, insulin resistance, metabolic syndrome and diabetes, which are often paired to NAFLD[1]. Indeed in at risk patients, such as patients with diabetes mellitus, the prevalence of NAFLD increases up to 40%-70%[2]. In addition, NAFLD can run a unfavourable course, given the possible evolution to cirrhosis and hepatocellular carcinoma and can constitute an indication for liver transplantation[3].

NAFLD and more specifically non-alcoholic steatohepatitis (NASH) are closely related to metabolic impairment, such as visceral adiposity, hyperinsulinaemia or diabetes, dyslipidaemia and arterial hypertension, which define the metabolic syndrome. NAFLD and NASH are considered the hepatic manifestation of the metabolic syndrome[4]. Moreover patients with NAFLD, and a fortiori NASH, are at higher risk of developing diabetes mellitus and are at increased risk of morbidity and mortality related to cardiovascular diseases[3,5].

These considerations arise the need of understanding the complex mechanisms underlying the onset of NASH. At the basis of a wide clinical spectrum of NAFLD that includes metabolic impairment at different levels, there is a complex interaction between different organs at the pathogenetic level. This is conceptualized in the "multiple parallel hit hypothesis"[6] and has been substantiated by further research. The liver damage, driven by insulin-resistance, iron accumulation, oxidative stress and hepatocyte death, can be triggered by an imbalance in anti- and pro-inflammatory factors originating from the liver itself or from extrahepatic sites that cross talk with the liver, particularly the adipose tissue and the gut[7]. Another key player in the pathogenesis of NASH is the immune system, including both the innate[8] and the adaptive[9] immune cells[10]. The specific role of the different cell-subsets and the reciprocal role of pro- and anti-inflammatory pathways, however, have not yet been fully clarified and is object of interest in NASH research. Understanding the reciprocal role of these cells in NAFLD should help identifying possible targets for treatment, as nowadays there is no pharmacological treatment licensed for NAFLD[4].

LIVER, ADIPOSE TISSUE AND THE IMMUNE SYSTEM

NAFLD and NASH are associated with the presence of low-grade inflammation. Numerous studies have demonstrated that both the innate and the adaptive immune system play an important role in the pathogenesis of NAFLD/NASH (for review see[10]) and, moreover, that the organ-specific immunity is involved in the onset and progression of this disease.

When considering the whole population of T lymphocytes ($CD3^+$ leucocytes) in the liver, it appears relatively stable in NASH. A variation of the various subtypes of $CD3^+$ cells, however, has been described in NASH, namely a relative increase of the hepatic $CD8^+$ cells in comparison with the $CD4^+$ cells (hence a higher $CD8^+/CD4^+$ ratio)[11]. Among the $CD4^+$ cells, an imbalance between the T helper (Th)1 and Th2 profile towards the pro-inflammatory Th1 has also been described[12]. Moreover a liver specific and reversible depletion of the regulatory T-cells (Tregs) was observed under high fat diet (HFD) in an animal model[13]. The Treg decrease in NASH can in part be explained by dendritic cells (DC) induced down-regulation. *In vitro* studies indeed demonstrated that intrahepatic DC are able to blunt the $CD25^+FOXP3^+$ Treg phenotype within the $CD4^+$ cells[11].

Opposite to these findings, in liver biopsies from a group of NAFLD patients, including NASH patients, the forkhead/winged helix transcription factor (FOXP3) positive cells (Tregs)[14] were more expressed in NASH patients with a more severe disease[15] in comparison with no-NASH patients, hence showing a Treg proliferation with the progression of the disease.

The Th17 pathway is another key player in liver disease, including NAFLD and NASH. In preclinical and clinical studies an increase of the Th17 cells was described together with an up-regulation of the Th17-related genes. Moreover interleukin 17 (IL17) appeared to be crucial in the induction of liver injury in a HFD context and is implicated in metabolic damage by interfering with the insulin signalling pathway[16]. A stimulation of the Th17 occurs, at least in part, *via* interaction between liver and adipose tissue. Indeed, leptin, an anorexigenig and pro-inflammatory adipokine which is increased in obesity due to a mechanism of leptin resistance[17], is able to increase the number of Th17 and the gene expression of the Th17-specific transcription nuclear factor RAR-related orphan receptor (ROR)γt and to stimulate the IL17 production[18]. In addition, the IL17 pathway is implicated in the onset of liver fibrosis: liver injury induces IL17 signalling, which in turn stimulates collagen deposition from the hepatic stellate cells (HSC) and hence the onset of fibrosis[19]. An impairment of the

balance between Tregs and Th17 is hence potentially of relevance for the onset and development of NASH, which opens perspectives for new treatment.

Natural killer T (NKT) cells are reduced in hepatic steatosis[20-22], but are increased in hepatic fibrosis in the context of NASH[20,23]. Indeed, human liver biopsies with advanced fibrosis showed increased levels of osteopontin and hedgehog, which are secreted by NKT, in comparison with early stages of fibrosis[24].

The resident macrophages in the liver, the Kupffer cells (KC), are sensitive to gut-derived endotoxin and modulate the activation of different cells in the liver, such as DCs, T lymphocytes and neutrophils[25]. They are actively implicated in the development and progression of NASH by the secretion of tumour necrosis factor (TNF)α, which plays an important role in the early phase of the disease, and of IL6, which is important in the liver disease evolution and in de onset of insulin resistance[7].

DCs in NASH are enrolled in the early phases. They display a decreased plasmocytoid and lymphoid fraction and an increased myeloid fraction and produce higher levels of pro-inflammatory cytokines and to mediate an allogenic T cell proliferation, an antigen-restricted $CD4^+$ T cell stimulation and a Treg down-regulation[11].

The adipose tissue is another key organ in the pathogenesis of NASH and the associated metabolic impairment. Moreover the NASH-related immune system impairment involves also the immune cells infiltrating this organ.

Considering the T lymphocytes, $CD8^+$ and $CD4^+$ are enriched in the adipose tissue[11]. Moreover there is a shift towards the pro-inflammatory Th1 cytokines in comparison with the anti-inflammatory Th2 ones, particularly in the visceral adipose tissue[12]. Interestingly, the Th1 stimulation, *via* INFγ, induces the infiltration of the adipose tissue by other pro-inflammatory cells, such as the M1-polarized macrophages[26].

The abdominal adipose tissue (but not the sub-cutaneous adipose tissue) is a preferential source of Tregs in mice fed a normal diet with a time-dependent kinetic. In insulin-resistant models of obesity Tregs are specifically reduced in the abdominal site[12,27], which can be explained, at least in part, by the suppression of Treg proliferation by leptin[28]. Moreover in obese patients FOXP3 RNA was expressed at a higher level in the subcutaneous adipose tissue and a negative correlation between body mass index (BMI) and the FOXP3 to CD3 ratio in omental *vs* subcutaneous fat was reported in these patients[27]. In leptin deficient obese mice Treg depletion leads to increased fasting blood glucose level, impaired insulin sensitivity and renal impairment, while Treg adoptive transfer improves insulin resistance[29]. In addition, in type 2 diabetes a deregulation of the balance between Tregs and Th17 occurs: there is a decrease of the Tregs/Th17 ratio and Tregs appear to be more prone to cell death[30]. Opposite to these findings, other studies suggested a potential beneficial effect of the IL17 in blunting the phenotypic and metabolic characteristics correlated to obesity. Preclinical studies showed a reduction of the Th17 in the visceral adipose tissue of mice fed a HFD[12] and demonstrated the role of IL17 as a negative regulator of adipogenesis and glucose metabolism in mice, delaying the onset of obesity[31]. In these experiments, IL17 deficiency enhanced diet-induced obesity, early adipose tissue accumulation and altered glucose homeostasis. In addition IL17 acted on preadipocytes and adipocytes to inhibit adipogenesis and moderate lipid and glucose uptake[31].

A depletion of invariant NKT cells (iNKT) has been reported in obesity, in correlation with pro-inflammatory macrophage infiltration. Indeed, iNKT-depleted NASH animal models show larger adipocytes while iNKT adoptive transfer decreases fat accumulation, leptin levels and insulin sensitivity[32].

In adipose tissue, an infiltration of DC has been shown in preclinical and clinical studies. In humans, the subcutaneous adipose tissue-derived DC have been described to correlate with metabolic impairment [high BMI and insulin resistance] and with increased Th17[33].

Considering the B lymphocytes, they contribute to the onset of insulin resistance. Mice fed a HFD display and increase of B lymphocytes in serum and adipose tissue, while when feeding B-cell-deficient mice a HFD lower insulin resistance is determined. Accordingly, adoptive transfer of B cells or IgG isolated from mice fed a HFD into B-cell-deficient mice induces insulin resistance. In addition, insulin-resistant patients have a distinct IgG profile compared to patients without it[34].

Macrophages derive from circulating monocytes and play a crucial role in the adipose tissue. They can activate as the "classically activated" pro-inflammatory M1 or as the "alternatively activated" anti-inflammatory M2 states. In obesity animal models pro-inflammatory M1 polarized macrophages infiltrate the adipose tissue[32] and create the characteristic "crown like" structures around necrotic adipocytes[32].

The obesity-related switch from the M2 to the M1 polarization is driven by a C-C chemokine receptor 2 (CCR2)-dependent monocyte recruitment[35]. CCR2 is therefore a potential target of therapy. Indeed, blunting macrophage accumulation, also *via* monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2) inhibition, induces an improvement of inflammation activity, insulin resistance and liver fibrosis[7].

These data summarize the multiple immune cell subtypes involved in the onset of NAFLD and NASH, which draw complex pathways and offer various possible targets to interfere with the onset of NASH.

A relevant role in the pathogenesis of NASH is played by adipose tissue-derived mediators, such as adiponectin and leptin[6], and other molecules such as ghrelin, visfatin and resistin[36,37].

Adiponectin and leptin are produced mainly by the adipose tissue. The former acts as an insulin sensitizing and an anti-inflammatory mediator. Hypoadiponectinemia has been found to be associated with the metabolic

Table 1 Treatment perspectives: Novel agents acting on the immune system

Treatment	Target	Effect
Anti-CD3 moAb	CD3	Reduction of liver enzymes and glucose and insulin levels
Imm124-E	Treg stimulation	Improvement of glucose metabolism parameters, lipid profile and liver injury
Adoptive transfer		
Tregs		Reduction of TNFα-related inflammation
$CD4^+$ T cells		Reverses weight gain and insulin resistance
NKT cells		Decreases body fat, triglyceride levels, leptin levels, hepatic steatosis and insulin sensitivity
RORγt ligands	RORγt	Th17 inhibition
Cenicriviroc	CCR2/5 inhibitor	Improvement of lipid metabolism and liver fibrosis
VAP-1	Lymphocytes recruitment	Anti-inflammatory en anti-fibrogenic effect

TNF: Tumour necrosis factor; ROR: RAR-related orphan receptor; CCR2: C-C chemokine receptor 2; VAP-1: Vascular adhesion protein-1; NKT: Natural killer T; Th17: T helper cell 17; Tregs: Regulatory T-cells; moAb: Monoclonal antibody.

syndrome and its components, including NASH[38]. The latter, under physiological conditions, has anorexigenic effects decreasing appetite and increasing energy expenditure, while in obese patients hyperleptinemia associated to leptin resistance has been described[17]. Moreover leptin has pro-inflammatory and pro-fibrogenic properties that play a role in liver disease, including NASH[37,39,40].

Adiponectin exerts its anti-inflammatory function inhibiting the pro-inflammatory cytokines (TNFα) and stimulating the anti-inflammatory cytokines (IL10 secreted by KC)[41] and *via* direct suppression of the macrophage function[42]. Adiponectin attenuates also oxidative stress and fibrogenesis, the latter through suppression of the activated HSC function[38].

Leptin is able to affect the production of acute-phase-reactants, such as IL1 and TNFα, to alterate the Th1/Th2/Tregs balance promoting a Th1 differentiation and a Treg down-regulation[40]. Hyperleptinemia is a condition correlated with obesity and can favour pro-inflammatory mechanisms. Namely it can induce a proliferation of Th1 cells in the adipose tissue, of $CD8^+$ T cells, macrophages and mast cells and stimulates pro-inflammatory cytokines (as TNFα, IL6 and IL12). Moreover they induce a down-regulation of the Treg in the adipose tissue, as previously described[40].

Ghrelin is a gut peptide that is involved in regulation of food intake and energy balance. Ghrelin has been reported to have protective effects on the liver and reduced levels of this hormone have been found in NAFLD patients[43].

Resistin, which is produced by adipose tissue and macrophages, is involved in insulin resistance, has pro-inflammatory (*via* stimulation of the secretion of TNFα and IL12 by macrophages and *via* regulation of IL6 and IL1β production) and pro-fibrogenic (acting on the HSC)[36]. Resistin has been correlated with the progression of liver damage in NAFLD and with the onset of NASH[44].

NASH patients show lower adiponectin, higher leptin and resisitin and unaltered ghrelin levels in comparison with control subjects. In these patients antioxidant treatment can induce an reversal of the hypoleptinemia and hypoadiponectinemia and is able to arise the ghrelin levels[37].

Visfatin is an insulin mimicking adipokine. It is able to induce IL6 secretion from $CD4^+$ T cells[45]. The specific contribution in NASH, however, has not been fully clarified.

TREATMENT PERSPECTIVES

Currently there is no approved pharmacological treatment available for NASH. Among the treatments used in the pharmacotherapy of NASH, some agents have failed to give a satisfactory improvement of NASH, such as metformin, statins and ursodeoxycholic acid. Vitamin E and thiazolidinediones have shown beneficial effects on liver histology in randomized control trials and can hence be used for the treatment of NASH, but are not approved for this indication[4]. Furthermore, there is some concern about the potential side effects associated with these drugs, which should hence be prescribed with caution[46]. Pioglitazone finds a possible indication in older patients with aggressive NASH and Vitamin E can be used in non-diabetic pre-cirrhotic adults[4]. Of note pioglitazone is also able to increase adiponectin levels[47] (Table 1).

Very recent preclinical data show the ability of the adiponectin receptor agonist AdipoRon to significantly ameliorate glucose metabolism and serum lipid levels. In the liver the AdipoRon reduces triglyceride content, oxidative stress, and inflammatory cytokine expression, suggesting its potential role in the treatment of NASH[48].

Another treatment approach exploits the possibility to interfere with the immune system, which is actively involved in the physiopathology of NASH, through immune-regulation[49].

Some data are available regarding the anti-CD3 monoclonal antibody (moAb), which prevents the onset and the evolution of inflammatory and autoimmune diseases.

The anti-CD3 moAb or its Fragment anti-binding $F(ab^1)_2$ have been shown to be effective in ameliorating insulin resistance in leptin deficient *ob/ob* mice where they restored Tregs in the visceral adipose tissue and improved glucose tolerance and insulin sensitivity[12].

The anti-CD3 moAb can be also administered in

combination with β-glucosylceramide, which is able to mediate the interaction with other immune cells such as NTK. Oral anti-CD3 antibody is rapidly absorbed by the gut-associated lymphoid tissue and induces $CD4^+CD25^-$ latency-associated peptide-positive Tregs, which act in a tumor growth factor-β-dependent manner. Treatment of *ob/ob* mice resulted in a better metabolic control and an improvement of the liver damage. A decrease in pancreatic islet cell hyperplasia, fat accumulation in the liver and inflammation in adipose tissue, accompanied by lower blood glucose and liver enzymes were observed[50].

The systemic administration of anti-CD3 moAb, however, can be hampered by serious side effects such as the cytokine release syndrome, a "cytokine storm" released as a consequence of generalized T cell activation, or the antiglobulin response[51]. To minimize the side effects of the systemic administration of the anti-CD3 moAb and to maximize its local effects, anti-CD3 can be orally administered. A single-blind randomized placebo-controlled phase 2a study showed the safety of oral anti-CD3 moAb in 36 NASH patients with impaired glucose control up to type-2 diabetes. Oral anti-CD3 moAb showed safety and were able to improve liver damage and glucose metabolism. This effect was coupled with a persistent Treg level increase[51].

The Treg-induction can be either antigen-specific or antigen nonspecific. The induction of antigen-specific Tregs has the potential advantage of inducing a specific immune modulation and of reduced side effects. This is, however, not achievable in conditions such as type 2 diabetes or NASH where there are to date no well-defined target antigens. In these conditions the induction of antigen non-specific Tregs by anti-CD3 may be a valid option. Further research will investigate the possibility of developing a combination of mucosal anti-CD3 with a given antigen[51].

Moreover Tregs are an important possible target for immunotherapy. Different therapeutic approaches have been used to modulate these cells. The Imm124-E, an anti-lipopolysaccharide hyperimmune bovine colostrum, has been tested, in an open label trial, in patients with biopsy-proven NASH and insulin resistance. Imm124-E was safe and effective in ameliorating the glucose metabolism parameters, the lipid profile and the liver injury. The improvement of the clinical parameters was paired with a Treg enhancement[52].

A redistribution of the Tregs, paired to an increase in NKTs, was reached in leptin deficient *ob/ob* and HFD mice treated with DT56a, a molecule contained in soybean able to activate estrogen receptors and to improve glucose homeostasis, the lipid profile and the liver enzymes[53].

Adoptive cell transfer refers to the transfer of immune cells into a recipient host aiming at transferring the immunological functionality into the host. In particular the Treg cell transfer is able to preserve and restore tolerance to self-antigens and alloantigens. The benefits of this treatment are the potential for antigen specificity, the lack of general immunosuppression and the long-lasting regulation[54]. Treg expansion in obese mice tempers TNFα-related inflammation[13] but it is not able to restore metabolic function in obesity[27].

Cellular therapy has also been tested with other cell subtypes. The $CD4^+$ Tcell transfer into obese mice reversed weight gain and insulin resistance[12]; iNKT transfer decreased body fat, triglyceride levels, leptin levels, hepatic steatosis and insulin sensitivity[32].

Although cellular therapy shows positive preliminary result and constitutes a conceptually potentially effective therapy, these treatments raise feasibility concerns in the clinical setting[55] and need further development and evaluation.

A further possible therapeutic approach involves the ROR pathway. RORα and RORγ are transcription factors implicated in the control of lipid and glucose metabolism, besides various immune functions. The absence of RORα protects against diet-induced obesity, adipose tissue-associated inflammation, liver injury (namely steatosis), and insulin resistance[56]; RORγ deficiency also protects against diet-induced insulin resistance[57]. Therefore, ROR antagonists may provide a novel therapeutic target in the management of various aspect of the metabolic syndrome.

Recently RORγt ligands have been studied in autoimmune diseases. They blunt the production of IL17 from the stimulated Th17 cells, by counteracting nuclear receptor specific for Th17 RORγt. These compounds constitute a promising strategy in the therapy of NASH, considering the central role of the Th17 pathway in the induction and progression of both the liver damage and the metabolic impairment.

Antioxidants constitute another potential therapy in NAFLD. Polyphenols, such as resveratrol contained in grapes and wine, are molecules of interest. Indeed resveratrol is able to improve insulin sensitivity and to modulate mitochondrial energetics[58]. Moreover resveratrol has been shown to be effective in ameliorating liver enzymes, insulin resistance and glucose and lipid metabolism in patients with NAFLD. Furthermore it induced a reduction of pro-inflammatory and pro-fibrogenic cytokine levels (namely TNFα, cytokeratin 18 fragment, and fibroblast growth factor) and an elevation of adiponectin levels[59].

Another potential target is the fibrosis pathway. The Chemokine receptors type 2 and 5 (CCR2-CC5) are expressed by cells involved in fibrogenesis, such as monocytes, macrophages, Kupffer cells and hepatic stellate cells. Preclinical studies in NASH and liver fibrosis animal models showed that a dual CCR2 and CCR5 inhibitor, cenicriviroc (CVC), has an anti-fibrogenic effect[60]. A clinical study conducted in human immunodeficiency virus (HIV) patients has shown that CVC is able to improve lipid metabolism (decreasing the total cholesterol, low-density lipoprotein and triglycerides levels and increasing the high-density lipoprotein levels) and the fibrosis scores aspartate aminotransferase to platelet ratio index (APRI)[61] and fibrosis-4 (FIB-4)[62,63]. This, together with the preclinical data, makes CVC a

good candidate for the treatment of NASH.

Very recently a new potential target of treatment for NAFLD has been identified. The Vascular adhesion protein-1 (VAP-1) is an amino-oxidase constitutively expressed on human hepatic endothelium that promotes lymphocyte recruitment in the liver. This molecule is increased in various models of liver disease, including NAFLD, and is implicated in both inflammation and fibrosis. In a NAFLD preclinical model VAP-1 inhibition leads to less leucocyte recruitment in the liver and, more specifically, a reduction of the $CD4^+$ T lymphocytes and of the NKT lymphocytes. This, together with its anti-fibrogenic effect, makes the VAP-1 inhibition a potential therapeutic target[64].

Further research is, however, urgently needed to unravel the exact pathogenetic mechanisms of NAFLD/NASH, also aiming at discovering new effective therapeutic options, given the increasing burden of this disease and its potential evolutive course.

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EDITORIAL

Current management of patients with hepatocellular carcinoma

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Abstract

The current management therapies for hepatocellular carcinoma (HCC) patients are discussed in this review. Despite the development of new therapies, HCC remains a "difficult to treat" cancer because HCC typically occurs in advanced liver disease or hepatic cirrhosis. The progression of multistep and multicentric HCC hampers the prevention of the recurrence of HCC. Many HCC patients are treated with surgical resection and radiofrequency ablation (RFA), although these modalities should be considered in only selected cases with a certain HCC number and size. Although there is a shortage of grafts, liver transplantation has the highest survival rates for HCC. Several modalities are salvage treatments; however, intensive care in combination with other modalities or in combination with surgical resection or RFA might offer a better prognosis. Sorafenib is useful for patients with advanced HCC. In the near future, HCC treatment will include stronger molecular targeted drugs, which will have greater potency and fewer adverse events. Further studies will be ongoing.

Key words: Hepatocellular carcinoma; Living donor liver transplantation; Radiofrequency ablation; Surgical resection

Core tip: Liver transplantation is the first-line treatment of hepatocellular carcinoma (HCC). Surgical resection and radiofrequency ablation (RFA) are second-line HCC treatments. Surgical resection and RFA should only be considered for selected cases. Sorafenib administration, transarterial chemoembolization, stereotactic body radiation treatments, or proton or carbon ion treatments

are available as salvage treatments for HCC. Laparoscopic liver resection appears to offer at least a short-term benefit in selected HCC patients. These HCC treatments should be carefully selected or combined in clinical practice.

