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Review Article

Current and forthcoming perspectives in linkage to care of hepatitis C virus infection: Assessment of an Italian focus group

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ABSTRACT

Hepatitis C virus (HCV) remains a significant public health problem and is one of the major causes of chronic liver disease worldwide. In recent years many new tools to facilitate widespread HCV screening and new therapeutic options with excellent efficacy and tolerability profiles and cost lowering policies have become available. To fully utilise these new tools, the link between local and specialist centres for the management of HCV infection must be reinforced. In order to GAIN further insight into these aspects, with a particular focus on the Italian scenario, a group of experts met to discuss relevant aspects and open issues on chronic HCV. As a summary of that meeting, the following aspects are here overviewed: (i) global situation of HCV; (ii) screening, diagnosis and indications for the treatment of HCV; (iii) the Italian situation of HCV referrals; (iv) 'hard to reach' patients; (v) treatment of HCV with extrahepatic manifestations; (vi) treatment of patients with advanced cirrhosis. It is the intention of the expert panel to further promote widespread screening and eradication policies that should be accompanied by greater interaction, by attempting to involve all healthcare providers in an organised process to facilitate linkage to care of patients with HCV infections.

1. Introduction

Hepatitis C virus (HCV) is an important public health problem as it remains as one of the major causes of chronic liver disease worldwide [1]. According to the World Health Organization, at least 75 million people harbour HCV, and of these, ̃70,000 die each year from an HCV-related cause [2]. However, these numbers are likely to be underestimated if one considers that there is a large number of individuals who are unaware that they are HCV positive until the disease progresses into cirrhosis and its complications. Considerable progress has been made in the management of the chronic hepatitis C largely due to better understanding of the pathophysiology of the infection and to developments in diagnostic procedures and prevention of the spread of HCV infection. Undoubtedly the most substantial progress has been made in HCV treatment by the advent of direct-acting antivirals (DAAs) that guarantee the extremely high likelihood of efficacy with almost no adverse effects [3]. Moreover, the risks of developing complications and liver-related mortality are significantly reduced by HCV eradication even in patients with cirrhosis. However, the progression of chronic liver injury should be still considered, especially in the presence of co-factors such as diabetes, liver steatosis, excessive alcohol consumption, and hepatitis B virus (HBV) infection [4–8]. HCV infection is also associated with several extrahepatic manifestations, most of which can be reversed by viral elimination with a concomitant reduction in all-cause mortality [9–12].

In consideration of the new tools for widespread HCV screening along with the large number of therapeutic options with excellent efficacy and tolerability profiles and cost lowering policies — to which the majority of HCV-positive individuals have access — it seems judicious to identify strategies that can further optimise linkage to care and treatment uptake. In this light, there is still the

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need to strengthen the link between local and specialist centres for the management of HCV infection.

With the aim of providing further insight into these issues, and to offer a particular focus on the Italian scenario, a group of experts convened to discuss relevant aspects and open issues on chronic hepatitis C. Herein, the most important aspects are presented. Beginning with an overview of the: (i) global situation of HCV, summaries are given on (ii) screening, diagnosis and indications for the treatment of HCV; (iii) the Italian situation of HCV referrals; (iv) 'hard to reach' patients; (v) treatment of HCV with extrahepatic manifestations; (vi) treatment of patients with advanced cirrhosis.

2. The global footprint of HCV

The burden of viral liver disease is significant, with approximately 90% of the 1.3 million deaths due to end-stage liver-related complications of HBV and HCV [13]. In 2016 the World Health Organization (WHO) established viral hepatitis elimination targets, with the aim of reducing deaths from HBV and HCV infections by 65% within 2030 [14]. In order to accomplish this, there needs to be a 90% reduction in new cases of chronic HBV and HCV infection, from 6 to 10 million in 2015 to 900,000 by 2030. These goals are part of a new perspective on the treatment of HCV, firstly targeted at the single individual by treating liver disease and viral hepatitis, and secondly aimed at the community to reduce the spread of infections and the burden of disease.

In this light, international guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) both recommend characterisation of liver disease in all infected patients regardless of the treatment regimen selected and provide universal access to therapy [15,16]. Thus, the overall strategy is that eradication can be achieved through elimination of the HCV infection, resulting in a reduction of the incidence, prevalence, morbidity, and mortality. However, several limitations need to be recognised, as global elimination of HCV will not be possible with therapeutic intervention alone, but will require an effective vaccine together with global efforts. As such, HCV infection needs to be recognised as a global health threat. The WHO, AASLD and EASL have prioritised the treatment of virtually all HCV-infected subjects, with the overall aims of preventing disease progression and onward transmission, and improving the quality of life [14–16].

Regarding the elimination targets established by the WHO, the annual number of people initiating DAAs for HCV worldwide has increased from around 1 million in 2015 to 1.5 million in 2016, bringing the overall number of patients accessing DAAs for HCV to nearly 3 million [17]. Nevertheless, it is acknowledged that the majority of the 71 million people with HCV still remain untreated. Of interest, in G7 countries, following the introduction of DAAs, the pool of treatment-experienced patients is apparently being cleared, and most future HCV patients will likely present with early-stage disease and treatment-naïve status [18]. Such a scenario has potential benefits since it can reduce the mortality associated with advanced liver disease and extrahepatic manifestations of HCV [19–23].

Finding and treating currently undiagnosed subjects will require greater efforts in screening, and the WHO has identified cohorts of individuals who should undergo viral testing, including people who inject drugs (PWID), men who have sex with men (MSM), migrants, prisoners, and certain birth cohorts, as well as people living in countries with limited access to treatment [13]. However, even after identification, it should be noted that most countries in Europe still do not treat HCV in non-hospital settings [24]. This highlights the need to optimize HCV monitoring to more comprehensively address policy issues. In Italy, as of December 2018, over 165,000 HCV treatments have been administered since 2015, according to the National registry data from the Italian Medicines Agency (AIFA). Considering this, Italy is close to meeting the WHO target of a 65% reduction in liver-related mortality by 2030, without requiring "strong" further interventions [25].

According to the expert discussion, the main barriers to improving HCV care in Italy are the low screening rates and lack of an effective linkage-to-care policy for HCV infection. Extrapolating data from the Sicilian RESIST-HCV registry (representing 9.2% of the Italian population), the prevalence of HCV-RNA positive individuals will decrease from 1 to 1.5% in 2016 to 0.4 to 0.8% in 2022, switching from a peak of over 55,000 treatments in 2018 to an estimated 7000 in 2022. While such numbers are indeed encouraging, this still means that a substantial pool of subjects remains to be identified and treated. Based on universal access to treatment, this should imply simplified therapies and an expansion of the pool of prescribers (e.g., GPs, extra-hospital specialists) in order to identify, manage and follow individuals with HCV infection.

Indeed, the plan for HCV elimination requires optimised screening policies and treatment strategy through a highly effective, well tolerated and affordable regimen with a rescue/re-treatment plan prior to initiating therapy. While long-term follow-up is recommended in patients with advanced fibrosis even after achieving sustained virologic response (SVR), GPs play a major role in the long-term follow-up of patients without advanced fibrosis but at high risk of re-infection.

3. Screening, diagnosis, and indications for treatment of HCV

Commonly employed screening strategies for HCV involve detection of anti-HCV antibodies in serum or plasma or on whole blood or dried blood spots by enzyme immunoassays, or in serum, plasma, fingerstick whole blood or saliva by rapid diagnostic tests. Importantly, anti-HCV antibody screening should be offered with linkage to a program of prevention of spreading, diagnostic assessment and early treatment [3]. In many cases, a 'test-and-treat' strategy can be used in which HCV therapy is started immediately after a confirmed HCV diagnosis. Such a strategy bears several advantages that include: (i) lean and fast pre-treatment assessments required with pangenotypic DAA regimens; (ii) lower probability for patients to be lost to follow-up; (iii) more patients linked to care. At present, the EASL recommends the so-called 'reflex' testing to increase the linkage to care. This requires the presence of HCV RNA in serum, plasma, or whole blood with prespecified detection limits based on the assay used [3]. Alternatively, the presence of HCV core antigen in serum or plasma by enzyme immunoassay can be used as confirmation of infection [3]. The endpoints of antiviral therapy are undetectable HCV RNA in serum or plasma by a sensitive assay (LOD $\leq$15 IU/mL) at 12 (SVR12) or 24 weeks (SVR24), undetectable HCV core antigen in serum or plasma by enzyme immunoassay after 24 weeks, or undetectable HCV RNA in serum or plasma at 24 weeks, using a qualitative HCV RNA assay with a lower limit of detection $\leq$1000 IU/mL, after end of treatment [3]. Genotyping is normally recommended prior to treatment initiation to determine the choice of therapy and its duration [3]. Testing for HCV resistance prior to treatment is not recommended, although RAS testing is mandatory after relapse.

While beyond the scope of the present review, a number of DAA regimens are available to treat patients across all genotypes and can be divided into genotype-specific regimens and pangenotypic regimens. At present, three pangenotypic DAA regimens are available in most European countries (sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, glecaprevir/pibrentasvir), which can cure the majority of patients across all genotypes and can be used in almost all patients.

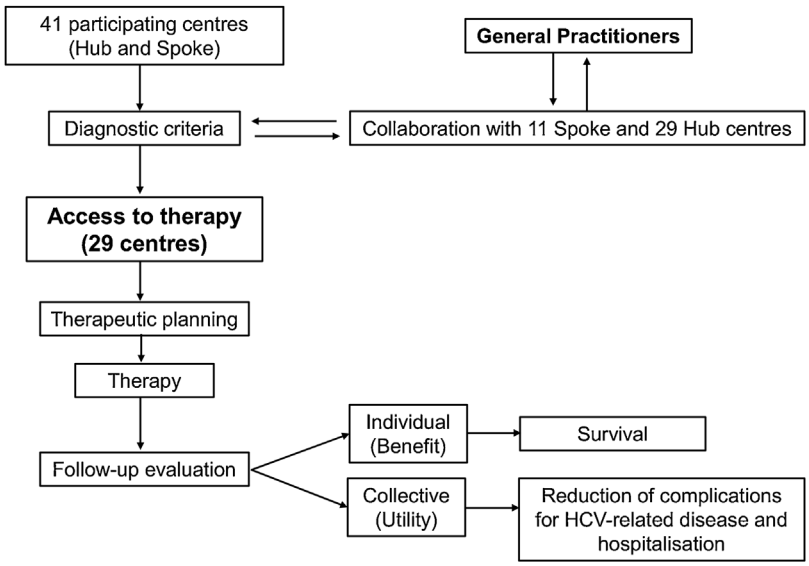

Fig. 1. The 'Hub and Spoke' model used in Sicily for hepatitis C virus screening, diagnosis, care, and follow-up. HCV, hepatitis C virus.