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HEPATOCELLULAR CARCINOMA

Globally, hepatocellular carcinoma (HCC) is a common malignancy with a poor prognosis worldwide, and the incidence of HCC is increasing in the United States[1,2]. In Asian countries, HCC is caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection[3-6]. Despite the ongoing development of new therapies, HCC remains a "difficult to treat" cancer[7] because the malignancy typically occurs in advanced liver disease or hepatic cirrhosis. In HCC treatments, such as surgical resection or percutaneous local ablation therapy, the liver function should always be considered[8-12]. The recurrence of HCC within 5 years after primary resection is as high as 70% because multistep and multicentric HCC develops most frequently after a resection or ablation treatment in patients with chronic liver disease[13,14].

CURRENT MANAGEMENT OF HCC

Surgical resection for HCC

The tumor status and liver function reserve of HCC patients determine whether a hepatectomy should be performed[9] (Figure 1A). Careful attention should be focused on the selection of appropriate candidates. Makuuchi's criteria for the selection of the operative procedures in patients with HCC and liver cirrhosis are available in Japan[8,15]. The criteria comprise the existence of ascites, the serum total bilirubin and indocyanine green (ICG) clearance rates. In patients without ascites and with total bilirubin levels < 2 mg/dL, a hepatectomy could be safely performed. Serum total bilirubin levels (< 1 mg/dL) and a normal range (10%-19%, 20%-29%, or ⩾ 30%) of ICG retention at 15 min suggest a trisegmentectomy or right hepatectomy, left hepatectomy or right segmentectomy, subsegmentectomy, or limited resection, respectively. Patients with serum total bilirubin levels of 1.1-1.9 mg/dL could receive a limited liver resection safely. Small HCC is a clinical entity with a high surgical cure rate[9]. Yamazaki *et al*[9] reported that the 5-year survival following a hepatectomy is 53%, with 26% morbidity and 0% mortality in patients within the Makuuchi's criteria; however, they reported that the 5-year survival in HCC patients in major institutions worldwide is 37%-53% following a hepatectomy, with 11%-45% morbidity and 0%-10% mortality. A hepatic venous pressure gradient ⩾ 10 mmHg as a direct measurement of relevant portal hypertension could be useful[16,17] because the concept of portal hypertension as a prognostic factor in patients undergoing resection has been validated[18]. An accepted application to measure and quantitate the liver reserve is debatable, and further studies are required.

The prognosis of patients with a portal vein tumor thrombus, which typically is poor, might be improved by surgical resection with or without pre-operative transarterial chemoembolization (TACE)[19,20]. A combination of aggressive surgical treatment and effective preoperative TACE for HCC with major vascular tumor invasion including invasion of the main trunk, the first-order branch of the portal vein, or the inferior vena cava might be beneficial for certain patients[19,21]. Because chemotherapy or antiviral treatment could be administered, a concomitant splenectomy and hepatectomy might extend the criteria for surgery in "selected" HCC patients with hypersplenism[22].

Percutaneous local ablation therapy: Ebara *et al*[23] reported that following percutaneous ethanol injection (PEI) therapy, the 1-, 2-, 3-, 4- and 5-year survival rates of 95 patients with an HCC smaller than 3 cm were 93%, 81%, 65%, 52% and 28%, respectively. This treatment could be performed for patients with Child's A as well as Child's B or C disease, although the survival rates of patients with Child's A or B status was higher than those in Child's C patients[23]. In cases of HCC recurrence, PEI was easily repeated[23], although a repeated hepatic resection was reported in selected patients[9]. Additionally, Shiina *et al*[10] reported that with a median follow-up of 51.6 mo, the 5-, 10- and 20-year survival rates of 2147 HCC-patients, were 49%, 18% and 7.2%, respectively. There were 45 complications (2.1%) and two deaths (0.1%)[10].

Radiofrequency ablation (RFA), instead of PEI (Figure 1A), is widely performed for HCC. Shiina *et al*[11] reported that the 5-, and 10-year survival rates of 1170 HCC-patients with a median follow-up of 38.2 mo were 60% and 27%, respectively. In that study, the survival rates of RFA were found to be superior to those of PEI[10,11], although it was not a head-to-head comparison. One death (0.03%) and 67 complications (2.2%) occurred[11], and the HCC was controlled by RFA. A randomized controlled trial of surgery *vs* RFA for small HCC has begun in Japan[24]. Additionally, it was reported that adjuvant RFA might provide palliative care for patients with metastatic cancer[25]. Further studies are required. The meta-analysis of the four randomized controlled trials demonstrated a significant improvement in the 3-year survival rate and that RFA was more effective than PEI[26].

Liver transplantation for HCC

Liver transplantation offers additional benefits for HCC patients because additional cancers might be

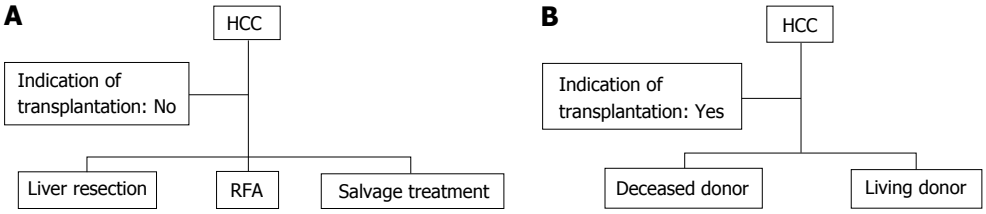

Figure 1 Treatment algorithm for hepatocellular carcinoma. A: In patients for which liver transplantation is unavailable. If possible, the patients should select surgical resection or radiofrequency ablation (RFA). Otherwise, other salvage treatments should be selected; B: In patients in which deceased-donor or living-donor liver transplantation is available. HCC: Hepatocellular carcinoma.

incidentally found during the examination of the explanted liver; additional cancers attribute to high HCC recurrence rates after primary surgical resection[27]. The criteria for liver transplantation have improved over many years[28-32]. According to the Milan criteria, patients are eligible for liver transplantation if they have a single HCC less than 5 cm in diameter or no more than three tumors less than 3 cm in diameter[30]. Liver transplantation is the first-line treatment option for these patients[16]. Mazzaferro *et al*[30] studied 48 patients within the Milan criteria; they reported an overall mortality rate of 17% after 4 years and that the actual survival rate and recurrence-free survival rate were 75% and 83%, respectively. Additionally, they reported that in 35 patients meeting the predetermined criteria for small HCCs in the pathology examination of the explanted liver, the overall and recurrence-free survival rates at four years were 85% and 92%, respectively[30]. These results suggest that liver transplantation is an effective treatment for small, unresectable HCCs in patients with cirrhosis. An excellent 5-year survival rate has been reported in cases in which the restrictive Milan criteria are used to select transplant candidates. HCC is a good indication for orthotopic liver transplantation, and cadaveric liver transplantation/deceased-donor liver transplantation is an excellent treatment for early HCC (Figure 1B). Additionally, living-donor liver transplantation is an excellent treatment for early HCC because deceased-donor liver transplantation is limited by the shortage of grafts[33,34]. In Japan and other Asian countries, living-donor liver transplantation will continue to be a mainstay treatment of HCC in cirrhotic patients[35,36].

HCC frequently occurs in cirrhotic liver patients infected with HBV or HCV. Although the viral infections are eradicated or controlled[37-45], the risk of developing HCC persists in patients with advanced liver disease. Elder patients tend to have more advanced fibrosis than younger patients[46-52]. Regardless of the liver function, in cases in which the restrictive Milan criteria are used to select transplant candidates, liver transplantation in patients within the criteria has a better prognosis. However, many difficulties exist, including a shortage of donors and whether a patient is eligible for transplantation because of age. Elderly patients with an increased risk for postoperative complications should be excluded from living donor liver transplantation, at least; previous published studies have shown that age is not a contraindication for deceased donor liver transplantation[53,54].

Down-staging the policies for HCCs exceeding the conventional criteria could not be recommended[16], and prospective studies should be conducted to explore the issue of expanded criteria for orthotopic liver transplantation, down staging and bridge therapies.

OTHER MODALITIES FOR HCC

Sorafenib

Treatment with sorafenib prolongs progression-free survival in patients with advanced clear-cell renal-cell carcinoma in whom previous therapy has failed; the treatment is associated with increased toxic effects[55]. Similarly, in 602 patients with advanced HCC (299 in the sorafenib group; 303 in the placebo group), overall survival (OS) was significant longer in the sorafenib group compared with the placebo group (OS of 10.7 mo *vs* 7.9 mo, respectively; hazard ratio in the sorafenib group, 0.69; 95%CI: 0.55-0.87; $P < 0.001$)[56]. Another study from the Asia-Pacific region[57] showed that sorafenib is effective for advanced HCC treatment in Child's A patients. Common adverse events such as hand-foot skin reactions, diarrhea and fatigue were observed in the study[57]. Molecular targeted therapy against HCCs is being developed and will augment the treatment of advanced HCC[58,59].

TACE: A Japanese prospective cohort study in 8510 patients with unresectable HCC showed a 5-year survival rate of 26%[60]. Superselective TACE for HCC showed overall median and 5-year survival rates of 3.3 years and 34%, respectively[61]. TACE showed higher survival rates in patients with fewer tumor numbers, smaller tumor size, and better liver function (Child's A or B). In Asian countries, TACE is the main therapeutic modality in advanced HCC-patients, and the overall therapeutic outcomes depend on the tumor size[62]. TACE has a long history in the treatment of unresectable HCC cases[63,64]. TACE, in combination with surgery or local ablation therapy, is frequently used in clinical practice. The timing and number of treatment sessions of TACE are not uniform for each patient, although new devices and treatments, including drug-eluting bead TACE and trans-arterial radio-embolization, have been

Table 1 Comparison of treatment modalities for hepatocellular carcinoma[84]

Modalities	Indication of the features of HCC
Surgical resection	Performance status 0, Child-Pugh A, single < 3 cm Normal bilirubin/normal portal pressure Associated diseases, no
RFA	Performance status 0, Child-Pugh A-B, single or 3 nodule ⩽ 3 cm Slightly increased bilirubin/increased portal pressure Associated diseases, yes or no
Liver transplantation	Performance status 0, single or 3 nodule ⩽ 3 cm Increased bilirubin/increased portal pressure Associated diseases, no
Sorafenib	Performance status 1-2, Child-Pugh A-B, Advanced stage (portal invasion), node classification 1, metastasis classification 1
TACE	Performance status 0, Child-Pugh A-B, Intermediate stage (multi nodular)

RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; HCC: Hepatocellular carcinoma.

developed and continue to develop[65,66].

Stereotactic body radiation therapy/stereotactic ablative radiotherapy: Stereotactic body radiation therapy (SBRT) for HCC has been documented in several recent studies[67-70]. Use of a cyberknife is an SBRT system that allows for real-time tracking of a tumor. The system affords good local tumor control and higher overall survival rates than other historical controls such as best supportive care or sorafenib therapy[70]. SBRT is a salvage treatment for unresectable HCC patients who failed or were unsuitable for TACE[71] or for patients with an unresectable massive HCC for whom standard treatment care is unsuitable[72]. Repeated stereotactic ablative radiotherapy in selected HCC patients might be feasible, if toxicity levels are acceptable[73].

Other therapies: Proton and carbon ion therapies for 343 HCC-patients showed that the 5-year local control and overall survival rates were 91% and 38%, respectively[74]. These therapies might be alternatives to conventional local therapies for HCC[74-77]. Additionally, laparoscopic liver resection appears to offer at least short-term benefits in selected HCC patients[78,79] whereas it is a widely employed alternative to open surgery in well-selected candidates. Standardization of surgical techniques might facilitate the performance of safe procedures[79].

FOLLOW-UP

After a curative treatment such as surgical resection or RFA, antiviral therapies should be considered in patients infected with chronic HBV and/or HCV[38,49,50,80,81]. In HCV-infected individuals, interferon-free regimens might be beneficial[82]. Hepatic resection was recommended in non-B and non-C patients[83] because unknown causes of HCC might be present in these patients, and particularly careful follow-up is needed.

CONCLUSION

Many reviews on this topic have been published in the last few years, and most prestigious scientific societies worldwide provide practical treatment guidelines that are regularly updated, including HCC treatment algorithms (Table 1)[16,84-87]. Liver transplantation and surgical resections are regarded as the only curative treatments; however, they have different indications. Although liver transplantation has not received priority over surgical resection, the most reliable therapy for HCC patients, presently, appears to be liver transplantation because its survival rate is superior to that of the other treatments. On this point, this review might differ from other practical guidelines or treatment algorithms. Deceased-donor liver-transplantation is limited by the shortage of grafts, and living-donor liver-transplantation should be discussed. If it is impossible for an HCC patient to undergo liver transplantation, then surgical resection or RFA, should be considered, in accordance with the liver function of the patient. We expect that stronger molecular targeted drugs will be used in the treatment of HCC patients and that these treatments will have more potency and fewer adverse events than are observed with sorafenib treatment. In the near future, methods of promoting hepatic regeneration might be improved. Further studies are ongoing.

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REVIEW

Psychiatric and substance use disorders co-morbidities and hepatitis C: Diagnostic and treatment implications

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Abstract

Chronic hepatitis C virus (HCV) viral infection is the most common blood-borne viral infection and approximately 2%-3% of the world's population or 170-200 million people are infected. In the United States as many as 3-5 million people may have HCV. Psychiatric and substance use disorders (SUDs) are common co-morbid conditions found in people with HCV and are factors in predisposing people to HCV infection. Also, these co-morbidities are reasons that clinicians exclude people from antiviral therapy in spite of evidence that people with HCV and co-morbid psychiatric and SUD can be safely and effectively treated. Furthermore, the neuropsychiatric side effects of interferon (IFN), until recently the mainstay of antiviral therapy, have necessitated an appreciation and assessment of psychiatric co-morbidities present in people with HCV. The availability of new medications and IFN-free antiviral therapy medication combinations will shorten the duration of treatment and exposure to IFN and thus decrease the risk of neuropsychiatric side effects. This will have the consequence of dramatically altering the clinical landscape of HCV care and will increase the number of eligible treatment candidates as treatment of people with HCV and co-morbid psychiatric and SUDs will become increasingly viable. While economically developed countries will rely on expensive IFN-free antiviral therapy, less developed countries will likely continue to use IFN-based therapies at least until such time as IFN-free antiviral medications become generic. The current manuscript discusses the efficacy and viability of treating HCV in people with psychiatric and SUDs comorbidities, the treatment of the neuropsychiatric side effects of IFN -based therapies and the impact of new medications and new treatment options for HCV that offer the promise of increasing the availability of antiviral therapy in this vulnerable population.

Key words: Hepatitis C; Psychiatric disorders; Substance use disorders; Antiviral treatment

Core tip: Hepatitis C viral (HCV) is among the most

common blood-borne viral infections in the world. Although disease management strategies are often complicated by the high rate of psychiatric and substance use disorders (SUDs) within this population, studies now indicate that neuropsychiatric side effects can be effectively managed during antiviral therapy and that individuals with pre-existing psychiatric and SUDs can be treated successfully and achieve sustained virologic response. Furthermore, the development of new medication options for the treatment of HCV has provided additional opportunities for treatment of people with HCV who have - or are at risk for - psychiatric illness.

Hauser P, Kern S. Psychiatric and substance use disorders co-morbidities and hepatitis C: Diagnostic and treatment implications. *World J Hepatol* 2015; 7(15): 1921-1935 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i15/1921.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i15.1921

HEPATITIS C: AN OVERVIEW

Prevalence

Hepatitis C virus (HCV) is among the most common blood-borne viral infections in the world. Approximately 3% of the world's population or 170-200 million people are infected, and an estimated 35 million people are infected in the United States[1-3]. HCV is often asymptomatic for a decade or longer after initial infection, and if undiagnosed and untreated, increases the risk of liver fibrosis, cirrhosis, liver cancer, liver failure, and ultimately, death[1].

A study that assessed mortality rates between 1999 and 2004 found that there were a total of 56409 HCV related deaths in the United States during this 5 year period[4]. Over this same time period, mortality rates increased by 123% with a steady increase for those between ages 55 to 64. In the year 2004 alone, 7427 deaths accounted for 148611 years of potential life lost[4]. Furthermore, a subsequent study of 34480 HCV infected individuals and non HCV infected controls showed that HCV infected individuals who initiated or completed treatment, had a significantly reduced risk of mortality[5]. For these reasons, early detection of HCV and prompt antiviral treatment are of the utmost importance. Psychiatric and substance use disorders (SUDs) are common co-morbidities among individuals with HCV and are often barriers to antiviral treatment.

Sources of infection

Among the most common routes of HCV transmission, intravenous drug use (IVDU) in particular continues to be the most common and contemporary source of infection[6-8]. While much less frequent, HCV can be transmitted through sexual contact, or to infants born from an HCV infected mother[2]. Other routes of transmission are no longer common including blood transfusion, needle stick injuries or non-professionally applied tattoos[9].

HCV AND HEALTH RELATED QUALITY OF LIFE

Individuals with gastrointestinal disease in general and HCV in particular have a lower health related quality of life (HRQOL) than the general population[10,11]. Factors such as poorer work and social adjustment, lower acceptance of illness, higher illness stigma, poorer reported neurocognitive functioning and concentration, and higher levels of subjective physical symptoms are associated with lower HRQOL and are highly correlated with depressive symptomatology in these individuals[12]. Several studies suggest that patients with chronic liver disease (and HCV in particular) also have disproportionately high rates of pain-related diagnoses which may impair their functioning[13-17]. HCV is associated with several medical comorbidities including peripheral neuropathy, arthritis, and fibromyalgia. In one retrospective chart review study of 8224, Veterans with HCV, 67% had co-occurring pain- related diagnoses including arthropathy, low back pain, and/or arthritis and 56% had past or present SUD diagnoses[13]. Additional studies indicate that biopsychosocial factors are significantly related to pain severity and interference, where emotional distress, mood symptoms (such as depression) and sleep disturbance predicted pain severity[14,15,18] (Table 1).

Individuals with HCV have higher rates of depression than those without HCV and also have higher rates of depression when compared to those with other gastrointestinal diseases such as irritable bowel disease and irritable bowel syndrome[10], non-alcoholic fatty liver disease and hepatitis B virus[11]. Individuals with HCV are most likely to have comorbid psychiatric conditions; depression is the most common psychiatric diagnosis among these individuals and is directly related to lower HRQOL[19-22]. One study of 881 Veterans with HCV found that 37% were prescribed an antidepressant medication[22] (Table 2).

Overall, HCV has a negative impact on quality of life and overall functioning[23]. The stigma associated with known infection has a demonstrated effect on HRQOL and is often related to a lack of adequate education on HCV and antiviral treatment[1]. Further efforts to educate both individuals with HCV and treatment providers on the viability of treating those with comorbid psychiatric conditions, and in particular, depression may be of benefit.

PSYCHIATRIC AND SUD COMORBIDITIES AND TREATMENT

Treatment issues and disease management strategies are complicated by the extremely high rate of psychiatric and SUD in those who have HCV[19,22,24-29].

Historically, people with HCV and comorbid psychiatric

Table 1 Hepatitis C and pain related diagnoses

Ref.	*n*	Design	Assessments	Outcome
Whitehead *et al*[13]	8224	Retrospective chart review	Clinical data, diagnoses, and medical history	Pain and SUD diagnoses were common among HCV patients, and opioids were frequently prescribed
Morasco *et al*[14]	49	Subjective assessment	Clinical interview, medical records BDI-Ⅱ, SDS, HRQOL SF-36	Psychosocial variables, particularly depression severity, account for variance in pain intensity and pain functioning
Rogal *et al*[17]	1286	Retrospective cohort study	Self-report, symptom checklist and medical record	There is a high prevalence of pain and opioid use in patients with chronic liver disease
Morasco *et al*[15]	119	Subjective assessment	TLFB, self-report; MPI, BDI-II, PCS, CPSS, CPCI, SCID	Biopsychosocial factors significantly affected pain severity and pain interference in patients with HCV

HCV: Hepatitis C virus; SUD: Substance use disorder; BDI-Ⅱ: Beck depression inventory, second edition; MPI: Multidimensional pain inventory; PCS: Pain catastrophizing scale; CPSS: Chronic pain self efficacy scale; CPCI: Chronic pain coping inventory; HRQOL SF-36: Health related quality of life short form-36 items; SCID: Structured clinical interview for The Diagnostic and Statistical Manual of Mental Disorders Ⅳ; TLFB: Time line follow back.

Table 2 Hepatitis C and psychiatric comorbidities

Ref.	*n*	Design	Assessments	Outcome
Lehman *et al*[20]	120	Subjective assessment	BDI-Ⅱ, ASI, PCL, AUDIT, medical records	Clinically significant levels of depression anxiety, PTSD and alcohol-related problems were observed in patients with HCV
Fireman *et al*[19]	293	Prospective assessment	AUDIT-C, BDI-Ⅱ	Psychiatric and substance use disorders are highly prevalent among veterans with chronic HCV
Rowan *et al*[21]	62	Subjective assessment	HRQOL SF-36	Psychosocial factors, especially depression, are strong indicators of impaired HRQOL for HCV-infected Veterans
Bini *et al*[41]	4084	Prospective cohort study	Eligibility for IFN therapy based on medical chart review of psychiatric and SUDs	The majority of veterans were not considered suitable candidates for HCV treatment because of substance use disorders, psychiatric disease, and comorbid medical disease
Mikocka-Walus *et al*[10]	139	Cross-sectional assessment	HADS, SCL-90, HRQOL SF-12, disease severity assessments	Patients with HCV had significantly higher prevalence of depression and lower HRQOL than patients with IBD and IBS, and the general population
Nelligan *et al*[22]	881	Subjective assessment	BDI-Ⅱ; medical records	Rates of depression are high among veterans with HCV and persist among those with antidepressant prescriptions
Weinstein *et al*[11]	878	Retrospective chart review	Clinical and demographic data, medical history	Individuals with HCV have a higher prevalence of depression than HBV and NAFLD patients and the general population

BDI-Ⅱ: Beck depression inventory, second edition; ASI: Anxiety severity index; PCL: Post traumatic stress disorder check-list; AUDIT: Alcohol use disorders identification test; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HRQOL SF-36: Health related quality of life short form-36 items; IFN: Interferon; IBD: Irritable bowel disease; IBS: Irritable bowel syndrome; SCL-90: Symptom checklist 90; HADS: Hamilton Anxiety and Depression Scale; PTSD: Post-traumatic stress disorder.

diagnoses were not included in initial research treatment studies for various reasons including the subjective belief that individuals with co-morbid psychiatric and SUDs would be less likely to be compliant and therefore not complete treatment, more likely to develop neuro-psychiatric side effects (in particular depression), and more likely to be re-infected if they continued IVDU[30,31].