Lastly, some existing comorbidities should be considered when initiating treatment. Some DAA combinations such as elbasvir/grazoprevir and glecaprevir/pibrentasvir can be used at all levels of renal function and insufficiency. One exception is sofosbuvir/velpatasvir, the safety and efficacy of which have not been tested in patients with eGFR <30 mL/min/1.73 m^2. In this regard, elbasvir/grazoprevir has been studied in stage 4–5 chronic kidney disease [26], and no dose adjustment is required in patients with mild, moderate, or severe renal impairment (including patients receiving haemodialysis or peritoneal dialysis).

In those with advanced liver disease such as Child–Turcotte–Pugh B and C cirrhosis, protease inhibitor-containing regimens (glecaprevir/pibrentasvir and elbasvir/grazoprevir) are contraindicated. While new DAA regimens have greatly simplified treatment, it is prudent that clinicians keep these limitations in mind and perform adequate testing of renal and hepatic function in patients prior to treatment.

4. The Italian situation for HCV referrals

When considering the development of a program of cure for HCV in Italy, several key points need to be kept in mind. These included the unrestricted availability of DAA access (already present), simplification of the "patient journey", minimal bureaucratic burden for clinicians, no co-payment for patients, and importantly, education and collaboration with GPs. Indeed, a variable proportion of patients are unaware of being HCV positive and need to be identified through targeted screening programs and collaboration with GPs. In a study performed in 5 urban areas in Italy, patients were randomly selected from lists of GPs and anti-HCV were sought by salivary testing; positive patients were tested for HCV RNA. In all, 20% of those found HCV RNA positive were unaware of their status [27]. The HCV Network Sicily is a web-based model that includes 41 clinical centres and 101 specialist physicians (gastroenterologists, hepatologists, infectivologists, internal medicine physicians) who are involved in the management and treatment of chronic HCV liver diseases. The information recorded on the web-based platform monitors patient data and allows dissemination of optimised strategies with the common goal of elimination of HCV infection in Sicily. The model shown in Fig. 1 follows a 'hub and spoke' approach with the following main characteristics: minimal congestion, a high degree of specialisation and collaboration, minimal redundancy of services, uniform diagnostic criteria and appropriate access to therapy. Such a network ensures good local epidemiological knowledge, diagnostic appropriateness, and adequate therapeutic management with the possibility to provide benefits for both the individual and the community.

An epidemiological survey conducted with the collaboration of a group of GPs from the various provinces of Sicily indicated that about 1% of the Sicilian population has chronic liver disease due to HCV infection and confirmed that more than one-half are over the age of 60 years. From March 2015 to December 2018, 16,500 patients were registered on the web platform (57% male, mean age 61 years, 34% >70 years), and of these, 12,300 underwent antiviral therapy. These latter patients represent 0.21% of the Sicilian population, and therefore it is likely that at least 0.8% of the Sicilian population (over 30,000 people) with chronic hepatitis C must still be identified and treated. Among the patients treated, >90% achieved SVR12. The rate of SVR12 was 95.1% in patients with chronic hepatitis, 93.2% in Child–Pugh A cirrhosis (93.2%), and 82.2% among those with Child–Pugh B cirrhosis.

In Sicily, a linkage-to-care program has also been implemented for patients with chronic HCV hepatitis which includes the following points:

1) Communication of therapeutic innovation to GPs through meetings organised in collaboration with the Italian Society of General Medicine (SIMG). To date, over 20 meetings have been organised in all provinces of Sicily in which 1180 GPs participated.
2) The opening of the web-based platform of HCV Network to GPs through computerised diaries, a shared diagnostic pathway, the availability of visits to specialist centres and the possibility to follow the diagnostic course and the therapeutic decisions of their patients directly on the web-based platform of the network. To date, 708 patients have been registered directly in the network by GPs.
3) The organisation of "round tables with GPs" as a model of patient co-management. In a 6-month period, 20 round tables are being organised in all provinces and health districts of Sicily. Approximately 20 GPs take part in each meeting to identify patients with chronic HCV-related hepatitis in their database and insert them into the network database. This model is estimated to allow the identification and linkage to care of 2000–4000 patients with known chronic HCV-related disease.