Until recently interferon-based therapies have been the standard of care for HCV treatment. However, these therapies are known to induce depression, among other neuropsychiatric problems including insomnia, irritability and mood changes[27,32-34]. Depression co-morbidity is of particular concern as interferon (IFN) precipitates depression in approximately 20%-30% of individuals who receive IFN-based antiviral therapies[24,27,35]. Those treated with IFN-α therapy often develop depressive symptoms, which can lead to reduction in medication dosage or treatment discontinuation, thus reducing the likelihood of antiviral therapy completion or achieving a sustained virologic response (SVR)[27]. IFN-based treatments are also likely to exacerbate preexisting psychiatric conditions including depression and bipolar disorder and in isolated cases, have led to suicidal ideation and suicide attempts[35-37]. The severity of depressive symptoms prior to beginning antiviral therapy but not the diagnosis of past or present major depressive disorder (if adequately treated with antidepressants - see Hauser *et al*[38], 2009) may be predictive of the onset and severity of depressive symptoms during IFN-based antiviral treatment[24,27,35,38,39] (Table 3).

Several studies suggest that individuals with psychiatric and alcohol use disorders are more likely to be considered ineligible for antiviral therapy even though other studies suggest that completion of therapy and achieving SVR among other variables is not different between people with HCV and co-morbid psychiatric disorders from those with HCV without psychiatric and SUDs[38,40-43]. One study that compared antiviral completion rates, SVR, emergency room visits and hospitalizations of HCV infected Veterans with pre-existing major depressive disorder (MDD) treated with antidepressants to those without MDD found no differences between groups[38].

People with schizophrenia and co-morbid HCV have

Table 3 Neuropsychiatric side effects of interferon and interferon-induced depression

Ref.	*n*	Design	Treatment	Outcomes
Fried *et al*[32]	-	Retrospective literature review	PEGIFN-α-2a and 2b with RBV, IFN-α -2b/RBV	Across studies, depression occurred in 22% of those treated with PEGIFN-α-2a/RBV, 31% with PEGIFN-α-2b/RBV and 30%-34% of those treated with standard IFN treatment (PEGIFN-α-2b/RBV)
Fried *et al*[33]	1121	Randomized clinical trial	PEGIFN-α-2a/RBV, IFN-α-2b/RBV, PEGIFN-α-2a	Patients treated with PEGIFN-α-2a plus RBV or placebo had a lower incidence of depression than those treated with IFN-α-2b plus RBV (22% and 20% *vs* 30%)
Loftis *et al*[16]	-	Retrospective literature review	IFN-α, IFN-β, and IFN-γ	Symptoms of depression induced by IFN therapy is common and can limit the treatment utility, often necessitate discontinuation of IFN treatment or the use of psychopharmacologic agents. Depression is also a suspected side effect of therapy with IFN-β and IFN-γ; however, the association has not been as convincingly confirmed
Hauser *et al*[34]	-	Retrospective literature review	IFN-α	Neuropsychiatric side effects such as depression, may develop as a result of IFN therapy and lead to lower HRQOL, dose reductions or discontinuation
Raison *et al*[35]	162	Longitudinal assessment	PEGIFN-α-2b	Moderate to severe depressive symptoms occurred frequently during PEGIFN/RBV treatment and was predicted by baseline depression scores and higher doses of RBV
Inder *et al*[37]	1	Retrospective case report	IFN-α-2a/RBV	Suicide attempt occurred during IFN-α treatment, improvements were only seen with drug discontinuation. Following re-challenge with combination therapy, patient again experienced suicidal ideation
Loftis *et al*[18]	32	Prospective cohort study	PEGIFN-α-2a and 2b/RBV	IFN therapy results in a significant increase in depressive symptoms over time, with neuro-vegetative and somatic symptoms of depression increasing more than other depressive symptoms

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; IFN: Interferon; HRQOL: Health related quality of life.

also been excluded from IFN-based antiviral therapy despite a higher prevalence of HCV among this group than in the general population[44,45]. However, retrospective chart review studies suggest that people with schizophrenia and co-morbid HCV can be treated safely with IFN-based antiviral therapy and achieve similar SVR rates as those without co-morbid psychiatric disorders and with no greater likelihood of adverse events or emergency room visits[43,46].

Previous studies have also indicated that individuals with SUDs, particularly intravenous drug users (IVDUer) are also underserved and undertreated for fear of decreased compliance and/or risk of reinfection[31]. Although findings are variable, more recent research indicates that treatment completion is viable when these individuals are carefully supervised, and furthermore, that risk of reinfection is minimal, even among those who continue to use intravenous (*iv*) drugs post- antiviral treatment[31,47,48] (Table 4).

While less common, IFN-based regimens can also induce muscle aches and pain which may only serve to exacerbate depressive symptoms. Neurocognitive and somatic symptoms associated with depression are known to be exacerbated with IFN regimens and, for those with preexisting pain conditions, depression severity may increase pain intensity[14,15,49]. Though somatic symptoms should not be used as a primary predictor of depression severity, pain should be assessed and monitored in relation to cognitive and affective symptoms, when monitoring patients prior to and during treatment for HCV[50].

Overall, the emergence or exacerbation of depressive symptoms is common in IFN-α therapy and can compromise the outcome of HCV treatment[30]. As such, routine screening for psychiatric disorders and early treatment intervention for psychiatric disorders not previously identified are necessary prior to initiation of antiviral therapy[19,51]. Also ongoing routine screening for new onset depression during antiviral therapy is indicated. Furthermore, treatment plans must include monitoring of comorbid psychiatric conditions throughout the course of antiviral therapy[51,52].

Untreated IFN-induced depression may lead to dose reductions and premature IFN therapy termination and in worst case scenarios risk of suicide. However, if well monitored and managed, psychiatric and SUD comorbidities do not pose a significant impediment to treatment completion and compliance[47,51,52].

DEPRESSION MANAGEMENT DURING IFN-BASED ANTIVIRAL THERAPY

As mentioned, studies suggest that preexisting psychiatric and SUDs should not be regarded as exclusionary to IFN-α therapy. Specific to depression, IFN may induce or exacerbate symptoms of depression but these symptoms can be managed during antiviral therapy and do not prevent/preclude individuals from completing treatment or achieving favorable viral clearance rates[24,36,38,52,53].

Studies suggest that the onset of depressive symptoms during IFN therapy is not predicted by age, gender, past history of MDD or substance use[24,27,35,52]. Some studies suggest that people with higher depressive symptom severity prior to antiviral therapy initiation as well as a family history of MDD are more likely to develop IFN-induced depression. However, open-label studies of antidepressants and specifically selective serotonin reuptake inhibitors (SSRIs) in people who develop IFN-induced depression during antiviral therapy, demonstrate

Table 4 Antiviral treatment response rates in patients with psychiatric and substance use disorders comorbidities

Ref.	*n*	Design	Treatment	Outcomes
Dalgard *et al*[31]	27	Longitudinal assessment	IFN-α-2a	Rate of reinfection was not significantly different among IVDUers treated for HCV as compared to non IVDUers despite reinitiation of injection drug use in 33% of IVDUers
Loftis *et al*[27]	39	Prospective cohort study	IFN-α-2b/RBV	Gender, past history of MDD, and past history of SUD were not significantly associated with response rates
Backmund *et al*[47]	18	Longitudinal assessment	IFN-α-2a, IFN-α-2a/RBV	IVDUers can be reinfected after treatment for HCV infection, but the reinfection rate is minimal and should not jeopardize the potential benefit for most patients
Chainuvati *et al*[40]	647	Retrospective database review	Eligibility/treatment rates for Interferon therapy	Therapy completion and SVR rates are similar among Veterans with and without psychiatric or SUDs, challenging the perception that adherence is worse as a result of psychiatric co-morbidities
Anand *et al*[42]	4061	Longitudinal assessment	IFN-α-2b/RBV	Patients with and without mild to moderate alcohol use had comparable completion and SVR rates to antiviral treatment
Hauser *et al*[38]	55	Retrospective chart review	PEGIFN/RBV, IFN/RBV	People with MDD had completion and SVR rates similar to those without psychiatric illness. Patients with MDD can be safely and effectively treated with antiviral therapy provided that they are on antidepressant medications during antiviral therapy
Huckans *et al*[43]	60	Retrospective chart review	PEGINF/RBV, IFN/RBV	Patients with schizophrenia experience similar rates of psychiatric symptoms on and off antiviral therapy
Grebely *et al*[48]	58	Prospective longitudinal follow up	IFN-α-2b/RBV, PEGIFN-α-2a, PEGIFN-α-2b	Rate of reinfection following treatment for HCV infection among current and former IVDUers engaged in a multidisciplinary program is low

IFN-α: Interferon alpha; IVDUer: Intravenous drug user; RBV: Ribavirin; MDD: Major depressive disorder; SUD: Substance use disorder; SVR: Sustained virologic response; PEGINF: Peglyated interferon (peginterferon); IFN: Interferon.

Table 5 Antidepressant treatment of interferon-induced depression

Ref.	*n*	Design	Antidepressant	Outcomes
Gleason *et al*[54]	15	Open-label clinical trial	Citalopram	IFN-induced MDD in patients with HCV may be effectively and safely treated with citalopram
Hauser *et al*[24]	39	Prospective cohort study	Citalopram and buproprion	33% of patients receiving IFN therapy develop IFN-induced MDD. There were no differences in age, gender, past history of MDD, or substance use between those who became depressed and those who did not. Of those who developed IFN-induced depression most responded to antidepressant treatment allowing continuation of antiviral therapy. Also the group who developed IFN-induced depression had significantly higher baseline BDI scores than the group who did not develop IFN- induced depression
Loftis *et al*[27]	-	Various antidepressants	IFN-α, IFN-β, and IFN-γ	Depression induced by IFN therapy is common and can limit treatment utility and necessitate discontinuation of antiviral treatment. However, the use of psychopharmacologic agents allows treatment continuation
Angelino *et al*[36]	-	Various antidepressants	IFN-α	Treatment with IFN may provoke episodes of depression however, several standard treatments for depression can mediate these symptoms, suggesting that depression may not be a barrier to effective treatment
Gleason *et al*[55]	18	Open-label clinical trial	Escitalopram	IFN-induced MDD in patients with HCV may be effectively and safely treated with escitalopram

HCV: Hepatitis C virus; IFN: Interferon; RBV: Ribavirin; MDD: Major depressive disorder; BDI-Ⅱ: Beck depression inventory, second edition.

that these medications can be effective in managing depressive symptoms during IFN therapy and allow people to remain on antiviral treatment[24,54,55] (Table 5).

Antidepressant prophylaxis of patients with HCV who receive antiviral therapy

Antidepressant prophylaxis may decrease the likelihood of the development of IFN-induced depressive symptoms and MDD in HCV infected patients, particularly those with a past history of IFN-induced MDD, and may increase the rates of treatment compliance and completion[36,56].

One study of people with HCV who failed antiviral therapy due to IFN-induced depression found that citalopram is effective both before and during IFN-α therapy; used as pretreatment for these people with HCV, it helped to reduce the incidence of MDD during the first 6 mo of antiviral treatment as compared with two control groups[57]. As mentioned several studies have shown that, for those who developed MDD during IFN therapy, treatment with SSRIs led to a reduction in depressive symptoms and continuation of antiviral therapy[24,54,55].

In contrast, two double blind, placebo-controlled trials that assessed the benefit of prophylactic treatment (or pre-treatment prior to initiation of antiviral therapy) with paroxetine to prevent development of IFN-induced depression found no benefit as compared with placebo in antiviral treatment naïve people with HCV[58,59]. However, in one of these studies, of 11 patients who developed IFN-induced depression during the study and were then

Table 6 Antidepressant prophylaxis

Ref.	*n*	Design	Antidepressant	Outcomes
Angelino *et al*[36]	-	Retrospective literature review	Citalopram; fluvoxamine	Prophylactic antidepressants might be well-considered for patients with a family history of - or previous episodes of - depression
Schaefer *et al*[57]	33	Prospective clinical trial	Citalopram	Pre-treatment of psychiatric patients with citalopram significantly reduced the incidence of IFN-induced MDD during the first 6 mo of antiviral treatment
Raison *et al*[59]	61	Double-blind, placebo-controlled clinical trial	Paroxetine	Data support the use of antidepressant pre-treatment in HCV patients with elevated depressive symptoms at baseline
Morasco *et al*[58]	33	Double-blind, placebo-controlled clinical trial	Paroxetine	A prophylactic approach to reduce IFN-α-induced depression may not be indicated in patients with HCV
Galvão-de Almeida *et al*[56]	-	Retrospective literature Review	Citalopram, paroxetine, escitalopram	Antidepressant prophylaxis may blunt the magnitude of depressive symptoms in HCV patients and raise the rates of treatment completion in those with psychiatric diagnosis
Morasco *et al*[60]	39	Double-blind, placebo-controlled clinical trial	Citalopram	Citalopram is not superior to placebo in preventing IFN-induced MDD

IFN: Interferon; MDD: Major depressive disorder; HCV: Hepatitis C virus.

entered into the open - label rescue arm of the study, 10 of 11 had a significant reduction of depressive symptoms that allowed continuation of antiviral treatment[58]. In the second study, assignment to paroxetine did not decrease the likelihood of IFN-induced depression but was associated with a significantly reduced depression symptom severity score. Although sample sizes were small, these results suggest that prophylactic treatment with paroxetine is not effective in preventing the onset of IFN-induced MDD but may have benefits in reducing overall depression symptom severity[58,59].

A more recent double-blind, placebo-controlled trial that assessed the benefit of prophylactic treatment with citalopram in 39 HCV infected patients who did not have significant symptoms of depression prior to initiation of antiviral therapy reported similar results. Randomization to citalopram did not significantly reduce the likelihood of developing IFN-induced depression as compared with placebo[60] (Table 6).

Overall, there is no substantive evidence that antidepressant prophylaxis during antiviral therapy for HCV has significant benefits. Potential benefits must be weighed against the risks of antidepressant use above and beyond their common side effects. The use of SSRIs, which have been associated with an increased incidence of gastrointestinal bleeding in the general population[61], may have adverse consequences in people with HCV who are at higher risk for low platelet count, coagulopathy, and esophageal varices[62]. Furthermore, SSRIs have been associated with retinal hemorrhages in people receiving high - dose IFN therapy for malignant melanoma[63]. Other observations in the general population suggest that mirtazapine and sertraline may increase the likelihood of neutropenia[64].

In summary, the wide-spread use of antidepressants to prevent IFN-induced depression in people receiving IFN-based therapy for HCV is not warranted. A more conservative approach involves screening all patients prior to initiation of antiviral therapy for depression, treating depression prior to beginning antiviral therapy, and proactively monitoring depressive symptomatology at regular intervals during the course of treatment.

Interdisciplinary team/integrated care

Optimal care for HCV is best provided by an interdisciplinary team approach that involves mental health care providers. Individuals with psychosocial comorbidities are able to successfully complete treatment, when an interdisciplinary team with both medical and mental health support is applied[65]. The early identification of depression during HCV treatment can be achieved using an integrated model of care and can also assist individuals who have both mild or severe psychiatric illness in initiating and completing antiviral treatment[66]. Individuals who receive care from an interdisciplinary team are more likely to complete the evaluation for HCV treatment and start antiviral treatment[67].

NEW MEDICATION TREATMENT OPTIONS FOR HCV

The use of new Food and Drug Administration (FDA)-approved medications for the treatment of HCV has distinct advantages when considering antiviral therapy in people with HCV and co-morbid psychiatric and SUDs, in large part, because the duration of antiviral therapy and therefore the period of risk for IFN-induced depression as well as other common neuropsychiatric side effects has been shortened. Moreover, medications in development to treat HCV will eliminate the need for IFN altogether. A review of new FDA-approved medications as well as medications under development and their neuropsychiatric side effects are reviewed briefly-below.

Telaprevir

Telaprevir used in combination with peginterferon α (PEGIFN-α) and ribavirin (RBV) has been shown to improve response rates in the treatment of HCV, genotype 1[68,69]. It can be used for those with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with IFN-based therapies, including prior non- responders, partial

Table 7 Telaprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Hézode *et al*[73]	334	Phase 2 randomized clinical trial	Telaprevir PEGIFN/RBV	HCV genotype 1 - treatment naïve	Telaprevir groups had significantly higher rates of SVR than PEGIFN/RBV alone. Depression occurred in 20%-23% of patients and was not significantly different across groups
McHutchison *et al*[68]	115	Randomized clinical trial	Telaprevir	HCV genotype 1 - previous non-responders to PEGINF/RBV	Re-treatment with telaprevir was more effective than PEGIFN-α/RBV alone. Depression occurred in 11%-17% of participants
Zeuzem *et al*[69]	663	Phase III randomized clinical trial	Telaprevir, PEGIFN-α-2a/ RBV	HCV genotype 1 - previous non responders, partial responders and relapsers	Telaprevir in combination with PEGIFN/RBV significantly improved rates of SVR and, as compared with PEGIFN/RBV alone showed no increase in neuropsychiatric side effects
Kumada *et al*[72]	1126	Multicenter randomized clinical trial	Telaprevir, PEGIFN-α-2b/RBV	HCV genotype 1 - treatment naive	Triple therapy with telaprevir-based regimen resulted in higher SVR with shorter duration. Depression was not listed as an adverse event
Sherman *et al*[74]	540	Randomized clinical trial	Telaprevir PEGIFN-α-2a/RBV	HCV genotype 1 - treatment naïve	Combination therapy with telaprevir for 24 wk was non inferior to standard therapy for 48 wk. Fifty-three percent of patients experienced psychiatric symptoms

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response.

responders, and relapsers[70].

Despite several known side effects associated with telaprevir, including fatigue, rash, nausea, anemia and influenza like symptoms, changes in mood or depression are not known to be direct side effects of this medication[69]. While depressive symptoms have been noted in some clinical trials, they have not been considered primary adverse events nor have they led to drop out or discontinuation of treatment[68,69,71,72].

Telaprevir in combination with PEGIFN/RBV is superior to PEGIFN/RBV alone and has higher SVR (approximately 72% *vs* 50%-60%); it is also known to increase response time[68,69,72,73].

Overall, telaprevir may increase the ability to achieve SVR, without a drastic influence on the side effects profile[68]. The risk of depression is not noted to be increased when using telaprevir in combination with PEGIFN/RBV (Table 7).

Boceprevir

Boceprevir, a medication that is similar to telaprevir, is a potent oral HCV-protease inhibitor that is also used in conjunction with PEGIFN/RBV for the treatment of patients infected with HCV genotype 1. Studies indicate that rates of SVR are improved significantly when boceprevir is used in combination with PEGIFN/RBV as compared with PEGIFN/RBV alone[75,76].

While some side effects (such as anemia) commonly associated with PEGIFN/RBV may be more likely to occur with the addition of boceprevir, side effects associated with PEGIFN/RBV treatment regimens including dysgeusia, rash, dry skin, headache and flu-like symptoms are no more likely to occur with addition of boceprevir[75-77].

Based on the results of the above studies as well as prescribing information published by the FDA, common psychiatric side effects associated with PEGIFN/RBV are not more likely to occur in patients with the addition of boceprevir[78] (Table 8).

Simeprevir

Several studies have assessed the efficacy of simeprevir in combination with PEGIFN/RBV for the treatment of hepatitis C. Simeprevir is a HCV NS3/4A protease inhibitor indicated as a component of a combination antiviral treatment for the treatment of HCV[78].

Studies suggest that simeprevir in combination with PEGIFN/RBV significantly improves rates of SVR as compared with PEGIFN/RBV alone. Studies also suggest that the addition of simeprevir can shorten the duration of antiviral therapy to 24 wk (instead of 48 wk with PEGIFN/RBV alone) without a change in SVR or the side effects profile[79-83].

The most common adverse events found with the use of simeprevir in combination with PEGIFN/RBV include fatigue, headache, pruritus, influenza like illness, nausea and neutropenia[79-81]. However, in these studies there were non-significant differences in frequency of adverse events between groups on simeprevir in combination with PEGIFN/RBV *vs* PEGIFN/RBV, suggesting the side effects may be attributable to the PEGIFN/RBV[79-82].

Depression was not assessed with symptom rating instruments and noted only by self-report in these studies; overall the rates of self-reported depression were not different between the group that received simeprevir in combination with PEGIFN/RBV *vs* the group that received PEGIFN/ RBV alone and there were very few subjects who experienced depression as a major contributing factor for discontinuation[79,80].

In summary simeprevir does not increase the risk of side effects attributable to PEGIFN/RBV and can shorten the duration of antiviral therapy and thus the length of exposure to PEGIFN and presumably side effects associated with peginterferon treatment[81] (Table 9).

Sofosbuvir

Sofosbuvir is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of HCV infection as a component of a combination antiviral treatment

Table 8 Boceprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Kwo *et al*[77]	520	Two part randomized clinical trial	Boceprevir	chronic HCV genotype 1 - treatment naïve	Boceprevir has the potential to double the SVR rate compared with standard treatment alone. Insomnia was the only psychiatric illness documented
Bacon *et al*[75]	403	Placebo controlled, randomized clinical trial	PEGIFN-α-2b/RBV boceprevir, PEGIFN-α-2b/RBV	Retreatment of patients with chronic HCV genotype 1 infection	Boceprevir resulted in significantly higher rates of SVR. Significant onset of depression was not indicated
Poordad *et al*[76]	1097	Double blind, placebo controlled randomized clinical trial	Boceprevir PEGIFN-α-2b/RBV	Chronic HCV genotype 1 - treatment naïve	Boceprevir significantly increased the rates of SVR. Insomnia was the only psychiatric condition identified as an adverse event

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response.

Table 9 Simeprevir

Ref.	*n*	Design	Treatment	Population	Outcome
Fried *et al*[80]	338	Phase 2b double blind, placebo controlled randomized clinical trial	Simeprevir PEGIFN-α-2a/RBV	Treatment-naıve patients with HCV genotype 1 infection.	Simeprevir in combination with PEGIFN/RBV significantly improved SVR rates and shortened therapy duration. Depression occurred in 10.4% of patients on simeprevir and 18.2% on standard treatment
Zeuzem *et al*[79]	396	Placebo controlled, randomized clinical trial	Simeprevir, PEGIFN-α-2a/RBV	patients with HCV genotype-1 infection previously treated with PEGIFN/RBV	12, 24, or 48 wk simeprevir with 48 wk PEGIFN/RBV significantly increased rates of SVR and was generally well tolerated. Depression occurred in 2/396 simeprevir patients
Jacobson *et al*[81]	394	Phase 3, randomized, double blind, placebo controlled multicenter clinical trial	Simeprevir, PEGIFN-α-2a/RBV	Treatment naïve patients with HCV genotype 1	Simeprevir with PEGIFN-α-2a/RBV shortens therapy without worsening the adverse event profiles associated with PEGIFN
Manns *et al*[82]	257	Phase 3 multicenter randomized, placebo controlled clinical trial	Simeprevir PEGIFN-α-2a or 2b/RBV	Treatment-naive patients with HCV genotype 1 infection	Addition of simeprevir to PEGIFN-α-2a or PEGIFN-α-2b plus RBV improved SVR without worsening the known adverse events associated with peginterferon
Kumada *et al*[83]	79	Open label non comparative multicenter trial	Simeprevir PEGIFN-α-2b/RBV	HCV genotype 1 - treatment-naïve or had previously received IFN-based therapy	Simeprevir combined with PEGIFN-α-2b/RBV was effective across both groups. One patient in the control group receiving standard therapy alone discontinued due to grade 2 depression

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

regimen; it is recommended to be used with PEGIFN-α/RBV or with RBV alone thus excluding the need for IFN altogether[78].

The most common adverse events when used with PEGIFN/RBV combination therapy are fatigue, headache, nausea, insomnia and anemia (similar to those found in other combination therapies with PEGIFN). The most common adverse events (≥ 20%) for sofosbuvir and RBV combination therapy are fatigue and headache[84,85].

Overall results indicate that psychiatric issues, including depression, are not significant side effects and are rarely the reason for study drop out or discontinuation[85-87]. However the rates of depression in these studies, when reported, are below the generally accepted rate of IFN-induced depression, which is 20%-30%. While this may reflect the decreased duration of IFN exposure, these lower rates of depression may also be due to relying on patient report of side effects.

In summary, results indicate the sofosbuvir in combination with other medications can lead to an early viral response as well as SVR with a shorter duration of treatment, with and without the use of PEGIFN. Furthermore, sofosbuvir provides an effective treatment with little evidence of psychiatric side effects and overall, is well tolerated. Authors suggest that for most, there is no additional benefit to prolonging treatment beyond 12 wk when using a sofosbuvir based medication regimen[86].

Previous studies have indicated that the majority of people who develop IFN-induced depression have an onset between 6 and 12 wk after antiviral therapy initiation but approximately one third develop IFN-induced depression after 12 wk of antiviral therapy[38]. Thus it's possible that the use of sofosbuvir in combination with other therapies or alone, may reduce the risk of onset of depressive symptoms by decreasing or eliminating exposure to PEGIFN (Table 10).

HCV ANTIVIRAL MEDICATIONS IN DEVELOPMENT

ABT-450/r-Ombitasvir and dasabuvir with RBV

A new medication combination of ABT-450/r-Ombitasvir

Table 10 Sofosbuvir

Ref.	*n*	Design	Treatment	Population	Outcome
Kowdley *et al*[86]	316	Multicenter, open label, phase 2 clinical trial	Sofosbuvir-2a PEGIFN-α-2a/ RBV	HCV genotype 1 - non-cirrhotic treatment-naive, patients	SVR occurred in 90% of patients treated with sofosbuvir and PEGIFN/RBV for 12 wk. Depression occurred in 8%-16% of patients across all groups but was not a primary reason for discontinuation
Lawitz *et al*[87]	147	Two-cohort, phase 2, placebo controlled, clinical trial	Sofosbuvir PEGIFN/RBV	Treatment-naive patients with genotype 1-3 HCV infection	SVR occurred in 90% of patients treated with sofosbuvir and PEGIFN/RBV and the side effects profile was similar to that of PEGIFN/RBV and did not include depression. Depression was not a significant adverse event in this study
Jacobson *et al*[85]	240	Phase 3 randomized placebo controlled clinical trials	Sofosbuvir RBV	Chronic HCV genotype 2 or 3 previously unable to be treated with IFN, or previously treated with IFN-based therapies	Sofosbuvir and RBV was effective at 12 wk for genotype 2 and 16 wk for genotype 3. Premature discontinuation of the study drug due to adverse events was uncommon in all groups. Depression was not a significant adverse event in this study
Gane *et al*[84]	75	Open label randomized clinical trial	Sofosbuvir, RBV	HCV genotype 2 or 3 infection. with no response to prior treatment or with no prior treatment	Sofosbuvir plus RBV for 12 wk was effective for patients with genotype 1, 2, or 3 infections. Insomnia occurred in 30%-67% of participants across groups and was the only significant psychiatric symptom to develop during treatment

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

with dasabuvir has also been assessed both with and without the addition of RBV. Though not yet FDA approved, this combination has yielded promising results; 95% of previously treated individuals with HCV genotype 1 had SVR after 12 wk of treatment[88].

The most commonly reported adverse events of this combination include headache and fatigue, with secondary effects of pruritus (> 10% of participants) anemia, vomiting, constipation, erythema, neck pain, neutropenia and a decrease in hemoglobin (< 10% of participants). Signs and symptoms of depression are not a significant side effect for this combination treatment and does not contribute to discontinuation or drop out[88].

ABT-450/Ombitasvir and dasabuvir has also been assessed with the addition of ritonavir, either with RBV or placebo. Those treated with this regimen (both with and without RBV) have SVR rates of between 96.6% and 100% after 12 wk of treatment[89].

The most common adverse events were fatigue and headache, along with nausea and decreased hemoglobin. Participants in the RBV group also experienced insomnia, anemia, rash and increased bilirubin levels (all known to be side effects of RBV). Serious adverse events included cellulitis, nephrolithiasis and osteoarthritis, though none were judged to be study drug related or led to discontinuation. Outside of insomnia (noted above) no other psychiatric symptoms were reported for either group, both with and without RBV[89].

Overall, it appears this combination with and without ritonavir and/or RBV, is useful in treating HCV without the use of IFN.

Daclatasvir

Daclatasvir is a potent NS5A replication complex inhibitor, and is generally well tolerated in phase 1 and phase 2 trials[90]. It has been used successfully in various HCV genotypes, and in both treatment naïve and non-responder/relapser populations[90,91]. Daclatasvir has been used in combination with several other medications including PEGIFN/RBV, asunaprevir and sofosbuvir, all of which show varying levels of treatment success, as measured by SVR after 12 and 24 wk of treatment, and in some studies, SVR was obtained after 8 wk treatment duration[91-93]. In certain combinations, daclatasvir allows the use of IFN-free combinations for those unable to tolerate IFN and have been shown effective in those who previously failed telaprevir/boceprevir regimens[93,94].

Across studies, the most frequently reported adverse events are diarrhea, headache and nasopharyngitis, all of which were reported to be mild. Less common adverse events include abdominal discomfort, malaise, constipation and back pain. No studies reported psychiatric symptoms or adverse events[91,93,94].

Ledipasvir

Ledipasvir, another NS5A inhibitor has also resulted in high rates of SVR among both previously treated as well as treatment naïve patients with HCV[95,96]. The rates of SVR ranged from 97%-99% across groups given combination therapy of ledipasvir and sofosbuvir, with and without RBV at 12 and 24 wk. Additional assessments indicate that ledipasvir-sofosbuvir regimens given for 8 wk is associated with a high rate of SVR among both previously treated and treatment naïve patients with HCV genotype 1 including those with cirrhosis. No additional benefit was associated with the addition of RBV to this combination or with extension of the duration of treatment to 12 wk[97,98] (Table 10).

The most common adverse events across studies were fatigue, headache, insomnia, and nausea[95]. The incidence of adverse events was lower among patients

Table 11 Newer medications and interferon free therapies

Ref.	*n*	Design	Treatment	Population	Outcome
Pol *et al*[92]	48	Double blind parallel group, dose finding phase 2a randomized, placebo controlled clinical trial	Daclatasvir PEGIFN-α-2a/RBV	HCV genotype 1 - treatment-naive (without cirrhosis)	Daclatasvir increases the antiviral potency of PEGIFN/RBV without increasing the side effects profile. Psychiatric adverse events were not significant in this study
Chayama *et al*[91]	10	Open label phase 2a clinical trial	Daclatasvir asunaprevir	Chronic HCV genotype 1b - previous null responders to PEGINF/RBV	Dual therapy with daclatasvir and asunaprevir alone can achieve high rates of SVR in difficult-to-treat patients and has minimal side effects
Herbst *et al*[90]	-	Retrospective literature review of phase 1 to phase 3 clinical trials	Daclatasvir	All genotypes; treatment naive and experienced cohorts	Daclatasvir has a potent antiviral effect and clinical efficacy across genotypes and in both treatment naive and experienced cohorts with no evidence of psychiatric adverse events
Suzuki *et al*[94]	43	Open label phase 2a clinical trial	Daclatasvir asunaprevir	HCV genotype 1b for patients with limited treatment options including those with complications of depression	Dual therapy with daclatasvir and asunaprevir was well tolerated and achieved high SVR rates. The adverse event profile was favorable; no psychiatric abnormalities were reported
Zeuzem *et al*[88]	394	Phase 3 placebo controlled randomized clinical trial	ABT-450 ritonavir (ABT-450/r), ombitasvir (ABT-267) dasabuvir (ABT-333) RBV	Retreatment of HCV in patients who were previously treated with peginterferon-ribavirin	Rates of response to a 12-wk IFN-free combination regimen were more than 95%. Psychiatric adverse events were not reported
Andreone *et al*[89]	179	Phase 3 open label randomized clinical trial	ABT-450, ritonavir, ombitasvir, dasabuvir RBV	HCV genotype 1b - treatment experienced patients	ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without RBV, produced a high rate of SVR. Both regimens were well tolerated with minimal adverse events
Sulkowski *et al*[93]	167	Two part, open label clinical trial	Daclatasvir sofosbuvir	HCV genotype 1, 2, or 3	Daclatasvir plus sofosbuvir was associated with high rates of SVR. Psychiatric problems were not listed as significant adverse events
Afdhal *et al*[96]	865	Phase 3, open-label randomized clinical trial	Ledipasvir sofosbuvir RBV	HCV genotype 1 - treatment naive	Ledipasvir–sofosbuvir with or without RBV for 12 or 24 wk was highly effective. The most common adverse events were fatigue, headache, Insomnia, and nausea
Lawitz *et al*[98]	100	Open label randomized clinical trial	Sofosbuvir ledipasvir RBV	HCV genotype 1 - treatment-naive or previously treated with a protease-inhibitor regimen	Sofosbuvir-ledipasvir alone or with RBV has the potential to cure most patients with genotype-1. Psychiatric symptoms were not a listed as significant adverse events
Afdhal *et al*[95]	440	Phase 3, randomized, open-label clinical trial	Ledipasvir sofosbuvir RBV	HCV genotype 1 - previously treated	Treatment with ledipasvir and sofosbuvir resulted in high rates of SVR. Neuropsychiatric side effects were minimal, but were observed more frequently among groups with the RBV-containing regimen than ledipasvir sofosbuvir alone
Kowdley *et al*[97]	647	Phase 3, open label clinical trial	Sofosbuvir ledipasvir	HCV genotype 1 - treatment naive	Ledipasvir-sofosbuvir was associated with a high rate of SVR. Adverse events were more common in the group that received RBV. No additional benefit was associated with the inclusion of RBV

PEGIFN: Pegylated interferon (peginterferon); RBV: Ribavirin; HCV: Hepatitis C virus; SVR: Sustained virologic response; IFN: Interferon.

receiving ledipasvir-sofosbuvir alone than among those receiving ledipasvir-sofosbuvir plus RBV[95-98]. Patients in the groups that received ledipasvir - sofosbuvir plus RBV for 12 or 24 wk had higher rates of events known to be associated with RBV therapy-fatigue, insomnia, asthenia, rash, cough, pruritus, and anemia-than did those in the corresponding groups that received ledipasvir-sofosbuvir without RBV[95,96]. Few to no patients dropped out of the study or discontinued due to adverse events, and in some cases, even those who discontinued still achieved a SVR[96]. Overall, no psychiatric adverse events were reported across studies and none led to discontinuation[95-98] (Table 11).

In summary, these new medications will shorten the duration of treatment and also allow IFN-free combination therapy, thus reducing dramatically the risk of neuropsychiatric symptoms and, in particular, depression.

SUMMARY

HCV infection is known to decrease HRQOL, an issue only exacerbated by various psychosocial factors and psychiatric illness. Antiviral therapy with HCV is often

complicated by pre-existing depression as well as other psychiatric illnesses including schizophrenia, bipolar disorder and SUD. The common neuropsychiatric side effects - in particular depression - associated with IFN-based therapies made antiviral therapy problematic and often resulted in exclusion of people who had pre-existing depression or other psychiatric illnesses. However, various studies have shown that neuropsychiatric side effects can be successfully managed during IFN-based antiviral therapy and that people with pre-existing psychiatric illness can be treated successfully and achieve SVR within interdisciplinary care models that involve mental health care providers. The use of interdisciplinary teams has been shown to increase the likelihood of treatment completion for patients with psychiatric illnesses. This approach must be fostered because IFN-free antiviral therapy will not be immediately available due to the prohibitively high cost of these medications. Furthermore, the cost will likely impact treatment viability in developing countries.

The development of new medication options for the treatment of HCV has provided additional opportunities for treatment of people with HCV who have - or are at risk for - psychiatric illness. For those who can tolerate the side effects of IFN and are compliant with treatment, the addition of telaprevir or simeprevir can significantly decrease treatment duration, and thereby decrease the likelihood of developing depressive and other psychiatric symptomatology. Moreover, sofosbuvir based regimens remain the most viable FDA approved drug at this time. New medications under development will allow IFN-free medication combinations and higher rates of SVR, with little to no risk of developing or exacerbating preexisting depressive symptoms.

LIMITATIONS

Despite new treatment options, there are several factors that should be considered. One consideration is that the use of newer direct acting antiviral (DAA) medications such as telaprevir, boceprevir, simeprevir, sofosbuvir, ombitasvir and dasabuvir may be limited by drug to drug interactions. While studies identify minimal neuropsychiatric risks directly associated with the use of various DAAs, they can potentially interact with a variety of psychotropic agents causing unwanted adverse effects which may alternatively and indirectly affect treatment outcomes[99,100]. Triazolam, oral midazolam, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine and pimozide, are among psychotropic medications known to be contraindicated with DAAs[99,100].

A second consideration is that medications under development may not be options for all genotypes of HCV or for those with severe liver disease. Furthermore, these medications are costly, with some estimated to be $1000/pill, and thus, may not be a viable option in less developed countries and/or families with low SES or lack of insurance for whom this cost is too great.

A final limitation of this review is that the vast majority of studies related to medications under development may have excluded patients with preexisting psychiatric diagnoses or those in historical underserved health disparity populations. So called "real world" clinical trials are necessary in order to assess the viability of these new medications in underserved populations. However, the shorter duration of antiviral therapy and the availability of IFN-free therapies hold great promise for the future of HCV treatment.

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REVIEW

Hepatitis C in human immunodeficiency virus co-infected individuals: Is this still a "special population"?

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Abstract

A substantial proportion of individuals with chronic hepatitis C virus (HCV) are co-infected with human immunodeficiency virus (HIV). Co-infected individuals are traditionally considered as one of the "special populations" amongst those with chronic HCV, mainly because of faster progression to end-stage liver disease and suboptimal responses to treatment with pegylated interferon alpha and ribavirin, the benefits of which are often outweighed by toxicity. The advent of the newer direct acting antivirals (DAAs) has given hope that the majority of co-infected individuals can clear HCV. However the "special population" designation may prove an obstacle for those with co-infection to gain access to the new agents, in terms of requirement for separate pre-licensing clinical trials and extensive drug-drug interaction studies. We review the global epidemiology, natural history and pathogenesis of chronic hepatitis C in HIV co-infection. The accelerated course of chronic hepatitis C in HIV co-infection is not adequately offset by successful combination antiretroviral therapy. We also review the treatment trials of chronic hepatitis C in HIV co-infected individuals with DAAs and compare them to trials in the HCV mono-infected. There is convincing evidence that HIV co-infection no longer diminishes the response to treatment against HCV in the new era of DAA-based therapy. The management of HCV co-infection should therefore become a priority in the care of HIV infected individuals, along with public health efforts to prevent new HCV infections, focusing particularly on specific patient groups at risk, such as men who have sex with men and injecting drug users.

Key words: Human immunodeficiency virus; Hepatitis C; Coinfection; Antiviral agents; Anti-retroviral agents; Natural history; Epidemiology; Pathogenesis; Therapy

Core tip: This manuscript focuses on hepatitis C virus/human immunodeficiency virus (HIV) co-infection, two intersecting epidemics with great global health interest. It reviews the epidemiology, pathogenesis and natural history of chronic hepatitis C in HIV infected individuals. It also reviews the impact of antiretroviral therapy on the natural history of chronic hepatitis C and the liver. Moreover, it shows that the outcomes of treatment with the newer direct acting antivirals against hepatitis C are similar in the mono-infected and co-infected patients, providing informative data extracted from relevant clinical trials. It argues that HIV infected individuals should no longer be designated as a "special population" among those with chronic hepatitis C, as this could delay their access to the new treatments.

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INTRODUCTION

Co-infection with the blood-borne hepatitis C Virus (HCV) and human immunodeficiency virus (HIV) is common due to their shared routes of transmission and the fact that individuals with HIV are at higher risk of contracting HCV. Estimates of HCV prevalence in the general population overall vary from 0.3% in Austria, England and Germany to 8.5% in Egypt[1]. However, in the HIV population, the prevalence of HCV/HIV co-infection has been reported between 9.2%-37.3%[2,3]. This population has long been considered a special risk population both in terms of disease progression and subsequent mortality, and in terms of their inferior responses to traditional HCV therapies. However, in the ever-evolving era of direct-acting antivirals (DAAs) we ask the question "Is this still a special population?".

EPIDEMIOLOGY OF HCV/HIV CO-INFECTION

Following its discovery 25 years ago and until recently, HCV was considered a disease of parenteral transmission, affecting people who inject drugs (PWIDs) who share needles or drug-taking equipment and of individuals who received infected blood products prior to the introduction of reliable screening in the 1990s. Largely this is still the case in less developed regions such as sub-Saharan Africa where HCV/HIV co-infected individuals tend to be older than those with HIV mono-infection, likely reflecting improvements to healthcare sterility and blood screening[4]. In almost all countries in the world there is a male preponderance for HCV infection overall, in keeping with higher levels of intravenous drug use in men, except in France and Germany where more women are affected, with the risk factor for acquisition being blood transfusion after childbirth[1].

It is estimated that in 2010 around 10 million PWIDs (range 6.0-15.2 million) were HCV seropositive. This is over three and a half times higher than the 2.8 million people estimated to be infected with HIV[5]. A review of worldwide systematic reviews demonstrated that the midpoint prevalence of co-infection in PWIDs varies greatly between countries ranging from 9.8% in Paraguay to 97% in Mexico. Those countries with the highest estimated populations of PWIDs were China, Russia and the United States with HCV prevalence of 67%, 72.5% and 73.4%, respectively. However, these statistics under-represent the total burden of HCV from drug use as they do not include former PWIDs who have previously been infected with HCV.

Blood-borne viruses account for much of the morbidity and cost associated with intravenous drug use and many countries around the world have invested in programmes to both treat drug addiction and promote safe injection practices. This may partly account for the reduction in HCV incidence in HIV-infected PWIDs that is currently being seen. The Swiss Cohort reported a decrease in incidence from 13.89 (95%CI: 8.20-22.39) per 100 person-years in 1998 to 2.24 (95%CI: 0.55-10.66) in 2011[6]. However, European surveillance data shows that although the number of newly diagnosed HIV infections related to intravenous drug use is decreasing following its peak in 2001-2002, only half the twelve countries with available data show decreases in HCV prevalence during 2005-2010[7]. These data however report prevalence rather than incidence and do not take into account probable increases in awareness and testing over the past decade. The economic recession that has struck countries like Greece worsens the efforts for tackling the HIV and HCV epidemics amongst PWIDs[8].

Transmission of HCV outside of these populations with healthcare-associated risks and intravenous drug-use has always been considered to be negligible and restricted to low numbers of new cases in regular sexual partners of individuals with HCV infection. However, a few years ago clinicians began to notice a significant rise in new HCV among men who have sex with men (MSM) and denied intravenous drug use and had no healthcare-associated risks. One survey of United Kingdom urban centre-based HIV clinics revealed a doubling of new HCV in MSM from 6.86 cases/person-years in 2002 to 11.58 in 2006, without an apparent change in testing policy[9].

This observed shift of new HCV infections from PWIDs to MSM was confirmed in analysis of the Swiss Cohort showing an alarming 18-fold increase in the incidence of new cases in MSM from 0.23 (95%CI: 0.08-0.54) per 100 person-years in 1998 to 4.09 (95%CI: 2.57-6.18) in 2011. This resulted in an increase in the proportion of MSM among incident HCV from 20% prior to 2006

to 75% after ($P < 0.001$)[10]. Significant increases were also shown in the Amsterdam MSM cohort from 2000 to 2005 (incidence rate ratio 3.41, 95%CI: 1.58-7.34), though there was a levelling off of new HCV infections in MSM from 2005 onwards[11].

Virus sequencing and phylogenetic analysis of 226 HIV-infected MSM diagnosed with acute HCV from urban centres in England, Netherlands, Germany, France and Australia revealed that the independently reported European outbreaks were actually part of a large European MSM-specific transmission network[12]. A second MSM-specific transmission network was found in Australia, with very little overlap with the European network. In contrast to the European network, only 18% of transmissions in this cohort were thought to be from sexual exposure, with intravenous drug exposure still the predominate risk factor (73%)[13]. Eighty-six percent of sexual transmissions were in MSM and all of those were HIV-positive. In this cohort social networks exist in HIV-infected MSM that contain both PWIDs and non-PWIDs.

In the European transmission networks of MSM the predominant HCV genotype has been shown to be genotype 1a (59%), with an unexpectedly high proportion of genotype 4d (23%)[12]. Thus, the difficult-to-treat genotypes 1 and 4 accounted for 90% of infections compared to 67% of the Australian cohort. This has clear implications for treatment and healthcare planning.

The cause of this epidemic of HCV in MSM is likely to be multi-factorial. There is certainly some evidence that risk of HCV transmission in HIV-infected MSM is associated with non-intravenous recreational drug taking. Recreational drug use may increase the risk of unprotected sex and may be associated with group sex or with more traumatic sexual practices. In the Multicenter AIDS Cohort Study (MACS) non-intravenous recreational drug use was found to double risk, however, in the Swiss cohort no association was found[6,14].

Risk of HCV acquisition in MSM has, unsurprisingly been found to be related to multiple sexual partners, receptive anal sex and inconsistent condom use[6,14]. The spread of HCV may in part, be related to the practice of serosorting. Though men may select sexual partners on the basis of HIV status, they may well be at risk of HCV; almost a third of HIV-positive individuals are unknowingly infected with HCV[15]. However, if HCV transmission among MSM was solely due to behavioural factors, higher rates would be expected in the HIV-negative MSM population, even taking into account serosorting. Interestingly, there has been no increase in HCV in HIV-negative MSM observed, and risk has been shown to be comparable or lower than the risks in the heterosexual population[16]. More recently, however, there are emerging reports of HCV infection amongst HIV-negative MSM, so this may well represent an emerging epidemic[17].