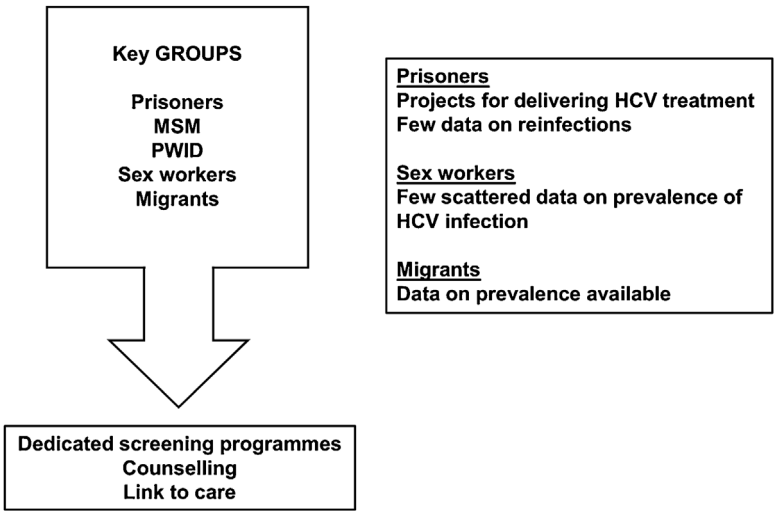

Fig. 2. Hard-to-reach groups of hepatitis C virus-positive individuals. HCV, hepatitis C virus; MSM, men who have sex with men; PWID, people who inject drugs.

In our opinion, HCV Network Sicily can represent a localised model for screening, treatment and management of patients with HCV. Importantly, the network involves a large proportion of local GPs and is actively involving them not only in identifying patients but making them a vital part of the entire clinical management pathway. The network is also in the advanced phases of identifying other high-risk individuals with HCV, including those with drug–alcohol abuse, prisoners, thalassaemic patients and those undergoing haemodialysis. With these additional efforts, it is expected that a much larger proportion of the HCV population can be identified and treated, with the overall goal of eradication of HCV in the island of Sicily in line with the goals set by the WHO.

5. 'Hard to reach' patients

Based on the dynamics of HCV transmission, hard-to-reach groups are also high transmitters of HCV. The main high-risk groups are detailed in Fig. 2, and include prisoners, MSM, PWID, sex workers, and migrants. Considering the latter group, migration is believed to be an important factor in the changing patterns of HCV infection in Europe [28]. There is limited data on HCV-positive immigrants in Italy. Current estimates have reported prevalences from roughly 3% to up to 26% in migrant populations living in Italy, with a prevalence of viral hepatitis of 12.5% among hospitalised immigrants [28]. Considering the migrant population, it has been estimated that migrants represent only a small contribution (about 5%) to the total number of cases of chronic HCV infection in Italy [29]. This is in contrast to countries such as the Netherlands (68%), Germany (53%) and France (35%). In this regard, the epidemiology of viral hepatitis in the migrant population all across Europe should be constantly updated along with the dynamics of the actual migratory flows.

In a screening program from 2012 to 2015 involving 1727 immigrants in the Campania and Apulia regions, 4.1% were anti-HCV-positive, and all unaware of their HCV status [30]. Importantly, the screening program can be considered positive as it was accepted by 85% of the subjects, and has the potential to identify a large number of individuals who are HCV positive. In a European wide study, HCV screening was seen as cost effective among migrants living in the EU/EEA (mean 14% of cases and >50% of cases in some countries) [31]. This is relevant since immigrants face many barriers in linkage to care and treatment due to the patient, practitioner, and healthcare system. Some of the solutions proposed to overcome these barriers include screening of high-risk children and adults and vaccination of younger children, combined with treatment of infection where possible [32]. However, it is clear that linkage to treatment requires greater attention, and that the goal of HCV elimination will only be possible if healthcare systems effectively include and treat migrants for HCV [31]. In this regard, there is a need for country-specific strategies and optimized allocation of resources since a substantial proportion of HCV patients remain untreated among migrant populations in Italy and elsewhere in Europe [33]. Early screening of migrants based on HCV prevalence estimates in the country of origin and combined with linkage to care and treatment may also help to prevent liver related sequelae [28]. The development of adequate communication systems will also be essential in improving access to healthcare services and to create links between immigrants and the healthcare system [34].

By reducing the pool of chronic HCV infected subjects, the number of new infections will also be reduced. Antiviral treatment as prevention appears to be effective in this regard. According to preliminary modelling data, the rapid scale-up of DAA treatment for HCV (>8% of total PWID per year) greatly increases the number of people with clearance of the virus, causing a progressive reduction of the overall prevalence of chronic HCV infection: as a result, the rate of HCV reinfection also is also bound to decrease [35]. According to the European Monitoring Centre for Drugs and Drug Addiction (http://www.emcdda.europa.eu/edr2018_en), Italy has a similar HCV prevalence among PWID compared to other European countries. However, it can be assumed that a relatively large proportion of these individuals are not yet being screened for HCV.

The combination of elbasvir/grazoprevir has been studied in PWID randomized to an immediate-treatment group (ITG) that received elbasvir/grazoprevir for 12 weeks or a deferred-treatment group (DTG) that received placebo for 12 weeks, no treatment for 4 weeks, and then open-label elbasvir/grazoprevir for 12 weeks. SVR12 was 91.5% for ITG and 89.5% in the active phase of the DTG arm [36]. Drug use at baseline and during treatment did not affect SVR12 or adherence to the therapy. Patients with HCV infection who were receiving opioid agonist therapy had high rates of SVR12, regardless of ongoing drug use, and it was thus suggested that drug use should be removed as a barrier to HCV antiviral treatment for patients receiving opioid agonist therapy.

As evidence that HCV infected people are not receiving adequate screening, a recent study was carried out involving 27 drug dependency centres in the Campania region (HCV Technical Board, Regione Campania, personal communication). Of the 14,630 patients followed, 9931 (67.9%) had been tested and of these 3796 (38.2%) were HCV positive. However, among the latter, only 20.7% had been treated. This example demonstrates some of the limita-

tions of linkage to care. Firstly, laboratory facilities for testing are not available in all drug dependency centres, and some patients refused screening and missed their appointments when referred to the laboratory. Secondly, DAAs are usually prescribed and delivered in specialist centres, and not in drug dependency centres. In the same region, simplified procedures have now been proposed for the screening and staging of liver fibrosis in order to circumvent some of these limitations. A recent modelling study reported that at the highest baseline HCV prevalence in people who inject drugs (85%), expanding treatment coverage does not significantly reduce the prevalence of HCV considering any treatment-as-prevention strategy [37]. Interestingly, when baseline HCV prevalence is at least 60% or even lower, treating >12% people per 1000 PWID per year was considered likely to eliminate HCV within a period of 10 years. Accordingly, the authors concluded that a successful strategy of HCV treatment as prevention should incorporate baseline HCV prevalence in order to achieve the greatest benefit.

When it comes to other high-risk populations, there are roughly 63,000 prisoners in Italy. Of these, around 30% are foreigners, and the annual turnover is 50%. It has been calculated that nearly one-fourth of the prison population is anti-HCV positive [38,39]. Unfortunately, there are still many limitations to improve HCV linkage to care in prisons, including overcrowding, fast site turnover, interactions with local health care services and bureaucratic issues related to the approval of drugs for prescription in prisons.

In summary, there are several common features of difficult to reach populations. Firstly, the prevalence of HCV infection among these groups usually justifies screening programs. Secondly, difficult to reach subjects are often active spreaders of the infection due to their lifestyle and environment. Indeed, the ultimate goal of linking to care the active spreaders is to reduce the burden of infection on the path towards global elimination. In order to achieve this, tailored models for HCV care will be needed based on a holistic approach.

6. Treatment of HCV and extrahepatic manifestations

In chronic HCV infection, extrahepatic manifestations are frequent and polymorphous and involve both immune-related complications (e.g., mixed cryoglobulinaemia, lymphoma) and inflammatory-related pathologies (e.g., cardiovascular and renal disorders, diabetes) [9].

Both the prevalence and risk of several extrahepatic manifestations of HCV infection is elevated among HCV-positive patients. Indeed, the frank association between HCV infection and extrahepatic diseases has been demonstrated by several epidemiological, clinical, immunological and pathological studies, leading to an increased risk of morbidity and mortality. The extrahepatic manifestations in HCV patients heavily impact prognosis, quality of life and economic costs [40]. Thus, chronic HCV infection should be viewed as a systemic disease in which extrahepatic consequences reinforce the need for effective viral eradication measures. This has been recently highlighted by the evidence-based recommendations from the International Study Group of Extrahepatic Manifestations related to HCV (ISG-EHCV) in which antiviral treatment is recommended for all patients with extrahepatic manifestations of HCV infection.

The beneficial impact of SVR on the extrahepatic manifestations of chronic HCV infection has also been demonstrated in a recent meta-analysis in which achieving SVR was associated with reduced extrahepatic mortality, higher rates of complete remission in patients with cryoglobulinaemic vasculitis, higher objective response in patients with malignant B-cell lymphoproliferative diseases, reduced insulin resistance at follow-up and a protective effect on the incidence of diabetes [41]. For instance, in cryoglobulinaemic vasculitis, therapy with DAAs was found to be highly effective and safe with a clinical response rate of 100% for vasculitis [42].

Within recently presented data (El-Serag et al. International Liver Congress 2018), HCV-positive patients were found to be four times more likely to develop mixed cryoglobulinemia than HCV-patients. Moreover, the prevalence of one or more among mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, Lichen planus, and Non-Hodgkin lymphomas, observed in the last four years was 7% (12,529/176,320) among HCV-positive cases.

A recent study on the long-term efficacy of IFN-free treatment regimens in 148 patients with HCV-associated cryoglobulinaemia and vasculitis reported that DAAs were associated with complete response in 72.6%, partial response in 22.6% and no response in 4.8% of cases [43]. Patients had received different DAAs (sofosbuvir/daclatasvir, n = 53; sofosbuvir + ribavirin, n = 51; sofosbuvir/ledipasvir, n = 23; or sofosbuvir/simeprevir, n = 18), for 12 or 24 weeks. Cryoglobulins were no longer detectable in the blood samples of 53.1% of the patients, and 97.2% had a SVR after a median follow-up time of 15.3 months. Thus, the majority of patients with HCV-associated cryoglobulinaemia vasculitis have a full or partial response to DAA therapy. However, despite the high rates of SVR, other authors have reported unsatisfactory rates of complete clinical response in patients with severe/life-threatening vasculitis [44]. Long-term outcomes will require further studies as other authors have suggested that some patients may have relapses of vasculitis within two years after achieving SVR [45].

As mentioned, it is now clear that HCV infection increases cardiovascular risk. According to a recent meta-analysis, compared with uninfected individuals, HCV-infected patients had increased risks of cardiovascular disease-related mortality (odds ratio [OR] 1.65), carotid plaques (OR 2.27), and cerebral-cardiovascular events (OR 1.30) [46]. Moreover, the increased cardiovascular risk appears to be especially relevant or even synergic in patients with other risk factors such as smoking, arterial hypertension, and diabetes mellitus [46]. Importantly, HCV eradication by DAAs improves carotid atherosclerosis, even after stratification for cardiovascular risk factors and in both patients with and without cirrhosis [47].