In both the Swiss and the MACS cohorts, risk was associated with past or recent syphilis infection, confirming either a shared route of acquisition or suggesting that potentially ulcerative sexually transmitted infection could increase the risk of HCV transmission[6,14]. Individuals with HCV/HIV co-infection have been shown to have higher HCV viral loads than HCV mono-infected individuals, which may well increase the risk of transmission, particularly in the presence of ulcerative lesions, as recognised in HIV transmission[18]. A change in the virulence of circulating HCV does not appear to account for the HCV epidemic is not supported by phylogenetic analysis showing strains in the populations belong to several different genotypes and subtypes[12]. There has also been the suggestion that transmission risk may increase with decreasing CD4 count. In the MACS cohort every 100 cells/mm^3 decrease was associated with a 7% increase in risk of transmission below 500, though no association was shown in other studies[6,14].

The reports of HCV outbreaks in MSM around 2000, shortly followed the introduction of combination antiretroviral therapy (cART) in 1996. It was thought that individuals on cART had increased their sexual risk taking as a result of having suppressed HIV viral loads and reduced risk perception from HIV and there is some data to support this[19]. However, no association with HCV seroconversion and use of cART has been found, and cohort analyses have shown incident infections since the 1980s, and increases in incidence since the 1990s, well before the introduction of cART[6,14,20]. Furthermore, in the phylogenetic studies described, for each cluster of new HCV infections, the date of the common ancestor was calculated using the molecular clock approach. In the Australian networks the earliest events were estimated to have occurred around 1989 and in the European clusters 15% of transmissions were estimated to have occurred prior 1996, though the majority of infections (63%) did occur after 2000[13,20].

NATURAL HISTORY OF HCV/HIV CO-INFECTION

Acute hepatitis C is usually asymptomatic or minimally symptomatic and rarely causes severe hepatitis. Depending on the characteristics of the population examined, around 80% of patients with newly acquired hepatitis C mono-infection will develop chronic hepatitis C[21]. Most of the chronically mono-infected hepatitis C are asymptomatic, but 20%-30% will progress to develop cirrhosis over about 30 years[22]. The risk of progression from advanced fibrosis to cirrhosis has been estimated at about 10% per year[23]. Individuals with compensated cirrhosis have approximately a 4% annual risk for hepatic decompensation and a 1%-2% annual risk for development of hepatocellular carcinoma[24,25]. Among those with a first episode of hepatic decompensation, almost half will die within the next 5 years[24,26].

Higher HCV plasma viral loads are seen in HIV co-

infected individuals[27]. The level of HCV viraemia has been inversely correlated with CD4 counts[28]. Although HCV viraemia is not thought to play a role in the rate of progression of liver disease, it is important in the treatment response to pegylated interferon (PegIFN)/ribavirin (RBV) therapy and may also play a role in the length of therapy required for likelihood of response to PegIFN-free therapy[29,30].

The likelihood of spontaneous clearance of acute hepatitis C infection appears to be lower in HIV-co-infected individuals[28]. This could correlate to weaker HCV-specific T-cell responses in individuals with HIV infection[31]. Immunogenetic factors, particularly a favourable interleukin-28B (IL28B) genotype, play a role in this regard, as in mono-infected individuals. Some high-risk HIV-infected individuals present with one or more reinfections after spontaneous clearance or successful treatment of hepatitis C. It has been suggested that the likelihood of clearance of a new episode of acute hepatitis C increases with the prior number of spontaneous clearances[32].

Numerous clinical studies have shown that HIV infection is an accelerator of hepatitis C related outcomes[33]. Whether the sequence of acquisition of the viruses is important in this regard has not been fully elucidated. Some experts argue that hepatitis C may progress more rapidly if acquired in a patient with pre-existing immunosuppression, as seen in the setting of the recurrence of hepatitis C after orthotopic liver transplantation[34]. There are case reports of HIV infected individuals developing decompensated cirrhosis and death within as soon as 2-8 years after HCV acquisition. Other studies, however, have not found such a malignant course after acute hepatitis C in HIV infected individuals[35].

The rate of fibrosis progression has been found to be faster in HCV/HIV co-infected individuals compared with HCV mono-infected ones. Lower CD4 counts and higher HIV viral load have been associated with a greater likelihood of fibrosis progression. Other risk factors for faster fibrosis progression among co-infected individuals include advanced age, alcohol use, viral co-infection, obesity, insulin resistance, and hepatic steatosis, the latter being more common with genotype 3 HCV infection[36-40].

In HCV/HIV co-infected individuals, as in those with HCV mono-infection, the likelihood of hepatic decompensation is associated with the stage of liver disease[41]. However, the likelihood of decompensation is higher for co-infected *vs* mono-infected individuals with a similar stage of liver disease, even if HIV control is achieved with antiretroviral therapy[42]. The prognosis following hepatic decompensation in co-infected individuals is generally poor. A median survival of 13 mo was noted in a prospective cohort of 153 HCV/HIV co-infected individuals after the first episode of hepatic decompensation[43]. The definitive treatment in decompensated cirrhosis is liver transplantation, the outcomes of which are less favourable for co-infected individuals[44]. HCV/HIV co-infected individuals have also a greater incidence of hepatocellular carcinoma than those with HCV mono-infection, which is observed at a younger age, is typically more advanced and more likely to be symptomatic at diagnosis, and has a worse prognosis[45].

With the effective control of HIV infection with potent antiretroviral therapy, non-AIDS related causes of death have become more prominent[46]. Among these, liver-related death, associated with chronic hepatitis, is one of the most common causes of death in the HIV-infected population[47,48]. Although the upwards trend of liver-related deaths among HIV infected individuals appears to be reversing, the proportion remains considerably high[46,48]. Liver-related death may be more likely in patients with lower CD4 counts[49]. The presence of HCV infection among HIV infected individuals has been associated with a negative impact on overall mortality[50].

All-cause hospitalization is also more likely in HCV/HIV co-infected compared with HIV mono-infected individuals[51]. Certain comorbid conditions have been observed more frequently in HCV/HIV co-infected individuals than those with HIV mono-infection. These include cardiovascular disease, neurocognitive disorders, chronic kidney disease, osteoporosis and bone fractures, as well as diabetes mellitus[52].

The achievement of a sustained virological response with anti-HCV treatment in HIV co-infected individuals has been associated with the same benefits on liver disease as those seen in HCV mono-infection, including decreases in fibrosis progression and greater likelihood for regression of fibrosis, as well as decreases in the rate of hepatic decompensation and liver-related mortality[39,53-55]. Although co-infected individuals with advanced fibrosis who have failed prior PegIFN/RBV therapy may fare better in terms of fibrosis progression than untreated individuals, maintenance PegIFN/RBV therapy in the setting of treatment failure has not proven beneficial[55,56]. Hepatocellular carcinoma can develop in individuals with cirrhosis despite effective treatment of chronic hepatitis C.

The effect of HCV infection on the natural history of HIV infection has not been well characterised[57]. Most studies suggest that chronic hepatitis C does not alter the course of HIV infection, however, in a multi-national HIV seroconvertor cohort, HCV appeared to increase risk of progression to AIDS and death[58].

PATHOGENETIC MECHANISMS

Several pathogenetic mechanisms could explain the faster liver disease progression rate in HCV/HIV co-infected individuals. Although HIV does not directly infect hepatocytes, it has been shown that HIV enhances the replication of HCV in hepatocytes *in vitro*. This effect could be mediated by the interaction between HIV and the co-receptors CCR5 and CXCR4 on hepatocytes, *via* a transforming growth factor (TGF)-β1-mediated pathway[59]. TGF-β1 is a key mediator in the process of

liver fibrosis, as it is one of the most pro-fibrinogenic cytokines. HIV can also promote fibrogenesis *via* the induction of production of reactive oxygen species by hepatocytes and hepatic stellate cells, *via* an nuclear factor kappa-B-dependent pathway; this effect is enhanced in the presence of HCV. HIV can also induce hepatocyte apoptosis through increased sensitivity to tumor necrosis factor-related apoptosis-inducing ligand[60]. The systemic immune activation in HIV-infection has been associated with activation of hepatic stellate cells, which have a central role in the development of fibrosis[61]. Direct infection of hepatic stellate cells by HIV has been documented, although the exact mechanism is unclear[62]. The activation of hepatic stellate cells may also relate to the diminished natural killer-cell cytotoxic responses against these cells that is seen in HIV infection, owing to loss and impaired function of $CD4^+$ cells[63].

HIV infection has been associated with higher hepcidin blood levels than HCV mono-infection or HCV/HIV co-infection[64,65]. Hepcidin is a peptide hormone that regulates iron homeostasis. Whether increased hepcidin results in increased liver iron stores in co-infected individuals than HCV mono-infected ones, remains to be proven. Of note, liver iron has been shown to stimulate hepatic stellate cells and negatively affects fibrosis progression in HCV mono-infected individuals[66].

The immune responses against HCV are compromised in HIV co-infected individuals. Lower CD4 counts lead to attenuated $CD8^+$ T cell HCV-specific immune responses[31,67]. The HCV infecting viral population appears to be genetically more diverse in co-infection[31,68]. This reflects weaker selection pressure from the immune system. Higher quasispecies heterogeneity might negatively affect the response to interferon-based treatment[69].

HIV leads to a state of immune activation and dysregulation. Decrease in CD4 cells in gut-associated lymphoid tissue, which occurs early in the course of HIV infection, leads to increase in microbial translocation through the intestinal mucosa[70]. This is evident by increase in the circulating lipopolysaccharide (LPS) and other relevant markers. Higher levels of circulating LPS have been associated with a higher likelihood of development of cirrhosis in HCV/HIV co-infected individuals[71].

THE IMPACT OF CART ON HCV/HIV CO-INFECTION

Since the introduction of cART, life expectancy for individuals living with HIV has become comparable to that associated with other long term conditions, though it is still lower than the general population[3,72]. Less people with HIV are dying from HIV/AIDS-related causes and with the increasing length of survival, the relative importance of comorbidities such as viral hepatitis has increased[73]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that since the introduction of cART, there has been a proportional increase in liver-related deaths (LRD) and that this was the most common cause of non-AIDS related death[49]. There was initial concern that this was a consequence of ART-related hepatotoxicity, however, in subsequent analyses it became clear that this excess liver-related mortality is largely a product of viral hepatitis, and that half of those that died in the D:A:D study had active HCV[73,74].

Individuals with HCV/HIV continue to do significantly worse in terms of mortality when compared with their HIV mono-infected peers. In a Spanish cohort, all cause mortality reduced by almost 50% in HIV mono-infected individuals, but no significant change was found in HCV/HIV co-infection[75]. A meta-analysis of cohort studies showed no increased risk of mortality associated with HCV/HIV co-infection in the pre-cART era, but since the introduction of cART the risk ratio was 1.12 (95%CI: 0.82-1.51) for AIDS-defining events and 1.35 (95%CI: 1.11-1.63) for overall mortality among co-infected patients, compared with that among patients with HIV mono-infection[50].

Though there is a risk of hepatitis flare when first initiating cART, there is no evidence that cumulative exposure to cART in itself is related to increased mortality[76,77]. The increased number of deaths in co-infected individuals after the introduction of cART is likely to reflect those individuals who would not have previously survived from HIV/AIDS related events rather indicating a hepatotoxic effect of cART. Moreover, any potential risk is outweighed by the benefits of treatment.

Though the benefits of cART to HIV disease are clear, its impact on liver disease progression in co-infected individuals has been debated. A meta-analysis in 2008 failed to show that cART had any significant effect on fibrosis progression or risk of cirrhosis. However, it did show that the risk of cirrhosis in the post-cART era was slightly lower than pre-cART[78]. Other studies since then have shown an association between the use of cART and a slower rate of liver fibrosis[79,80]. One study of 638 co-infected individuals, 69% of whom were on cART, showed that both current cART and HIV viral suppression were independently associated with decreased incidence of all-cause events and a 66% reduction in liver-related events such as end-stage liver disease (ESLD), hepatocellular carcinoma (HCC) and LRD[41]. Another study found evidence that cART reduces the risk of hepatic decompensation in those with advanced liver disease[81].

As a result of these benefits, national and international guidelines have changed to recommend initiation of cART in HCV/HIV co-infection at earlier stages of HIV disease[82,83]. One mathematical model has been used in South Africa to estimate the benefit of expanding cART eligibility from those with CD4 < 350 cells/mm^3 to those with CD4 < 500 cells/mm^3. Factoring in the assumptions that co-infection accelerates liver disease 2.5-fold and

that cART reduces progression by one third, this model simulated disease progression in both HIV mono-infection and individuals co-infected with viral hepatitis. Significant benefits were shown in hepatitis B virus (HBV)/HIV co-infection, and HIV mono-infection in terms of deaths averted and disability-adjusted life-years (DALY). However, in HCV/HIV co-infection, expanding eligibility of cART actually increased the share of LRD by 34% as individuals survive for longer. Expanding eligibility was estimated to avert only 3.9 DALYs compared to 4.8 for HIV mono-infection and 5.1 for HBV/HIV co-infection. Authors estimated cART would need to reduce liver disease progression by 70% to show any significant benefit[84].

The obvious reason for this discrepancy in the benefit of cART between HBV/HIV and HCV/HIV co-infections is that while HBV can be easily controlled with well tolerated anti-hepatitis B containing cART, HCV has, until now, required long courses of poorly-tolerated subcutaneous PegIFN with RBV. The EuroSIDA study demonstrated that from 1998 to 2007, 22% of patients with at least F2 fibrosis remained untreated and that there were significant variations of treatment uptake across Europe and across transmission groups[85]. There has been a rise observed in HCV treatment uptake in co-infected individuals from 22% in 1991 one study to 88% in 2012[10]. However, a decline in 2013 was noted as individuals with less advanced disease inevitably await the availability of newer treatments[1].

Several studies have confirmed that PWIDs are less likely to receive treatment for their HCV than MSM[10,85]. Intravenous drug use is independently associated with poorer outcome in terms of all-cause mortality, LRD, ESLD and HCC[3,41,49]. Barriers to treatment in PWIDs include persistent drug or alcohol addiction, difficulties accessing care, concerns over drug side effects, poverty, discrimination and general poor health. Co-infected PWIDs are less likely to complete HCV treatment compared to mono-infected PWIDs. Adherence however, can be improved with addiction treatments, though coverage of opioid substitution and needle/syringe programmes is very variable across Europe with particularly low coverage in central and south-east Europe[7,86]. Addiction treatment can also have benefits for HIV treatment in terms of compliance and improved virological success[87]. After the roll-out of shorter, oral treatments for HCV with fewer side effects, requiring less intensive monitoring, it is hoped that uptake of HCV treatments will improve, but particular focus must still given to the hard-to-reach PWID population.

TREATMENT OF HCV IN CO-INFECTED INDIVIDUALS

The response to PegIFN alpha plus RBV for the treatment of chronic hepatitis C in individuals with HIV co-infection is lower than in those with HCV mono-infection[88,89]. The basis of the viral clearance of HCV with PegIFN/RBV therapy is immunologic. PegIFN acts primarily by enhancing the innate antiviral immune response and can also potentiate adaptive immune responses[90]. Ribavirin is thought to exert various, not well characterised antiviral effects and to potentiate the effect of PegIFN[91]. An important predictor of the treatment success with PegIFN/RBV against chronic hepatitis C genotype 1 or 4 infection is a favourable interleukin 28B genotype[29,92].

The integrity of the immune system appears to be less important when direct acting antivirals are used for the treatment of HCV infection. The introduction in 2011 of the direct acting antivirals boceprevir and telaprevir, which are first generation, first wave NS3/4A protease inhibitors, has allowed for a substantial increase in the likelihood for sustained virological response (SVR) in genotype 1 HCV/HIV co-infected patients (Table 1). The absolute treatment benefit achieved with these agents is similar to that observed in HCV mono-infected individuals[93,94]. In a recently published study, telaprevir in combination with PegIFN/RBV had high effectiveness (SVR24 80%) in PegIFN/RBV treatment-experienced genotype 1 HCV/HIV co-infected individuals[95]. This population would have been considered to be a "difficult-to-treat" one in the era before DAAs. The likelihood of treatment success did not differ by the fibrosis stage, IL28B genotype, HCV 1a or 1b genotype, CD4 cell count, type of previous response to HCV treatment, baseline HCV-RNA level or the rapidity of HCV-RNA response.

Despite their antiviral activity, boceprevir and telaprevir have many limitations including the requirement for a long course of therapy in combination with PegIFN/RBV, a high rate of adverse effects, the need for multiple daily dosing including the requirement for co-administration with food, high pill burden, low barrier to resistance, and a high potential for drug-drug interactions[96]. Some of these issues are particularly important in the context of HIV co-infection and concomitant antiretroviral therapy.

Newer DAAs have now been marketed and numerous others are in the later stages of clinical development[97]. The drug targets include the NS3/4A serine protease, the NS5A replication complex, and the NS5B RNA polymerase; the latter enzyme can be targeted by nucleos(t)ide or non-nucleoside inhibitors. Following the paradigm of combination antiretroviral therapy, the combination of two or more antiviral agents (depending on potency, genetic barrier to resistance and activity against the different HCV genotypes), has made interferon-free therapy possible[98,99]. As of this writing, sofosbuvir (NS5B RNA polymerase nucleotide inhibitor), simeprevir (NS3/4A protease inhibitor), daclatasvir and ledipasvir (NS5A inhibitors) have been approved by the European Medicines Agency.

Table 1 presents the characteristics and findings of the main trials of direct acting antivirals, with or without PegIFN, in HCV/HIV co-infection[95,100-110]. The newer interferon-free regimens are expected to allow for a high likelihood (> 90%) of achieving SVR, with shorter

Table 1 Trials of direct-acting antivirals for chronic hepatitis C infection in human immunodeficiency virus co-infected patients

Study	GT	Tx regimen	Tx duration (wk)	Hepatitis C characteristics	SVR12		
					GT	Fibrosis stage	Treatment status
P05411[100]	1	PegIFNα-2b + RBV wb (600-1400 mg) + BOC *vs* placebo	BOC: 44 PegIFN/RBV: 48	Tx naïve Metavir F0-4 Cirrhosis: 3%	BOC GT1: 42/64 (66%) GT1a: 32/51 (63%) GT1b: 7/12 (58%) Placebo GT1: 9/34 (26%)		
VX08-950-110[101]	1	PegIFNα-2a + RBV 800 mg or wb (1000-1200 mg) + TVR *vs* placebo	TPV: 12 PegIFN/RBV: 48	Tx naïve Metavir F0-4	TPV GT1: 28/38 (74%) GT1a: 20/27 (74%) GT1b: 7/11 (64%) Placebo GT1: 10/22 (45%) GT1a: 4/14 (29%) GT1b: 4/6 (67%)		
ANRS HC26 TelapreVIH[95]	1	PegIFNα-2a + RBV wb (1000-1200 mg) + TVR	TPV: 12 PegIFN/RBV (RGT): 44 or 72	Tx exp Metavir F0-4 Both cirrhosis and prior null-response excluded	GT1: 55/69 (80%) GT1a: 36/48 (75%) GT1b: 19/21 (90%)	F1-2 34/42 (81%) F3-4 21/27 (78%)	Relapse 20/27 (74%) Breakthrough 5/6 (83%) Partial response 15/15 (100%) Null response 15/21 (71%)
P7977-1910[102]	1-4	SOF + PegIFNα-2a + RBV wb (1000-1200 mg)	12	Tx naïve No cirrhosis	All GTs: 21/23 (91%) GT1: 17/19 (89%) [GT1a: 13/15 (87%) GT1b: 4/4] GT2: 1/1 GT3: 2/2 GT4: 1/1		
STARTVerso4[103,104]	1	FDV 240 mg (EFV) or 120 mg (ATV/r or DRV/r) or 120 *vs* 240 mg (RAL or MVC or no ART) + PegIFNα-2a + RBV wb (1000-1200 mg)	FDV: 24 or (12 *vs* 24), PegIFN/RBV (RGT): 48 or 24 wk *vs* 48 wk	PegIFN/RBV Tx naïve or prior relapse Compensated cirrhosis: 15%	GT1: 221/308 (72%) GT1a: 171/242 (71%) GT1b: 50/66 (76%)	No Cirrhosis 187/261 (72%) Cirrhosis 33/45 (73%)	Tx naïve 164/239 (69%) Relapse 57/69 (83%)
C212[105]	1	SMV + PegIFNα-2a + RBV wb (1000-1200 mg)	SMV: 12 PegIFN/RBV RGT: (24 *vs* 48) for Tx naïve or prior relapse or 48 for partial- or null-response or cirrhosis	PegIFN/RBV Tx naïve or Tx exp Metavir F0-4; Cirrhosis: 6%-30% by Tx arm	GT1: 78/106 (74%) GT1a: 62/88 (70%) GT1b: 16/18 (89%)	F0-2 36/45 (80%) F3-4 14/22 (64%)	Tx naïve 42/53 (79%) Relapse 13/15 (87%) Partial response 7/10 (70%) Null response 16/28 (57%)
PHOTON-1[106]	1-3	SOF + RBV wb (1000-1200 mg)	GT 1: 24 GT 2-3 Tx naïve: 12 GT 2-3 Tx exp: 24	Tx naïve (GT1-3) or exp (GT2-3) Cirrhosis ⩽ 20%	GT1: 87/114 (76%) [GT1a: 74/90 (82%) GT1b: 13/24 (54%)] GT2: 44/50 (88%)	No Cirrhosis GT1: 84/109 (77%) GT2: 22/25 (88%) GT3: 24/36 (67%)	Tx naïve GT1: 87/114 (76%) GT2: 23/26 (88%) GT3: 28/42 (67%)

					GT3: 44/59 (75%)	Cirrhosis GT1: 3/5 (60%) GT2: 1/1 GT3: 4/6 (67%)	Tx exp GT2: 22/24 (92%) GT3: 16/17 (94%)
PHOTON-2[107]	1-4	SOF + RBV wb (1000-1200 mg)	GT 1, 3, 4: 24 GT 2 Tx naïve: 12 GT 2 Tx exp: 24	Tx naïve (GT1-4) or exp (GT 2-3) Compensated cirrhosis: 20% of patients	GT1: 95/112 (85%) [GT1a: 84/100 (84%) GT1b: 10/11 (91%)] GT2: 22/25 (88%) GT3: 94/106 (89%) GT4: 26/31 (84%)	No Cirrhosis GT1: 84/95 (88%) GT2: 19/22 (86%) GT3: 73/80 (91%) GT4: 19/23 (83%) Cirrhosis GT1: 11/17 (65%) GT2: 3/3 GT3: 21/26 (81%) GT4: 7/8 (88%)	Tx naïve GT 1: 95/112 (85%) GT2: 17/19 (89%) GT3: 52/57 (91%) GT4: 26/31 (84%) Tx exp: GT2: 5/6 (83%) GT3: 41/49 (84%)
TURQUOISE-I[108]	1	Paritaprevir/r/Ombitasvir + Dasabuvir + RBV wb (1000-1200 mg)	12 or 24	Tx naïve or PegIFN/RBV exp Cirrhosis ⩽ 30%	Tx for 12 wk GT1: 29/31 (94%) Tx for 24 wk 19/20 (95%)		
ERADICATE[109]	1	SOF/LDV	12	Tx naïve Knodell F0-3	Untreated HIV Infection GT1: 10/10		
C-WORTHY[110]	1	Grazoprevir + MK-8742 +/- RBV	12	Tx naïve No cirrhosis Metavir F0-3	With RBV 28/29 (97%) Without RBV 26/29 (90%)		

/: Indicates co-formulation; +/-: With or without; GT: HCV genotype and subtype; RGT: Response guided therapy; Tx (exp): Treatment (experienced); *vs*: Indicates randomisation; wb: Weight based; ATV: Atazanavir; BOC: Boceprevir; DRV: Darunavir; EFV: Efavirenz; FDV: Faldaprevir; LDV: Ledipasvir; PegIFN: Pegylated Interferon; r: Ritonavir boosted; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; TVR: Telaprevir.

treatment duration, a favourable side-effect profile (similar to that observed in mono-infected individuals), and convenient dosing schedules. The genotype 3 now appears as the most challenging HCV genotype to treat, as few of the newer DAAs have potent specific antiviral activity. This is important as genotype 3 is more common amongst PWIDs, who also have a substantial rate of HIV co-infection[111,112].

The effectiveness of DAA-based therapy does not appear to differ between HCV mono-infected and HCV/HIV co-infected individuals according to data from different trials, as shown in Figure 1[93,94,100-103,105-110,113-126]. For that reason, experts recommend that the same DAA-based regimens should be used in HCV/HIV co-infected individuals as those used in HCV mono-infected individuals[127,128]. The same position is held by the European Association for the Study of Liver, with a note for attention to potential drug-drug interactions[129]. In the United States, the pertinent guidelines consider HIV co-infected patients as one of four "unique patient populations"[130]. The United States Food and Drug Administration regards the HCV/HIV co-infected population as "a population with unmet medical needs"[131]. It warrants that industry sponsors for the development of DAAs to present specific clinical trial data on drug-drug interactions with the antiretroviral agents and the safety for HIV infection. In our opinion, drug developers must make sure that such recommendations do not lead to unnecessary delay in the licensure and availability of the newer agents for HCV/HIV co-infected individuals.

Routine screening for hepatitis C infection in HIV-infected individuals allows for many cases of acute hepatitis C infection to be recognised. This is important given the rising incidence of HCV acquisition among HIV-infected MSM in many countries seen over the past 10 years and the high incidence of HCV acquisition among PWIDs. Treatment of acute HCV infection with PegIFN results in a high likelihood of treatment success in mono-infected individuals, although in HIV co-infected individuals the addition of RBV is recommended[132]. Trials are under way for testing new DAA-based regimens for this indication, which might allow for a shorter duration of treatment, fewer side effects and great treatment effectiveness[133].

Reinfection with hepatitis C is not infrequent in certain HIV infected populations, particularly those with ongoing sexual risk-taking behaviour and illicit drug use[134].

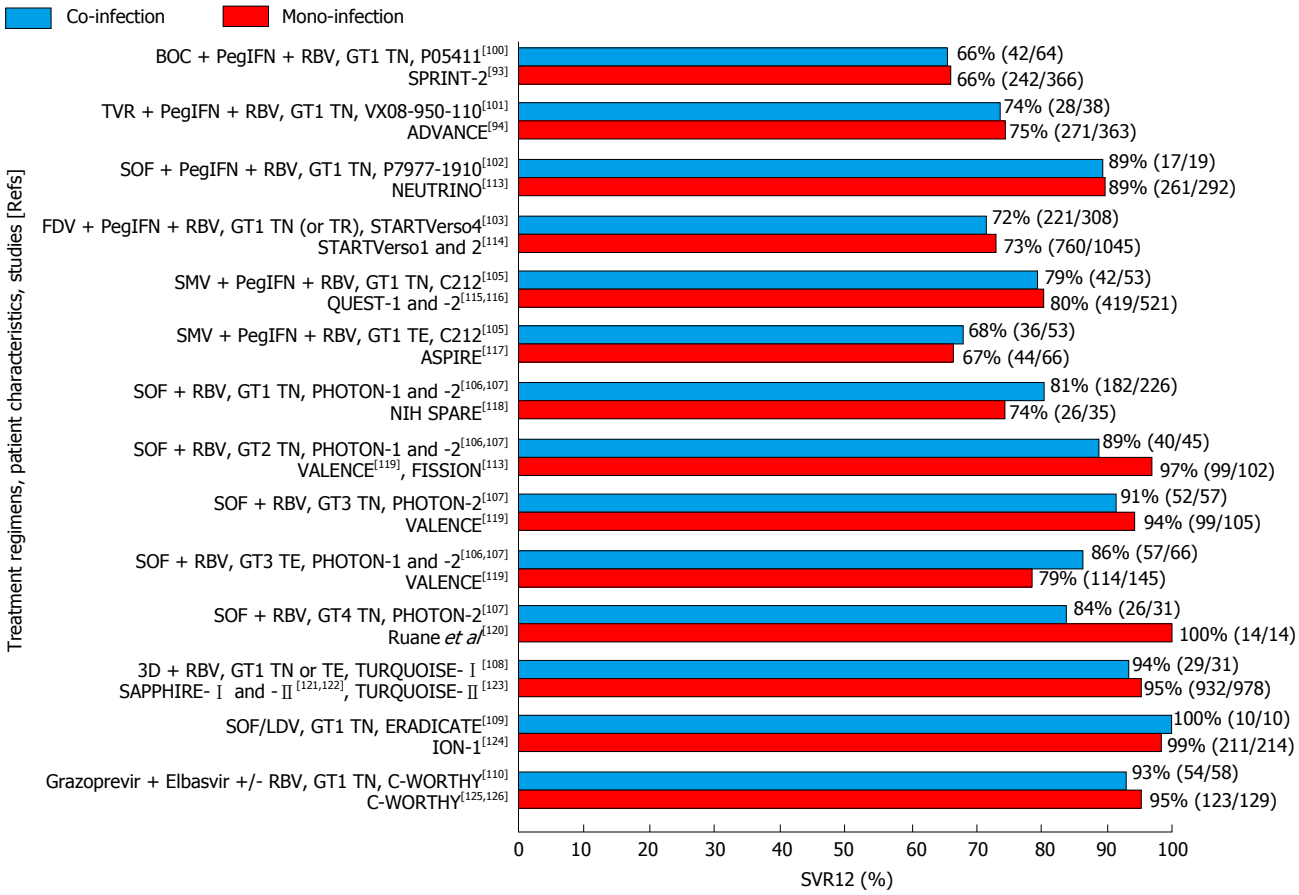

Figure 1 Comparison of week-12 sustained virological response rates between patients co-infected with hepatitis C virus and human immunodeficiency virus mono-infected patients treated with the same regimens containing direct acting antivirals in clinical trials (Data from similar studies were arithmetically pooled). 3D: Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir; BOC: Boceprevir; FDV: Faldaprevir; GT: HCV genotype; LDV: Ledipasvir; PegIFN: Pegylated Interferon; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; TE: Treatment experienced; TN: Treatment naïve; TR: Prior relapse after treatment; TVR: Telaprevir; /: Indicates co-formulation; +/-: With or without.

Reinfection with a new HCV strain can in some cases complicate the assessment of the effectiveness of treatment against hepatitis C if it occurs during or shortly after the completion of treatment[135]. Data from phylogenetic analyses of paired samples from the same individuals are reassuring that true late relapses are generally rare in co-infected individuals, as is the case for mono-infected individuals[136].

SPECIAL ISSUES IN THE MANAGEMENT OF CO-INFECTED INDIVIDUALS

Despite the effectiveness of DAAs in achieving SVR in HCV/HIV co-infected individuals, there are several issues that should be considered in the management of this population. As discussed, the treatment regimens must be selected carefully in view of the potential for drug-drug interactions between several DAAs and antiretroviral agents. This might require changes in dosage, as is the case for daclatasvir when used with efavirenz or boosted HIV protease inhibitors, or even avoidance of certain combinations. Moreover, the pharmacokinetics of different agents might change with different degrees of hepatic insufficiency and there is clearly a need for more data in this field[137]. Polypharmacy is common in HIV-infected individuals and a careful review of all drugs is needed before the addition of DAAs.

The sequence of treatment against each infection in newly diagnosed HCV/HIV co-infection could have been important with regard to treatment with PegIFN/RBV. Although chronic hepatitis C treatment can be treated prior to the commencement of antiretroviral therapy in patients with a high (> 500 per mm^3) CD4 cell count, achieving HIV-RNA suppression first might increase the likelihood of SVR[138]. These considerations might not be important in the era of new DAAs.

Interferon alpha has been shown to reduce HIV-RNA plasma viral load by about 1 log_{10} after one week of therapy and to have sustained activity against HIV over a treatment period of 24-28 wk[139,140]. This effect might be protective in terms of control of HIV in the case that drug-drug interactions result in lower exposure to antiretroviral drugs. With the newer DAAs, interferon-free treatment courses as short as 12 wk have been used and even shorter courses are under investigation. Treatment for such a short duration can mitigate the effect of any potential drug-drug interactions of DAAs

with ARVs on the control of HIV infection.

Adverse drug reactions in patients receiving treatment for hepatitis C might be more common in those co-infected with HIV. This has been a problem with boceprevir and telaprevir, but newer DAAs appear to have a similar safety profile in mono-infected compared to co-infected individuals.

Many of the HIV-infected individuals who are engaged into care have built over time strong relationships with their treating physicians and are well educated about several health issues[141-143]. Their care generally includes screening and immunisation against hepatitis A and B (if at risk) and monitoring for drug adherence and substance abuse disorders. The healthcare structures for these individuals often provide social and psychological support for those with social/financial problems, substance abuse issues or psychiatric comorbidity. Thus, many HIV infected individuals could be well-prepared for receiving treatment for concomitant hepatitis C infection. In the case of MSM, preventing transmission of HCV to their sexual partners might be an additional incentive for a successful treatment outcome. Moreover, HIV-infected individuals receiving long-term antiretroviral therapy are familiar with the need of taking a long-term drug regimen[144]. It may be easier for them to incorporate DAAs in their daily schedule than individuals who have never taken long-term therapy.

TREATMENT PRIORITIZATION

The substantial drug costs of DAAs raise the issue of the access to the new treatments and of treatment prioritisation. Clearly those with advanced liver disease, whether mono-infected or HCV/HIV co-infected are in the greatest need for the new treatments.

In general, HCV/HIV co-infected individuals should be considered as a population in need for treatment of hepatitis C with the new DAAs. The uptake of PegIFN/RBV treatment has been low in this population, due to the presence of comorbidity or other conditions that render many patients ineligible, low treatment effectiveness, difficulties in staging of liver disease, or relative inexperience of some infectious diseases/HIV-medicine providers[145-147]. As mentioned above, the progression of HCV infection is accelerated in the presence of HIV co-infection and a not insignificant minority of individuals can progress rapidly after acute infection. The fact that the HIV population is ageing is another factor that makes treatment of hepatitis C important, as liver-related complications increase in the elderly[148]. HIV co-infected individuals may not have good access to liver transplantation in case that decompensated cirrhosis or HCC develops, while the management of these patients post-transplant is still challenging[149]. Thus, a decision to defer treatment for hepatitis C must be weighed against the above considerations.

The access to the new DAAs for the co-infected population is also important from a public health perspective in order to decrease the incidence of new infections, which is particularly high for certain subgroups[150]. In contrast, many mono-infected individuals have acquired HCV iatrogenically in the distant past, and are of relatively low risk of transmitting the virus to others. The ultimate goal would be the eradication of HCV[151]. Although this necessitates the allocation of substantial healthcare resources, the containment of the epidemic in certain high-risk subgroups through active screening and administration of effective and highly tolerable treatment can be a more feasible goal[150]. Treatment cannot however constitute the only form of prevention; public health efforts including reaching and educating high-risk populations about prevention and treatment, screening for HCV infection and providing good linkage to care are also important in this regard.

CONCLUSION

Although HIV co-infected individuals represent a substantial minority, they have traditionally been considered to be one of the "special populations" amongst the HCV infected ones. This was mainly attributed to the lower likelihood of cure from PegIFN/RBV therapy. Moreover, the uptake of this type of therapy has generally been low due to various complicating factors. The advent of newer DAA-based therapy offers the opportunity of a very high rate of treatment success with short treatment courses and a favourable side effect profile. Yet, the HCV/HIV co-infected population remains one with unmet medical needs, given the faster progression of liver disease compared with mono-infected individuals. Although successful cART ameliorates the course of chronic hepatitis C in HIV co-infected individuals, they retain increased liver-related risk when compared with the HCV mono-infected individuals. Specific issues relating to the treatment of hepatitis C in HIV co-infected individuals, particularly drug-drug interactions, should be addressed in a timely manner in the process of DAA drug development so that the newer treatment options become readily available to this population. Significant and sustained improvements in mortality and morbidity and control of the current HCV epidemic in HIV-infected subgroups could then become a feasible goal.

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MINIREVIEWS

Hepatitis C: Treatment of difficult to treat patients

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Abstract

Over the past several years, more so recently, treatment options for hepatitis C virus (HCV) have seemed to exponentially grow. Up until recently, the regimen of pegylated interferon (peg-IFN) and ribavirin (RBV) stood as the standard of care. Direct acting antivirals, which target nonstructural proteins involved in replication and infection of HCV were first approved in 2011 as an addition to the peg-IFN and RBV regimen and with them have come increased sustained virological response rates (SVR). The previously reported 50%-70% SVR rates using the combination of peg-IFN and RBV are no longer the standard of care with direct acting antiviral (DAA) based regimens now achieving SVR of 70%-90%. Peg-IFN free as well as "all oral" regimens are also available. The current randomized controlled trials available show favorable SVRs in patients who are naive to treatment, non-cirrhotic, and not human immunodeficiency virus (HIV)-co-infected. What about patients who do not fit into these categories? In this review, we aim to discuss the currently approved and soon to be approved DAAs while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV. In this discussion, review of the clinical trials leading to recent consensus guidelines as well as discussion of barriers to treatment will occur. A case will attempt will be made that social services, including financial support and drug/alcohol treatment, should be provided to all HCV infected patients to improve chances of cure and thus prevention of late stage sequela.

Key words: Hepatitis C virus; Direct acting antiviral; Human immunodeficiency virus; Cirrhosis; Treatment experienced

Core tip: The current randomized controlled trials available show favorable sustained virologic responses

in patients who are naive to treatment, non-cirrhotic, and not human immunodeficiency virus (HIV)-co-infected. What about patients who do not fit into these categories? In this review, we aim to discuss the currently approved and soon to be approved direct acting antivirals while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV.

Hilgenfeldt EG, Schlachterman A, Firpi RJ. Hepatitis C: Treatment of difficult to treat patients. *World J Hepatol* 2015; 7(15): 1953-1963 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i15/1953.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i15.1953

INTRODUCTION

In the most recent national health and nutrition examination survey the estimated prevalence of hepatitis C virus (HCV) infection was approximately 3.9 million in the United States alone, with an estimated 2.7 million with chronic infection[1]. Worldwide, the number living with chronic hepatitis C approaches 150 million[2]. These estimates likely fall significantly short given that nearly half of all infected patients have never been tested for HCV. This survey also excluded prisoners and the homeless; two well-known high-risk populations. Over the past several years, more so recently, treatment options for HCV have seemed to exponentially grow. Treatment for HCV began with Food and Drug Administration approval of interferon (IFN) in 1991, followed by combined IFN and ribavirin (RBV) in 1998, and later with pegylated IFN (peg-IFN) in 2001. Up until recently, the regimen of peg-IFN and RBV stood as the standard of care. Direct acting antivirals (DAAs), which target nonstructural proteins involved in replication and infection of HCV were first approved in 2011 as an addition to the peg-IFN and RBV regimen (Table 1).

Sustained virologic response (SVR), which is commonly defined as a lack of HCV detection 12-24 wk following treatment, with RBV and peg-IFN alone was marginal but has continued to improve. By understanding the genome of the HCV, scientists and researchers have been able to exploit its mechanism of transmission by creating inhibitors against several of the nonstructural proteins that are integral to HCV replication and function. As it currently stands, four classes of DAA exist which can be categorized according to the protein they inhibit. They include the NS3/4 protease, NS5A polymerase, and NS5B polymerases (nucleoside and non-nucleoside). The approval of telaprevir (TVR) and boceprevir (BOC) in 2011 marked the start of this new era. The approval of these NS3/4 protease inhibitors occurred following studies showing increased SVR, in comparison to IFN and RBV alone. Two years later this was followed by approval of sofosbuvir (SOF), a nucleoside NS5B inhibitor, and simeprevir (SIM), an NS3/4 protease inhibitor (Table 2). Several other agents are currently undergoing late stage clinical trials and expected to be approved in the near future (Table 3).

The previously reported 50%-70% SVR rates using the combination of peg-IFN and RBV are no longer the standard of care (Figure 1). New guidelines clearly echo this[3]. IFN free as well as "all oral" regimens are already in place for genotype 2 and probably for genotypes 1 and 4 by the end of the year. RBV free regimens are also being explored[4]. The current randomized controlled trials available convincingly show favorable SVR in patients who are naïve to treatment, non-cirrhotic, and in non-human immunodeficiency virus (HIV)-co-infected, but what about patients who do not fit into these categories? Furthermore, concern for side-effect profile, unfamiliar practitioners and concern for drug-drug interaction has led to avoidance in all but treatment-naive and otherwise healthy patients.

In this review, we aim to discuss the currently approved and soon to be approved DAAs while focusing on their roles in patients that are treatment experienced, cirrhotic, or co-infected with HIV. In this discussion, particular attention will be paid to the continued barriers of treatment including ongoing psychological conditions such as addiction or depression, lack of access to care, poor social support, lack of financial resources, and many others. A case will attempt to be made that social services such as financial support and drug or alcohol treatment should be provided to all HCV infected patients in hopes that cure of hepatitis C will become a preventative measure for future development of HCV associated conditions; the most well-known being cirrhosis and hepatocellular carcinoma.

TREATMENT-EXPERIENCED PATIENTS

Treatment-experienced patients is perhaps the largest percentage of the patients to be discussed in this review. Patients who have been previously treated pose perhaps one of the most common dilemmas that practitioners face. This group can be divided into patients who have relapsed, those who partially responded to therapy, and to those who did not respond to treatment or null responders. Other variables to be considered are those that underwent incomplete treatment secondary to drop out and noncompliance.

TVR and BOC

REALIZE: Previous peg-IFN + RBV treated and peg-IFN + RBV failures: Non-responders, partial responders or those who have suffered a relapse were randomized into three treatment groups separated by treatment duration. An SVR rate of 66% was achieve in the 12-wk treatment arm utilizing TVR, peg-IFN, and RBV. Additionally, this study was also able to show a decreased relapse rate of 1% compared to 26% in the control group[5]. In a study published by the *Journal of Hepatology* treatment of prior non-responders, partial responders, and those with relapse using BOC

Table 1 Chronologically listed, Food and Drug Administration approved treatment regimens for hepatitis C virus

HCV (identified in 1989)
Approved drugs 1991-2001
Interferon (approved in 1991)
RBV + standard interferon (1998)
Peg-IFNs (approved in 2001)
Peg-IFN
Peg-IFN + RBV
DAAs 2011-present
Telaprevir and boceprevir
Increase SVR rates and provide the option of response-guided therapy and retreatment for genotype 1 patients
Telaprevir + peg-IFN + RBV, genotype 1 only (2011)
Boceprevir + peg-IFN + RBV, genotype 1 only (2011)
Sofosbuvir
Approved for use in all genotypes. High SVR rates with better tolerability, shorter duration, use in HIV-HCV co-infection, and first interferon-free all-oral regimen in genotype 2, 3 and certain other patients
Sofosbuvir + peg-IFN + RBV, in genotype 1 only (2013)
Sofosbuvir + RBV, without interferon, in genotype 2 and 3, in HIV-HCV co-infection, with any genotype, and in selected situations of genotype 1 (2013)
Simeprevir
High SVR rates with better tolerability and shorter duration for genotype 1
Simeprevir + peg-IFN + RBV, in genotype 1 only (2013)

Adapted from http://www.hepatitis.va.gov. DAAs: Direct acting antivirals; SVR: Sustained virological response; HIV: Human immunodeficiency virus; HCV: Hepatitis C virus; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

Table 2 Currently available Food and Drug Administration approved pharmaceuticals for treatment of hepatitis C virus

Approved treatments for hepatitis C		
Brand name	**Generic names**	**Manufacturer name**
Sovaldi	SOF	Gilead Sciences
Olysio	SIM	Janssen
Incivek	TVR	Vertex
Victrelis	BOC	Merck and Co.
Pegasys	Peg-IFN	Roche
CoPegus	RBV	Roche
Pegintron	Peg-IFN alpha-2b	Schering
Intron A	IFN alpha-2b	Schering
Rebetol	RBV	Schering
Roferon	IFN alpha-2a	Roche
Infergen	IFN aphacon-1	Three Rivers Pharma

Adapted from http://www.fda.gov/. SOF: Sofosbuvir; SIM: Simeprevir; TVR: Telaprevir; BOC: Boceprevir; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

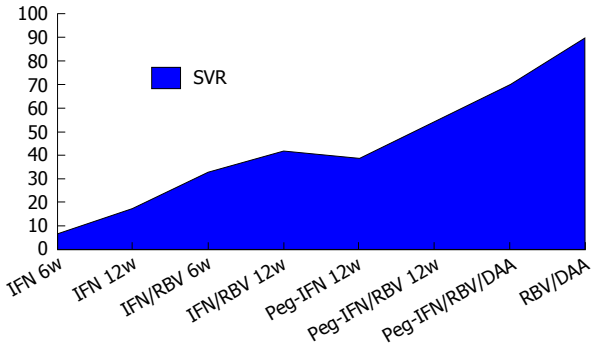

Figure 1 Sustained virologic response of various treatment regimens. DAAs: Direct acting antivirals; RBV: Ribavirin; Peg-IFN: Pegylated interferon.

in combination peg-IFN and RBV was able to achieve rates of SVR of 63% percent of all treated followed by 38%, 67%, 93% respectively for each subgroup. The most commonly reported adverse events related to combination therapy utilizing BOC included anemia, fatigue, and dysgeusia[6].

RESPOND-2: Previous peg-IFN + RBV failure: In the RESPOND-2 trial conducted by Bacon *et al*[7] over 400 patients were randomized to receive treatment with BOC along with peg-IFN and RBV following previously failed treatment to peg-IFN and RBV alone. In this trial an SVR of 59%-66% in the BOC group, was achieved as compared with the control group SVR of 21%.