HCV infection appears to be associated with an increased risk of diabetes mellitus independently of the severity of liver disease, as the prevalence of HCV infection in diabetic patients is higher than in non-diabetic controls, with the risk being even higher in cirrhotic HCV subjects [48]. Considering the role of antiviral therapy in diabetic patients, achieving SVR has been shown to be associated with improvement of glycaemic control in diabetic HCV-patients, even in the presence of significant weight increase [49]. Achieving SVR is also associated with improvement in glucose and glycated haemoglobin (HbA_{1c}) levels as well as HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) [49]. Thus, unsurprisingly, improved glycaemic control has been documented after successful treatment of HCV, and provide additional validation for the use of antiviral treatment in patients with diabetes. Indeed, an integrated approach to both HCV and diabetes should help to maximise the benefits to both diseases [50].

7. Treatment of patients with advanced cirrhosis

There are several key aspects to consider when treating HCV patients with advanced liver disease. Firstly, there appears to be a significant survival benefit of achieving SVR compared to unsuccessful treatment in HCV patients, even in those with cirrhosis [51]. Treated patients with compensated cirrhosis experience a 75% reduction in mortality [51]. The benefits in terms of all-cause mortality are demonstrated in patients with HCC, liver transplantation and liver failure [8]. In addition, the majority of these patients are able to achieve SVR, even if treatment options are more lim-

Table 1
Potential benefits and harms of direct-acting antivirals in patients with hepatitis C virus infection.

Potential benefits	Potential harms
Possibility to have an impact on the goal of viral eradication	Potentially greater risk of drug toxicity with decompensated liver disease
In non-transplant candidates, high SVR rates can be achieved (mostly in CTP B)	Lower SVR rates in the decompensated group compared with post-transplant
Post-transplant HCV recurrence can be abated	Lowering of MELD resulting in reduced priority for LT (purgatory effect)
Cirrhosis progression can be reduced	May disadvantage patients from receiving HCV-positive grafts
Mortality while on waiting list can be reduced	
Potential increase in eligibility for therapy for HCC (bridging to LT or not)	
Improved quality of life (on or off wait list)	
Currently no evidence of increased HCC activity after SVR	

CTP—Child-Turcotte-Pugh classification; HCC—hepatocellular carcinoma; HCV—hepatitis C virus; LT—liver transplant; MELD—Model for End-Stage Liver Disease; SVR—sustained virologic response.

ited along with the increasing severity of liver disease. As most treatments can be considered to be well-tolerated and safe and to guarantee a reduced risk of liver-related complications and an improvement of liver-related and overall survival, the choice for treatment seems indisputable. Nevertheless, it should be taken into account that as liver disease becomes decompensated there are fewer DAA options, with the risk of dying before SVR is achieved or with only modest or no benefits in the short term.

So far, sofosbuvir, velpatasvir, daclatasvir, and ribavirin, in various combinations, have been demonstrated to be safe and effective in patients with decompensated cirrhosis with SVR rates that are similar to those reported in compensated cirrhosis [52]. More recently, in the ASTRAL-4 trial, for instance, treatment with sofosbuvir–velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir–velpatasvir for 24 weeks was associated with high rates of SVR in patients with HCV infection and decompensated cirrhosis [53]. However, a major concern, especially in potential liver transplant candidates as well as in severe post-transplant HCV recurrence, is the achievement of SVR with no improvement in hepatic function and in survival [54–57]. In this context, improved predictors of liver function are needed so that clinicians can better select patients for DAA therapy.

This leads to important considerations about who should and who should not be treated. There is general consensus that patients without a reasonably high chance of achieving SVR and surviving beyond SVR should not receive DAA therapy, especially in those subjects who are also ineligible for ribavirin, who had prior NS5Ai failure or who harbour complex viral resistance profile and/or have renal failure. Patients with advanced HCC and other serious comorbidities are also not likely to be good candidates for DAA treatment. This is also in consideration of the finding that the annual risk of HCC is likely to remain somewhat high among patients with cirrhosis (1.4%) [58]. It has been reported that DAAs successfully cured HCV in patients with advanced liver disease and that SVR was associated with improvement in liver function, even if the long-term impact of treatment in patients with decompensated cirrhosis is still unclear [59].

According to the available clinical data, the decision to start DAA treatment should be balanced between the potential benefits and potential harms for patients and are summarised in Table 1. The recently developed BE3A score has been proposed with the aim of helping the clinical decision making before starting antiviral treatment [60]. This score uses 5 baseline factors (body mass index, encephalopathy, ascites, serum levels of alanine aminotransferase and albumin) and was found to be associated with a reduction of Child–Pugh score in patients with HCV-associated decompensated cirrhosis receiving DAA therapy [60]. Such a predictive tool offers the possibility to quantify the potential benefits of DAA therapy for patients with decompensated cirrhosis.