CUPIC: Previous peg-IFN + RBV failure: In this trial Hézode *et al*[8] looked at genotype-1, previously treated with peg-interferon and RBV patients with a baseline MELD < 13 and Child-Pugh A compensated cirrhosis and examined SVR rates using TVR or BOC in combination with interferon and RBV. Compared with the REALIZE and RESPOND-2 trial, similar rates of SVR at 12 wk was achieved. In the TVR treatment arm an SVR of 75%, 40% and 20% were achieved in previously relapsed patients, partial responders, and null-responders, respectively. The BOC treatment group received slightly less encouraging results with rates of 54%, 38%, 0%, comparatively. Significant side effects occurred in almost half of all those treated in the study. Fifty patients (10%) experienced severe complications or death, with nearly half of these occurring during the first 12 wk of treatment. As has been previously noted in prior studies, severe anemia, requiring either discontinuation or reduction in dosing, as well as transfusion occurred in 134 and 78 of the 511 studied patients, respectively. Multivariate analysis suggested higher risk of side effects in patients with severe hypoalbuminemia and thrombocytopenia. Given the poor response of prior

Table 3 Food and Drug Administration approved and investigational drugs by mechanism of action

HCV NS3/4 protease inhibitors	Nucleos(t)ide HCV NS5B polymerase inhibitors	Non-nucleos(t)ide HCV NS5B polymerase inhibitors	HCV NS5A inhibitors
Telaprevir[1]	Sofosbuvir[1]	BI-207127	Daclatasvir
Boceprevir[1]	Mericitabine	VX-222	Ledipasvir
Danoprevir		ABT-333	ABT-267
Simeprevir[1]		BMS-791325	
ABT-450 (with ritonavir)		Tegobuvir	
Faldaprevir		GS-9669	
Asunaprevir			
GS-9451			

[1]Drugs have received Food and Drug Administration approval. Adapted from http://www.hepatitis.va.gov. HCV: Hepatitis C virus.

null responders, treatment utilizing BOC or TVR in combination with peg-IFN and RBV is not recommended. Due to adverse events, the authors also recommend considering not treating patients with platelet counts < 100000/mm^3 and serum albumin < 3.5 g/dL.

Simeprevir

In a phase Ⅱ clinic trial by Zeuzem *et al*[9], previously treated, genotype-1 infected patients underwent randomization to receive simeprevir in combination with peg-IFN and RBV for either 12, 24, or 48 wk or peg-IFN and RBV alone for 48 wk. The rate of overall SVR was significantly higher in the simeprevir group with 61%-80% *vs* 23% in the peg-IFN + RBV (PR) group. When examining prior null responders, an SVR rate of 38%-59% *vs* 19% was noted. Partial responders and relapsers achieved even higher rates; 48%-86% and 77%-89%, respectively. All groups had comparable numbers of adverse events.

In follow-up, a phase Ⅲ trial conducted by Forns *et al*[10] randomized genotype 1, PR failure patients into either a 12 wk course of SIM + PR (followed by either a 12 or 36 wk course of PR) or 48 wk of PR. SVR12 of 79.2% *vs* 36.1% was noted in the study groups, respectively. Similar adverse events were noted regardless of therapy.

SOF

FUSION: Previous PR + PR failures: Jacobson *et al*[11] looked at treatment with SOF and RBV in genotype 2 and 3 patients who previously failed peg-IFN based therapy. Patients were randomized to receive either 12 or 16 wk of treatment. Patients receiving 16 wk of therapy fared better than the 12 wk group and were able to achieve rates of SVR at 12 wk post therapy of 50% (50/100) and 73% (69/95), respectively. Breakdown of subgroups identified that genotype 2 patients had higher SVR rates than genotype 3. Additionally, non-cirrhotic patients had higher rates of response as compared with cirrhotic patients.

SOF/simeprevir

COSMOS: Previous PR failures: A phase Ⅱ clinical trial randomized 167 treatment naive and previously treated genotype 1 patients to receive both SOF and SIM alone or in combination with RBV[12]. Additionally, these patients were selected to receive either a 12 or 24-wk course of treatment. Among prior null responders with Metavir scores of F0-2 and without the Q80K mutation an SVR12 of 100% was achieved regardless of treatment regimen or duration. In patients with either F3-4 Metavir scores SVR12 fell slightly to 92% (38/41) in the 12 wk treatment arm regardless of treatment regimen. Among all subgroups, the presence of the Q80K mutation in genotype 1a patients conferred a decreased chance of achieving SVR. The extent of treatment resistance remains an area of future study but never the less should be noted when considering simeprevir-containing regimens.

SOF/ledipasvir

ION-2: Previous PR and DAA + PR failures: A trial by Afdhal *et al*[13] published in New England *Journal of Medicine* in 2014 looked at 440 patients who had failed previous peg-IFN and RBV therapy and treated them with SOF and ledipasvir (LED), a nucleoside 5A inhibitor, either with or without RBV. Treatment course was either 12 or 24 wk. In the 12 wk group, triple therapy with RBV resulted in a 96% SVR compared with a 94% in the dual treatment group. When the duration of treatment was extended to 24 wk both treatment arms had 99% SVR.

LONESTAR: Previous DAA + DAA failure: Lawitz *et al*[14] gathered 40 patients previously treated with BOC or TVR who then went on to fail therapy or have recurrence and randomized them to receive SOF and LED with or without RBV for a total of 12 wk. At 12 wk following therapy 95% (18/19) achieved SVR in the dual therapy group *vs* 100% (21/21) in the triple therapy group. Anemia was more common with those treated with RBV, occurring in 6 of the 21 patients, but did not lead to treatment failure or discontinuation.

SOF/daclatasvir

In a study by Sulkowski *et al*[4], 41 of 211 patients with genotype 1 were noted to have previously been treated with protease inhibitors, either BOC or TVR,

without achieving SVR. In this subgroup, randomization to daclatasvir, a nucleoside 5A inhibitor, and SOF with or without RBV for a total of 24 wk showed SVR12 of 100% (21/21) and 95% (19/20), respectively. Notable side effects included nausea, fatigue and headache and were reported in a majority of subjects. Side effects did not lead to discontinuation of treatment.

ABT-450/r/ombitasvir/dasabuvir/RBV

SAPPHIRE-Ⅱ: Previous PR failures: In a phase Ⅲ trial conducted by Zeuzem *et al*[15], 394 genotype 1 patients with prior treatment failure underwent randomization to receive 12 wk of treatment with the study drug regimen or placebo. SVR12 in the active regimen group was noted to be 96.3% (286/297). With only 1% drop out due to side effects and only 4.7% experiencing grade 2 or 3 anemia, this regimen shows some of the best results for HCV therapy to date. Additionally, SVR12 of prior null responders was 95.3% (139/146).

HIV/HCV CO-INFECTION

HIV-infected individuals with concomitant hepatitis C are known to have an increased morbidity and mortality[16]. They are also known to have relatively poor responses to peg-IFN and RBV therapy, as compared with mono-infected patients[17,18]. In a study by Benhamou *et al*[19] which examined HCV-related liver fibrosis progression, a CD4 count below 200/microliter, heavy alcohol consumption, and absence of protease inhibitor therapy were all identified as independent risk factors for progression to cirrhosis in HIV co-infected patients. Several mechanisms are described throughout the literature aiming to address this finding. On a molecular level, it has been noticed that when compared to the HCV mono-infected, HCV-HIV co-infected persons have higher levels of HCV RNA. The higher viral lode of HCV RNA is suspected to be secondary to an increased replication of HCV RNA by HIV proteins[20]. It is also thought that the overall state of immunodeficiency leads to an environment of rapid hepatocyte destruction and fibrosis progression[21].

Following the development of highly active anti-retroviral therapy (HAART) there has been an ever-increasing percentage of HIV infected patients who are dying from liver disease. In HIV infected patients, death from liver disease remains far more prevalent than death attributable to HIV-related complications[22,23]. The increased mortality from liver-related illness appears to be uniquely associated with co-infected patients only. In a large, multi-center, prospective trial examining HAART-related liver mortality in patients not infected with HCV or HBV the rate of death was 0.04/1000 person-years. Of the 12 recorded liver related deaths, seven were deemed to be due to excessive alcohol use while the other five were deemed to be related to HAART-related toxicity[24]. There also exists a mechanism by which HCV and HIV co-infection is thought to increase the risk for both HAART-related liver toxicity and cirrhosis. This mechanism consists of direct cell stress, mitochondrial dysfunction and immune reaction[25]. Though not completely clear, liver related deaths in HIV co-infected patients has been speculated to be the result of either of two reasons; increased lifespan from appropriately treated HIV (leading to the natural progression of HCV related cirrhosis and liver dysfunction) or HAART therapy induced liver toxicity[26]. Confound this with the potential drug-drug interactions, particularly with the newest of DAAs, and it is no wonder trepidation to providing treatment exists[27,28].

Prior to the creation of DAA, RBV and peg-IFN had been used with modest results. In a study published by Torriani *et al*[17] in the *New England Journal of Medicine*, 868 co-infected patients were randomized to receive either peg-IFN and RBV or peg-interferon and placebo for a total of 48 wk. Among the genotype-1 patients who received both peg-IFN as well as RBV an SVR of 29% compared with 62% in those with genotype 2 or 3 was achieved. In particular, a subgroup utilizing a higher dosing regimen proved to be the most efficacious, albeit with a greater prevalence of RBV associated anemia. Additional studies showing similar results exist[29-31].

TVR

With the approval of DAAs, subsequent studies looking at rates of SVR in the HIV co-infected population have shown promising results. In a study by Sulkowski *et al*[32] published in the Annals of Internal Medicine in 2013, a relatively small, yet randomized treatment population underwent combination therapy utilizing TVR in addition to peg-IFN and RBV. In this study 62 patients co-infected with both HCV and HIV were enrolled at multiple investigational sites. Genotype-1 infected patients, without cirrhosis, who had not had any previous HCV treatment and were noted to have "stable HIV disease" where eligible. Stable disease was classified as CD4 counts greater than 0.500×10^9 cells/L and HIV RNA levels < 100000 copies/mL. Antiretroviral regimens were allowed. SVR occurred in 74% (28/30) patients receiving TVR, peg-IFN and RBV *vs* 45% (10/22) of patients receiving peg-IFN and RBV alone. Side effects of pruritus, headache, rash and rectal pain were noted to be higher in the treatment group. Two patients were noted to have HCV breakthrough with TVR resistant variants. With these findings TVR in combination with peg-IFN and RBV improved upon previous rates SVR without appreciable drug-drug interaction or significant side effect.

BOC

In a phase Ⅱ trial by Sulkowski *et al*[33] 99 patients with co-infection of HIV and HCV were randomized in a 1:2 ratio to receive a 48-wk treatment course of either placebo or BOC in combination with RBV and peg-IFN. SVR in the triple therapy group was noted to be 63% compared with 29% in the control group. Adverse events were more common in the triple therapy arm

leading to significant amount of dropout (12 of 65). Reported adverse events included anemia, pyrexia, dysgeusia, vomiting and neutropenia. Additionally, HIV virological breakthrough occurred in seven patients; three receiving triple therapy and four in the control group. Considerable variability among patients that had breakthrough existed. In comparison to patients with HCV alone, co-infected patients who did not achieve SVR were noted to have significantly more (80% *vs* 53%) had resistant variants. Given some of the findings in this study, larger trials should be done to better characterize safety and efficacy of this regimen.

SOF

PHOTON-1: Genotype 1 patients with HIV infection: Sulkowski *et al*[34] conducted a trial utilizing an interferon sparing, 24-wk regimen comprised of SOF and RBV in genotype-1, 2 and 3. In the genotype 1 group an SVR of 76% regardless of antiretroviral regimen and with minimal drug-drug interactions was achieved. Based on this study, extrapolations of this data in co-infected patients with genotypes 2, 4, 5, and 6 current HCV guidelines recommend treatment with SOF in combination with RBV for 12 wk. Genotype 1 and 3 patients are recommended to undergo treatment with a 12 or 24-wk course of SOF, RBV and peg-IFN, respectively. Alternatives for patients who are peg-IFN intolerant exist. These regimens typically include combination therapy with SOF, simeprevir and RBV[3].

SOF/LED

NIAID ERADICATE: Genotype 1 patients with HIV infection: In the abstract presented by Osinusi *et al*[35], 50 HCV and HIV co-infected patients were given a 12-wk course of SOF and LED. Grouping based on HAART naivevs on HAART showed no difference in the 100% SVR rates achieved in both groups. No adverse events or discontinuations were noted during the treatment period.

CIRRHOTIC PATIENTS

Development of cirrhosis in patients with chronic hepatitis C infection occurs by molecular mechanisms involving inappropriate collagen deposition *via* the hepatic stellate cell. As described by Fontana *et al*[36] HCV infection is thought first to lead to release of metalloproteinases, which break down the surrounding low-density matrix within the sub-endothelial space. Then, recruitment and activation of stellate and Kupffer cells go on to deposit various forms of collagen within the extracellular matrix, forming what is termed fibrosis. More specifically, fibrosis is characterized by the presence of portal-central and portal-portal bands of this deposited collagen. With this change in the typical architecture, eventual disruption of normal processes of blood flow and nutrient exchange occurs, leading to the physiological manifestations of cirrhosis. Although new imaging modalities such as computed tomography, magnetic resonance imaging, ultrasound and transient elastography remain promising noninvasive methods for diagnosing and grading cirrhosis, the ability to distinguish moderate, less advanced, disease is lacking. The gold standard for diagnosis and monitoring both the extent of fibrosis and portal hypertension remains liver biopsy and measurement of the hepatic venous portal gradient, respectively[37]. Of all patients with HCV, 80% are estimated to go on to developed chronic infection, 10%-15% of which will develop cirrhosis at 20 years after contracting the illness[38].

BOC

Cirrhosis, regardless of its level of compensation, has been documented on several occasions to result in decreased SVR in patients being treated for HCV. A meta-analysis done by Vierling *et al*[6] examined 5, phase Ⅲ, clinical trials of biopsy proven cirrhosis patients treated with either RBV and peg-IFN alone or in combination with BOC. Pooled estimates from these studies revealed a 55% SVR in the triple therapy group compared with 17% in the RBV and peg-IFN group. In terms of adverse side effects, anemia and diarrhea were significantly more prevalent in the triple therapy treatment arm. This postulated to be the result of either added side effects of BOC or the patient's underlying cirrhosis.

Simeprevir

PROMISE: Genotype 1, previous PR, with cirrhosis: In the trial by Forns *et al*[10] as mentioned above, a subpopulation of patients with cirrhosis/advanced fibrosis were studied and were able to achieve an SVR of 74%, compared to 79% when not taking into account presence of cirrhosis. Common adverse events included rash, flulike illness, pruritus and therefore had a better side effect profile than its predecessor's BOC and TVR. One factor that must be considered when using simeprevir is testing for the Q80K mutation prior to treatment initiation. Diminished responses were noted in genotype 1A with the mutation.

SOF

FISSION: Genotype 2 and genotype 3, treatment naïve, with and without cirrhosis: Four hundred and ninety nine genotype 2 and 3 patients were treated with either 12 wk of SOF and RBV or 24 wk of peg-IFN and RBV. Of the 499, 70% were genotype 3 and of these 20% were documented cirrhotic. The trial met the non-inferiority endpoint, showing an overall SVR rate of 67%, however analysis based on HCV genotype showed genotype 2 patients achieved 93% SVR, compared to only 56% in genotype 3 patients. Furthermore, liver fibrosis further decreased SVR to 34%. Cirrhosis in the genotype-2 patients did not influence SVR rates (91%) comparatively[14].

FUSION: Genotype 2 and genotype 3, previous PR, with and without cirrhosis: In the FUSION trial,

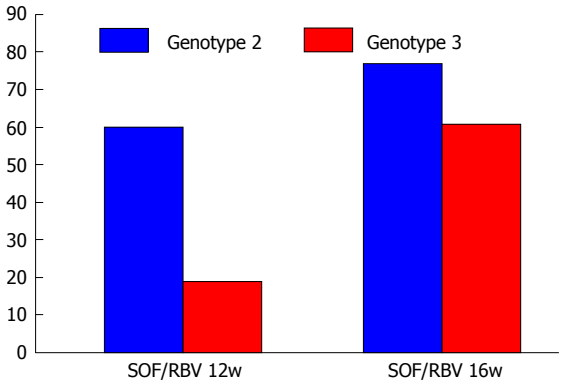

Figure 2 Cirrhotic patients in the fusion trial. SOF: Sofosbuvir; RBV: Ribavirin.

subgroup analysis among cirrhotic patients with HCV treated with either 12 or 16 wk of SOF and RBV showed favorable results among genotype 2 patients treated for 16 wk. In this group an SVR of 78% was achieved. Less favorable results were noted in the 12-wk group with slightly better results occurring in those with genotype 2 (Figure 2).

SOF/LED

A recently published randomized trial by Gane *et al*[39] in Gastroenterology focusing on treatment with SOF in combination with LED with or without RBV for treatment of null responders with cirrhosis showed promising results. All patients (9/9) receiving triple therapy were able to achieve SVR. In the group of those receiving only SOF and LED, 7 of 10 achieved SVR. Both the unknown degree of cirrhosis and the small sample size remain limiting factors in this study. Adverse effects related to the RBV regimen are consistent with prior studies of cirrhotic patients showing a greater percentage of anemia in this group. In the RBV free regimen patients remained with stable hemoglobin levels suggesting that RBV and not cirrhosis itself contributes the anemia seen with typical treatment regimens.

LONESTAR: Previous DAA + DAA failure: In the trial by Lawitz *et al*[14], similar success rates in cirrhotic patients being treated with SOF based regimens *vs* non-cirrhotic patients was noted. Twenty two of 40 previously treated patients with compensated cirrhosis fared well overall, given that 39/40 of the patients achieved SVR, however this study is limited by its relatively small size.

It remains essential that we understand that development of cirrhosis in patients with hepatitis C leads to a potentially devastating disease. Once decompensation with either development of ascites, variceal hemorrhage, encephalopathy, coagulopathy, the probability of survival is only 50% at five years, with a median survival of only two years[40,41]. Therefore, pursuit of a cure using direct antiviral therapy should be pursued. Of the discussed DAAs, SOF-based regimens appear to provide the best chance of this and are consistent with the recommended treatment regimens of recently published consensus guidelines.

BARRIERS TO TREATMENT

Hepatitis C is a physical, mental, and social disease affecting not only the individual, but also the individual's loved ones and society as a whole. Considered a global disease, and for that matter the only currently curable chronic viral infection, the importance of pursuing treatment for hepatitis C remains paramount. Despite this, several barriers hindering this effort have been identified. These include: awareness of available therapy, financial constraints, and practitioners willing to prescribe treatment.

Comorbid psychiatric illness

It is well known the concomitant psychiatric illness plagues patients with hepatitis C. It is currently estimated that the largest at risk population for contracting hepatitis C is it that of intravenous (*iv*) drug users[42]. The problem is two-fold, in a study done by Johnson *et al*[43] in the American *Journal of Gastroenterology*, 309 current *iv* drug users undergoing substance abuse treatment were evaluated. In this group over 50% of test subjects were found to be positive for HCV antibodies and of the HCV positive patients, over half were noted to have concomitant depression. In addition to the pre-existing depression seen in this group, the treatment for HCV itself up until this point had also significantly contributed to depressive symptoms. Interferon in particular, has had a documented side effect profile consisting of fatigue, anxiety, and depression. Despite the black box warning associated with peg-IFN, studies show that patients with mood disorders currently in remission and receiving treatment should not be excluded from receiving interferon therapy[44]. Additionally, treatment of interferon associated depression and cognitive disorders can be achieved with the use of antidepressants and stimulators[45,46].

It is estimated that one in six incarcerated patients have hepatitis C and therefor the public perception remains that hepatitis C is acquired illness. As such, I anticipate continued difficulty obtaining social and financial support for concomitant *iv* drug use treatment, despite the fact that studies show co-administration of strict drug treatment program decreased risk of relapse and increase completion of treatment and monitoring.

Cost

Despite the excitement and promise these new therapies all hold, the cost-effectiveness of pursuing cure for hepatitis C has been a tougher pill to swallow than the actual treatment itself. SOF has been drawing attention recently. At around one thousand dollars per pill, 12 wk, a standard treatment course would run the patient and their insurance provider approximately $84000 with other DAA sharing similar price tags. The endeavor of validating coverage depends on the potential long-term savings from providing a cure. It is

difficult to estimate the exact savings per patient due to the various other factors involved, however rough estimates are possible. Consider this, the average annual health care costs for patients with chronic hepatitis C infection without cirrhosis is $17277. Once cirrhosis develops costs rise to $22752 among patients with compensated cirrhosis, and $59995 once end-stage liver disease develops[47]. Patients with compensated cirrhosis have been documented to live for at least a decade prior to development of decompensation[40]. This would amount to approximately $275000 in health care costs over this decade. Considering the median two-year survival for decompensated cirrhosis an additional $120000 would accrue. Lastly, if a candidate, liver transplantation with an average price tag ranging in upwards of $575000, per United Network for Organ Sharing, brings the total to over $1 million in health care costs[48]. Looking back at the treatment price tag of $84000 little hesitation should be had. This is not the case however because many variables play a part. Notably, incomplete treatment, unsuccessful treatment, and reinfection are always possible, particularly in patients with comorbid psychiatric illness, concomitant drug addiction, and poor social support; all known risks factors for contracting HCV[49]. In the long run this issue should continue to fade in its controversy given that minimum manufacturing costs for producing direct acting antivirals have been estimated at $100-$250 for a 12 wk course of treatment once patent expires and production of generic versions is available[50].

Aside from the cost savings achieved when no longer needing to treat the manifestations of chronic hepatitis C, cure of hepatitis C has been shown to provide additional benefits. Beside the improvement in psychological and social well-being which accompanies cure of hepatitis C, treatment also has been shown to decrease and potentially reverse cirrhosis, esophageal varices, and the risk for development of hepatocellular carcinoma[51-53].

Practitioner experience

In patients who are co-infected with HIV as well as HCV, the potential for complex drug interactions between HAART and direct antiviral agents can lead to trepidation among primary care providers when debating the initiation of treatment for HCV. Additionally, a practitioner's concerns about reinfection as well as their bias regarding *iv* drug users also represent barriers to engagement in treatment of HCV in patients[54]. Therefore, it is recommended, as outlined in the recent consensus article published in The Infectious Disease Society of America, that only practitioners who are comfortable in routine treatment of HIV, cirrhosis, and/or have familiarity with DAA should be involved in treatment for HCV. Therefor infectious disease specialists and hepatologists should be the providers responsible for initiating treatment of HCV for co-infected individuals, cirrhotic patients, and patients who have previously failed treatment.

Tolerability

Treatment for HCV had long been known to be as unpleasant as it was burdensome, leading to noncompliance and decreased quality of life during treatment. IFN based regimens, in particular, are riddled with adverse side effects[55]. For example, both the BOC and TVR regimens have complex dosing schedules and heavy pill burdens that will invariably lead to both incomplete compliance and treatment dropout[56]. As new treatments arise, the effect of the various regimens should not only be examined for response rates but should be evaluated for their tolerability. In several studies, Younossi *et al*[57,58] did just that. Examination of patient reported outcomes and health related quality of life data of patients in four different phase Ⅲ clinical trials noted that patients who received treatment with the peg-IFN free regimen of SOF and RBV noted the smallest decline in quality of life scores among all treatment groups suggesting that INF free regimens lead to better tolerability and better adherence; both factors essential in increasing compliance. Aside from side effects, route of administration will surely have patients asking for IFN free regimens[59].

CONCLUSION

As indicated in several of the studies reviewed, SOF appears to currently be one of the best choices in all-comers. Further studies with larger populations of difficult to treat patients are warranted to fully assess the continued success, safety and side effects. Based on the studies examined, most of which included phase Ⅱ and Ⅲ trials, the current literature favors usage of a SOF-based regimen in patients with cirrhosis, HIV/HCV co-infection and prior treatment failure. As shown, SOF has proven efficacy in both cirrhotic and non-cirrhotic patients and also appears to span all genotypes. The limited drug-drug interactions make it a favorable option in patients co-infected with HIV. Additionally, the route of administration and the favorable side effect profile will lead to overall improvement in quality of life and compliance. Treatment and cure of hepatitis C is now probable, even in "difficult to treat" patients. Without financial assistance programs, practitioner awareness, and co-administered substance abuse treatment programs the potential gains these revolutionary drugs offer will fail to render an impact on prevention of long-term hepatitis C complications.

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MINIREVIEWS

Mechanisms of hepatocellular carcinoma and challenges and opportunities for molecular targeted therapy

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Abstract

The incidence and mortality of hepatocellular carcinoma (HCC) have fallen dramatically in China and elsewhere over the past several decades. Nonetheless, HCC remains a major public health issue as one of the most common malignant tumors worldwide and one of the leading causes of death caused by cancer in China. Hepatocarcinogenesis is a very complex biological process associated with many environmental risk factors and factors in heredity, including abnormal activation of cellular and molecular signaling pathways such as Wnt/β-catenin, hedgehog, MAPK, AKT, and ERK signaling pathways, and the balance between the activation and inactivation of the proto-oncogenes and anti-oncogenes, and the differentiation of liver cancer stem cells. Molecule-targeted therapy, a new approach for the treatment of liver cancer, blocks the growth of cancer cells by interfering with the molecules required for carcinogenesis and tumor growth, making it both specific and selective. However, there is no one drug completely designed for liver cancer, and further development in the research of liver cancer targeted drugs is now almost stagnant. The purpose of this review is to discuss recent advances in our understanding of the molecular mechanisms underlying the development of HCC and in the development of novel strategies for cancer therapeutics.

Key words: Hepatocellular carcinoma; Oncogene; Signal pathway; Cancer stem cell; Molecular targeted therapy

Core tip: The molecular mechanism of hepatocarcinogenesis is complex and is associated with the regulation function of a variety of signal transduction pathways and key molecules. Presently, there are many drugs that target the molecules that are involved in tumor development (molecule-targeted drugs), but the specificity of such drugs is lacking. This paper summarizes the targeted molecular drugs which may be useful for the clinical treatment of liver cancer, and lays the theoretical foundation for the further study of more specific and effective drugs that target the molecules involved in liver cancer.

Chen C, Wang G. Mechanisms of hepatocellular carcinoma and challenges and opportunities for molecular targeted therapy. *World J Hepatol* 2015; 7(15): 1964-1970 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i15/1964.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i15.1964

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and severely harms public health. In China, mortality caused by liver cancer accounts for about 50% of the total mortality due to liver cancer worldwide, making China one of the countries most affected by this disease. Surgical treatment is still the most effective way to treat liver cancer. However, a low curative resection ratio and high recurrent metastasis ratio make this treatment less than ideal[1,2]. Molecule-targeted therapy is a new approach in liver cancer treatment and is based upon the study of HCC carcinogenic mechanisms and the molecular biology of liver cancer. The key point in the study of molecule-targeting drugs for the treatment of liver cancer is to clarify the molecular mechanism of hepatocarcinogenesis and identify the important target molecules.

This paper examines the molecular mechanisms that control hepatocarcinogenesis and discusses the challenges and potential new approaches to studying molecule-targeting drugs for the treatment of HCC.

THE MOLECULAR MECHANISM OF HEPATOCARCINOGENESIS

In recent years, research on the molecular mechanisms of tumor development has been advancing very rapidly, and many new theories have been proposed. However, progress in the research of hepatocarcinogenesis mechanisms is relatively slow, and practical studies that fully examine the interplay between these mechanisms are few. Therefore, we still do not fully understand the mechanisms of hepatocarcinogenesis which is closely related to the specialized functions of the liver.

The competition between proto-oncogene and anti-oncogene

An important contributing factor to the development of a tumor is the balance between the activation and inactivation of the proto-oncogenes and anti-oncogenes. Proto-oncogenes activate cells to enter the proliferation cycle, prevent apoptosis and inhibit differentiation. In healthy cells, proto-oncogenes are expressed at very low levels are not expressed at all. However, environmental influences such as ionizing radiation, physical damage, and specific chemicals can cause genetic mutations to occur in these genes, activating the proto-oncogenes into oncogenes. In liver cancer, N-ras and hepatitis B virus (HBV) X protein are the most common proto-oncogenes[3].

A strong correlation between chronic HBV infection and HCC has been identified, among HBV proteins, HBx has been termed "viral oncoprotein" because of its multifunctional activities on cellular signal transduction pathways, transcriptional regulations, cell cycle progress, DNA repair, apoptosis, and genetic stability by interacting with different host factors[4]. HBx is often expressed from integrated fragments of the HBV genome in HCC tissues, and mice expressing HBx in their liver either develop HCC spontaneously or display increased susceptibility to hepatocarcinogens. Moreover, HBx also interacts with various signaling pathways that are linked to cell proliferation and survival, such as RAS/RAF/MAPK, MEKK1/JNK and PI3K/AKT/mTOR. Additionally, HBx can modulate apoptosis and immune response by direct or indirect interaction with host factors.

Anti-oncogenes (antioncogenes) are recessive and act as susceptibility genes for cancer. They are expressed in normal cells and regulate the proliferation and differentiation of cells. These genes can inhibit cells from entering the proliferation cycle, induce terminal differentiation and cell apoptosis, are essential for the maintenance of organism genome integrity and inhibit tumor growth. The *p53*, *Rb*, *p21* and *PTEN* genes are the most common anti-oncogenes[5]. The formation of malignant tumors is a multi-step process involving many kinds of oncogene activation and anti-oncogene inactivation. Moreover, apart from the competition between proto-oncogenes and anti-oncogenes, some anti-oncogenes may participate in gene regulation pathways that have normal anticancer functions but have not been completely proven to be anti-oncogenes. They have been proven to play an important role in the initiation and progression of the tumor. For example, B cell translocation gene-2 (*BTG2*) is a member of the anti-proliferative gene family located on human chromosome locus 1q32 and encodes a protein of 158 amino acids with a molecular weight of about 17 kDa. BTG2 contains the response element of the wild-type *p53* gene at position-74 to -122. Many experiments have shown that BTG2 activation requires the assistance of p53 activation[6]. BTG2 is a member of the family of early response genes, connecting the upstream p53 and downstream cell cycle proteins, inhibiting cell proliferation, and is expressed at low levels in a variety of tumors. Our previous studies have shown that the expression of BTG2 decreased significantly in HCC, but expression correlated positively relative to the expression of p53 and negatively relative to the expression of cyclin E. However, in rat models of liver cancer, BTG2 expression was significantly increased in primary cancers of the liver, but dramatically decreased in advanced tumors[7]. BTG2 functions as a tumor suppressor, but due to a lack of evidence of mutations in tumors, BTG2 cannot be confirmed to be an anti-oncogene. However, numerous studies have suggested BTG2 to be a potential anti-oncogene. Of course, the function of many proto-oncogenes and anti-oncogenes is unknown,

and the balanced expression of these genes is currently considered to be a central regulator of homeostasis. Once this balance is upset, tumor formation may occur.

Abnormal activation of molecules signaling pathway

Research of tumor signal transduction has been a hot topic in the field of tumor basic research and has served as the theoretical basis of a variety of molecule-targeted drugs. It is thought that abnormal activation of many molecules in various signaling pathways contributes to the progression of liver cancer, and the foundation of molecule-targeted drugs is to selectively block these signal transduction pathways and disrupt that regulatory mechanism, including the following several kinds of classic signal transduction pathways.

Ras/Raf/MAPK signaling pathway

Among the investigated signaling pathways involved in HCC, the Ras/Raf/MAPK is the most critical pathway in the development of HCC. Signals from membrane-bound tyrosine kinase receptors, such as endothelial growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR), vascular EGFR, c-Met and platelet derived growth factor receptor (PDGFR), are transduced to the cell nucleus through Ras/Raf/MAPK pathway in order to regulate multiple cellular functions including cell growth and survival, and differentiation. Dysregulation of this pathway leads to inappropriate cellular activities including enhanced cell growth, differentiation, and survival, and ultimately to cancer[8]. Up-regulated activation of the Ras/Raf/MAPK signaling pathway has been well studied in HCC and correlates with advanced stage. Mechanisms for the increased activity of the Ras/Raf/MAPK signaling pathway in HCC include aberrant upstream signals (EGFR signaling, IGF signaling), inactivation of Raf kinase inhibitor protein (a suppressor of the Ras/Raf/MAPK pathway) and induction by hepatitis viral proteins (such as the hepatitis B x protein and the hepatitis C core protein)[9]. Potent drugs blocking Ras/Raf/MAPK signaling are still at exploratory phase, except for sorafenib that has activity inhibiting B-Raf.

PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway, which plays a significant function in cell growth, survival regulation, metabolism, and antiapoptosis also plays an important role in HCC and is activated in 30%-50% of HCC. In normal tissue, this pathway is negatively regulated by the tumor suppressor phosphatase on chromosome 10 [phosphatase and tensin homolog (PTEN)], which targets the lipid products of PI3K for dephosphorylation. Anomalies in PTEN function may lead to overactivation of the PI3K/AKT/mTOR pathway in HCC. PTEN expression is reduced in nearly half of all HCC tumors, resulting in constitutive activation of the PI3K/AKT/mTOR pathway[10]. A tissue microarray analysis of HCC samples revealed that the loss of PTEN and overexpression of pAkt and p-mTOR were correlated with tumor grade, intrahepatic metastasis, vascular invasion, TNM stage, Ki-67 labeling index, and matrix metalloproteinase (MMP)-2 and (MMP)-9 upregulation[11].

Wnt/β-catenin signaling pathways

The Wnt/β-catenin signaling pathway, often called the Wnt classic signaling pathway, is composed of the Wnt protein, Wnt protein ligand (frizzled protein), and related regulator proteins such as GSK-3β and β-catenin. A study found that the Wnt/β-catenin signaling pathway is an important signaling pathway in the process of growth and development, and its abnormal activation is closely related to the occurrence of cancer. When the pathway is activated by upstream stimulation, the Wnt protein binds to its ligand and β-catenin accumulates in cells, where it is activated and transferred into nucleus. In the nucleus, β-catenin dimerizes with the downstream specific transcription factor LEF/TCF, which regulates the transcription of key genes such as cyclin D[12,13]. The abnormal activation of Wnt/β-catenin is an important signaling pathway in the carcinogenesis of hepatoma, and aberrant β-catenin could be detected in 90% liver cancer[14]. Calvisi *et al*[15] reported that transgenic c-myc/TGF-P mice developed liver cancer, and this was associated with a gene mutation in β-catenin, suggesting that the activation of the β-catenin gene may increase the growth and metastasis of cancer. Infection with HBV and HCV can induce high levels of β-catenin, and promote the occurrence of liver cancer[16,17].

Hedgehog signaling pathways

Currently, the hedgehog (Hh) signaling pathway is a key regulation pathway in the formation of liver cancer. In mammals, the Hh signaling pathway is mainly composed of the Hedgehog ligand, two transmembrane protein receptors (Ptch and Smo), and the nuclear transcription factor Glib and downstream genes. When the Hh signaling pathway is activated, the Hh ligands bind to the Ptch receptors, and block the inhibitory effect on Ptch on Smo. Smo enters into the cytoplasm to activate downstream transcription factor Gli, inducing the expression of specific genes, thereby regulating cell growth, proliferation and differentiation. The Hh signaling pathway in liver cancer is abnormally activated, but in mature normal liver tissue, the Hh signaling pathway is not initiated[18-20]. Studies by Sicklick *et al*[21] suggested a dysfunction of Hh signaling in human liver, and found a high expression of Hh signaling as demonstrated by elevated expression of Shh, Ptch, Smo and Gli1, all of which regulate c-myc gene expression mediated by Smo. Kim *et al*[22] found that in liver cancer tissues, the inhibition of the *Gli2* gene can decrease the expression of c-myc and Bcl-2 and increase the expression of p27, which regulates the cell cycle, inhibits proliferation and abrogates the growth of liver cancer cells.

Other signaling pathways

There are many other cell signaling pathways involved in liver cancer, including Notch signaling pathway[23-25],

IGF/IGFR signaling pathway[26,27], HGF/c-Met signaling pathway[28,29] and EGFR signaling pathway[30]. They are the important regulatory pathways of liver cancer and are important for initiation and development of metastasis. Many gene regulatory points in these pathways have been used as targets for targeted therapy of cancer in clinical trials, and these molecular targeted drugs designed for these pathways are expected to become the new direction for the treatment of liver cancer.

Liver stem cells and liver cancer stem cells

The tumor stem cell theory postulates that there are cancer stem cells in the human body that give rise to cancerous tissues. There are two main liver cancer stem cell theories[31,32]. One theory states that liver cancer stem cells are derived from mature hepatocytes. The other theory argues that liver cancer cells are derived from intrahepatic undifferentiated stem cells or abnormal differentiated cells of oval cells. Of course, the latter theory is supported by the greatest number of studies. Liver cancer can be initiated by stem cells and their daughter cells. This may occur in depolarized mature hepatocytes and bile duct epithelial cells. Baumann *et al*[33] found that the occurrence and pathological polymorphism of primary liver cancer was due to the blocking of liver stem cell differentiation. It is characterized by poorly differentiated liver cancer cells when they are blocked in their early stage of development, in between a HCC and a cholangio cell. However, when these cells are locked in later stages of differentiation, they are characterized as HCC and cholangio cells. More recently, the Henry Lilian Stratton basic research single theme meeting at the American association for the study of liver diseases reported on the research progress of stem cells in liver diseases and cancer. They focused on the identification of hepatic stem cells and liver cancer stem cells, research progress in our understanding of their functions and clinical transformation of these cells in patients. Liver stem cells begin as liver progenitor cells (LPCs), and then de-differentiate into pluripotent stem cells, and then transdifferentiate to become disease-specific liver stem cells. However, the occurrence of tumor-initiating stem-like cells and the abnormalities of some signaling proteins, such as transforming growth factor β, β-catenin and LPCs markers, become potential signs of chronic liver damage and liver cancer[34]. Among them, the original stem cell-like cells of the tumor play an important role in cell transcription and reverse transcription in the formation of liver cancer, and the detection and treatment for this kind of cell is considered to be the new focus liver cancer research and treatment[35].

TARGETED THERAPIES IN LIVER CANCER

The theory has been put forward that a potentially revolutionary change in tumor medical treatment will occur with the development of molecule-targeted therapy. With the continuous progress of tumor basic research, more and more new tumor targeted drugs are used in the clinic, effectively improving the survival time of patients with tumors. In our opinion, the recent decade has seen the fastest growth in tumor targeted drugs, creating a new approach for tumor treatment.

Molecule-targeting drugs for liver cancer

Sorafenib was approved by the Food and Drug Administration (FDA) as a molecule-targeting drug for the treatment of primary liver cancer, mainly for advanced hepatocellular carcinoma[36,37]. It was originally designed for the treatment of kidney cancer and non-small cell lung cancer, and was the first multiple targeted drugs against Raf kinase. Its main mechanism of action is to block signal transduction mediated by the Raf/MEK/ERK pathway, and inhibit various tyrosine kinases, including vascular endothelial growth factor-2 (VEGF-2), VEGF-3, PDGFR-β and c-Kit protein. All of these tyrosine kinases are associated with tumor growth, and inhibition of tumor growth can be demonstrated when these drugs are applied[38,39]. Currently, phase Ⅱ clinical trials have shown that sorafenib and doxorubicin is a safe and effective treatment for the degradation of microspheres for embolization, and it is worth noting that the efficacy and safety of sorafenib in patients with hepatic insufficiency is not yet clear. Studies have found that the iron chelator (deferoxamine) can inhibit the cell cycle and induce apoptosis to protect the liver and inhibit cancer formation. In recent reports, deferoxamine has shown satisfactory efficacy and safety in 10 patients with advanced liver cancer, which has suggested that deferoxamine is appropriate for patients with poor liver function and advanced liver cancer, and might be considered a useful supplement for sorafenib[40]. However, in 2013, Rimassa *et al*[41] reported a phase Ⅱ clinical trial that concluded that for those patients with advanced liver cancer after radiation treatment failure, when the sorafenib dose increased from 400 mg, 2 times/d, to 600 mg, 2 times/d, survival time and their quality of life failed to improve. This observation suggests that an increased dose of sorafenib does not necessarily translate into a clinical benefit for patients with advanced liver cancer. Brivanib is another promising targeted drug for the treatment of liver cancer. It is a small molecule tyrosine kinase inhibitor of VEGF and the fibroblast growth factor receptor family, whose main mechanism of action is to inhibit vascular endothelial growth factor and fibroblast growth factor receptors[42,43]. In 2011, phase Ⅱ clinical trials with brivanib as a first-line treatment for advanced liver cancer suggested that the drug is safe. In the study, a brivanib dose of 800 mg, 1/d was used and liver cancer patients on the drug showed a progression-free survival ratio of 18.2%. In this same patient population, the median disease-free survival was 2.7 mo, there was a complete remission in one case, a partial response (PR) in three cases, stable disease (SD) in 22 cases, and the median survival period was 10 mo[44]. Recently, Finn

Table 1 Molecular targets and potential therapeutic agents for hepatocellular carcinoma

Molecular targets	Therapeutic agents	Phase study	Mechanism of action
VEGF/VEGFR	Bebacizumab	Ⅱ	Anti-angiogenic
	Vatalanib (PTK787)	Ⅰ - Ⅱ	
	Cediranib (AZD2171)		
	Brivanib		
	Sunitinib	Ⅱ - Ⅲ	
	Linifanib (ABT869)		
	Ramucirumab		
EGFR/ErbB1/Her1	Cetuximab		EGFR inhibitor
EGFR/ErbB1/Her1	Erlotinib	Ⅲ	
EGFR/ErbB1/Her1	Gefitinib	Ⅰ - Ⅱ	
EGFR/ErbB1/Her1 and ErbB2/Her2/Neu	Lapatinib		
IGF/IGFR	OSI-906		
	IMC-A12		
	AVE1642		
	BIIB922		
Ras/Raf/MEK/ERK	Sorafenib	Ⅲ	Multi-kinase inhibitor
PI3K/Akt/mTOR	AZD8055		mTOR inhibitor
	Everolimus	Ⅲ	
	Sirolimus	Ⅰ - Ⅱ	
	Temsirolimus		
Wnt-β-catenin	PFK118-310		
	PFK115-584		
	CGP049090		
MET	Tivanitib	Ⅱ	HGF/c-MET inhibitor
HSP-90	STA-9090	Ⅰ - Ⅱ	HSP-90 inhibitor

VEGFR: Vascular endothelial growth factor receptor; EGFR: Endothelial growth factor receptor; IGF: Insulin-like growth factor; mTOR: Mammalian target of rapamycin; MET: MNNG HOS transforming gene; HGF: Hepatocyte growth factor; HSP: Heat shock protein; STA-9090: Ganetespib, Hsp90 inhibitor.

et al[45] reported on clinical trials of brivanib as second-line therapy in advanced liver cancer in patients that were receiving the same dose of brivanib (800 mg, 1/d). In the 46 patients studied, there was PR in two cases (4.3%), SD in 19 cases (41.3%), and progressive diseases in 19 cases (41.3%). The tumor response rate was 4.3%, the disease control rate was 45.7%, and the median survival time as 9.79 mo. Ultimately, they came to the conclusion that brivanib and sorafenib are safe and effective treatments in patients with advanced liver cancer. Table 1 lists the results of the most recent clinical trials, and the various therapies currently used to treat HCC.

Bottleneck of molecular targeted therapy of liver cancer

Molecule-targeted therapy is the most active area of in the tumor treatment research, and we have made great progress in improving the survival time of cancer patients using these types of therapies. However, there is not one drug completely designed for liver cancer, and further development in the research of liver targeted drugs is now almost stagnant. The main reasons for this are as follows: (1) The mechanism of liver cancer is complex, so it is difficult for the development of specific targeting drugs. Liver cancer is the result of the combined action of multiple factors, all of which we know very little about, and the liver cell has its own characteristics and proliferates rapidly. Once the cancer occurs, the hyperplasia or resistance mechanism of the liver cancer cell varies, so it is not easy to find specific targets; (2) The most targeted therapeutic drugs are less effective, and the curative effect is not ideal; (3) The selectivity of targeted drugs for the treatment of liver cancer targets is not high, there are adverse reactions, there is a high resistance such as the "off-target effect", and the research cost is high, so it is difficult to put into widespread use; and (4) Different responses to targeted drugs may occur in liver cancer patients, based upon extrinsic or intrinsic factors such as ethnic and gender differences. We are still unable to accurately detect and monitor liver cancer cell change sat the molecular level, so the potential for disease monitoring is not sufficient.

OPPORTUNITIES AND CHALLENGES

The treatment of liver cancer fundamentally depends upon the systemic understanding of the pathogenesis of liver cancer. Surgery, interventional embolization, chemotherapy and radiation are still the main treatments for liver cancer. A better recognition and re-development of existing treatments may likely bring about new hope for the treatment of liver cancer. With the development of new biological technologies and an increase in our knowledge of the molecular mechanisms of liver cancer, the treatment of liver cancer is facing new opportunities and challenges. Molecule-targeted therapy will gradually become a new favorite for the treatment of liver cancer, and also represent the future developmental direction of the treatment of liver cancer. Furthermore, basic

research breakthroughs will create more effective methods of liver cancer targeted therapy, and in conjunction with normalized and individualized clinical treatments, they will eventually result in new successes in the treatment of liver cancer.

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