In patients with hepatocellular carcinoma (HCC), the data on management and tumour behaviour upon antiviral treatment with DAAs are controversial. However, achieving SVR with DAAs does not seem to reduce the risk of HCC development [61]. De novo HCC lesions appear to develop significantly later than recurrent lesions in patients treated with DAAs, with response rates that are significantly lower in the latter subjects [62]. Moreover, a case-control study on patients with HCV-related HCC reported that HCC behaviour was more aggressive in DAA-treated patients than in non-DAA patients in terms of portal vein thrombosis, malignant lymphadenopathy and HCC imaging characteristics [63]. In this regard, it is apparent that more studies are expected to allow drawing clear conclusions [64].

8. Conclusions

The expert meeting served as an important point of reference to summarise several key aspects of screening and care of patients with HCV, especially in consideration of the recent, significant advances in screening and therapy. To adopt these new tools to their full extent, the collaboration between local healthcare professional and specialist centres should be strengthened. The linkage to care model described in Italy shows that building relationships with GPs can have an important impact on screening for HCV, although it is clear that much work still remains. However, it nonetheless demonstrates that collaborative efforts are worthwhile and can identify a greater number of individuals who require treatment. Universal access to care is critical to achieving the goal of HCV eradication, while keeping in mind that much progress remains to be made in adequately treating the comorbidities associated with HCV infection.

Conflicts of interest

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References

[1] Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–76.
[2] World Health Organizaton (WHO). Available at: http://www.who.int/medicines/areas/access/hepCtreat_key_facts/en/. [Accessed 10 September 2017].
[3] European Association for the Study of the Liver (EASL). Available at: http://www.easl.eu/medias/cpg/2018/EASL%20Recommendations%20on%20Treatment%20of%20Hepatitis%20C%202018/English-report.pdf.

[4] Arase Y, Kobayashi M, Suzuki F, et al. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatology 2013;57:964–73.
[5] Bruno S, Di Marco V, Iavarone M, et al. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol 2016;64:1217–23.
[6] Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology 2017;152, 142-156.e2.
[7] Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529–38.
[8] van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–93.
[9] Cacoub P, Gragnani L, Comarmond C, et al. Extrahepatic manifestations of chronic hepatitis C virus infection. Dig Liver Dis 2014;46(Suppl. 5):S165–73.
[10] Mahale P, Engels EA, Li R, et al. The effect of sustained virological response on the risk of extrahepatic manifestations of hepatitis C virus infection. Gut 2018;67:553–61.
[11] Negro F, Forton D, Craxi A, et al. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345–60.
[12] van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. J Hepatol 2016;65:S95–108.
[13] World Health Organizaton (WHO). Available at: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/.
[14] World Health Organizaton (WHO). Available at: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/.
[15] American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA). Available at: www.hcvguidelines.org.
[16] European Association for the Study of the Liver (EASL). EASL recommendations on treatment of hepatitis C 2018. J Hepatol 2018;69:461–511.
[17] World Health Organizaton (WHO). http://www.who.int/hepatitis/publications/hep-c-access-report-2018/en/.
[18] World Health Organizaton (WHO). Available at: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf. [Accessed 10 September 2017].
[19] Butt AA, Yan P, Lo Re 3rd V, et al. Liver fibrosis progression in hepatitis C virus infection after seroconversion. JAMA Intern Med 2015;175:178–85.
[20] Dusheiko G. The impact of antiviral therapy for hepatitis C on the quality of life: a perspective. Liver Int 2017;37(Suppl. 1):7–12.
[21] Harris RJ, Martin NK, Rand E, et al. New treatments for hepatitis C virus (HCV): scope for preventing liver disease and HCV transmission in England. J Viral Hepat 2016;23:631–43.
[22] Lee MH, Yang HI, Lu SN, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis 2012;206:469–77.
[23] Martin NK, Vickerman P, Dore GJ, et al. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. J Hepatol 2016;65:17–25.
[24] Lazarus JV, Stumo SR, Harris M, et al. Hep-CORE: a cross-sectional study of the viral hepatitis policy environment reported by patient groups in 25 European countries in 2016 and 2017. J Int AIDS Soc 2018;21(Suppl. 2):e25052.
[25] Kondili LA, Robbins S, Blach S, et al. Forecasting hepatitis C liver disease burden on real-life data. Does the hidden iceberg matter to reach the elimination goals? Liver Int 2018;38:2190–8.
[26] Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386:1537–45.
[27] Andriulli A, Stroffolini T, Mariano A, et al. Declining prevalence and increasing awareness of HCV infection in Italy: a population-based survey in five metropolitan areas. Eur J Intern Med 2018;53:79–84.
[28] Galli M, Ridolfo A, van denBogaart L, et al. HCV and immigration in Italy. Acta Biomed 2018;89:19–32.
[29] Falla AM, Hofstraat SHI, Duffell E, et al. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. BMC Infect Dis 2018;18:79.
[30] Sagnelli C, Alessio L, Sagnelli C, et al. Clinical findings of HCV chronic infection in undocumented immigrants and low-income refugees in three areas of Southern Italy. Ann Hepatol 2018;1:47–53.
[31] Greenaway C, Makarenko I, Chakra CNA, et al. The effectiveness and cost-effectiveness of hepatitis C screening for migrants in the EU/EEA: a systematic review. Int J Environ Res Public Health 2018;15.
[32] Myran DT, Morton R, Biggs BA, et al. The effectiveness and cost-effectiveness of screening for and vaccination against hepatitis B virus among migrants in the EU/EEA: a systematic review. Int J Environ Res Public Health 2018;15.
[33] Papatheodoridis GV, Tsochatzis E, Hardtke S, et al. Barriers to care and treatment for patients with chronic viral hepatitis in Europe: a systematic review. Liver Int 2014;34:1452–63.
[34] Brindicci G, Trillo G, Santoro CR, et al. Access to health services for undocumented immigrants in Apulia. J Immigr Minor Health 2015;17:618–23.
[35] Razavi H. Reducing a country's HCV-disease burden. The 4th international symposium on hepatitis in substance users (INHSU 2015) 2015:7–9.
[36] Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med 2016;165:625–34.
[37] Zelenev A, Li J, Mazhnaya A, et al. Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study. Lancet Infect Dis 2018;18:215–24.
[38] Brandolini M, Novati S, De Silvestri A, et al. Prevalence and epidemiological correlates and treatment outcome of HCV infection in an Italian prison setting. BMC Public Health 2013;13:981.
[39] Sagnelli E, Starnini G, Sagnelli C, et al. Blood born viral infections, sexually transmitted diseases and latent tuberculosis in Italian prisons: a preliminary report of a large multicenter study. Eur Rev Med Pharmacol Sci 2012;16:2142–6.
[40] Younossi Z, Park H, Henry L, et al. Extrahepatic manifestations of hepatitis C: a meta-analysis of prevalence, quality of life, and economic burden. Gastroenterology 2016;150:1599–608.
[41] Cacoub P, Desbois AC, Comarmond C, et al. Impact of sustained virological response on the extrahepatic manifestations of chronic hepatitis C: a meta-analysis. Gut 2018;67:2025–34.
[42] Gragnani L, Visentini M, Fognani E, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. Hepatology 2016;64:1473–82.
[43] Cacoub P, Si Ahmed SN, Ferfar Y, et al. Long-term efficacy of interferon-free antiviral treatment regimens in patients with hepatitis C virus-associated cryoglobulinemia vasculitis. Clin Gastroenterol Hepatol 2019;17:518–26.
[44] Emery JS, Kuczynski M, La D, et al. Efficacy and safety of direct acting antivirals for the treatment of mixed cryoglobulinemia. Am J Gastroenterol 2017;112:1298–308.
[45] Bonacci M, Lens S, Marino Z, et al. Long-term outcomes of patients with HCV-associated cryoglobulinemic vasculitis after virologic cure. Gastroenterology 2018;155, 311-3115.e6.
[46] Petta S, Maida M, Macaluso FS, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. Gastroenterology 2016;150, 145-155.e4; quiz e15-6.
[47] Petta S, Adinolfi LE, Fracanzani AL, et al. Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis. J Hepatol 2018;69:18–24.
[48] Fabiani S, Fallahi P, Ferrari SM, et al. Hepatitis C virus infection and development of type 2 diabetes mellitus: systematic review and meta-analysis of the literature. Rev Endocr Metab Disord 2018;19:405–20.
[49] Ciancio A, Bosio R, Bo S, et al. Significant improvement of glycemic control in diabetic patients with HCV infection responding to direct-acting antiviral agents. J Med Virol 2018;90:320–7.
[50] Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. Diabetes Care 2017;40:1173–80.
[51] Simmons B, Saleem J, Heath K, et al. Long-term treatment outcomes of patients infected with hepatitis C virus: a systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis 2015;61:730–40.
[52] Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? the ironic conundrum in the era of effective and well-tolerated therapy. J Viral Hepat 2016;23:408–18.
[53] Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–28.
[54] Belli LS, Duvoux C, Berenguer M, et al. ELITA consensus statements on the use of DAAs in liver transplant candidates and recipients. J Hepatol 2017;67:585–602.
[55] Belli LS, Perricone G, Adam R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810–7.
[56] Donato MF, Morelli C, Romagnoli R, et al. Prevention of hepatitis C recurrence by bridging sofosbuvir/ribavirin from pre- to post-liver transplant: a real-life strategy. Liver Int 2017;37:678–83.
[57] Vukotic R, Conti F, Fagiuoli S, et al. Long-term outcomes of direct acting antivirals in post-transplant advanced hepatitis C virus recurrence and fibrosing cholestatic hepatitis. J Viral Hepat 2017;24:858–64.
[58] El-Serag HB, Kanwal F, Richardson P, et al. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. Hepatology 2016;64:130–7.
[59] Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–31.
[60] El-Sherif O, Jiang ZG, Tapper EB, et al. Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection. Gastroenterology 2018;154, 2111-2121.e8.
[61] Ravaioli F, Conti F, Brillanti S, et al. Hepatocellular carcinoma risk assessment by the measurement of liver stiffness variations in HCV cirrhotics treated with direct acting antivirals. Dig Liver Dis 2018;50:573–9.
[62] Abdelaziz AO, Nabil MM, Abdelmaksoud AH, et al. De-novo versus recurrent hepatocellular carcinoma following direct-acting antiviral therapy for hepatitis C virus. Eur J Gastroenterol Hepatol 2018;30:39–43.
[63] Abdelaziz AO, Nabil MM, Abdelmaksoud AH, et al. Tumor behavior of hepatocellular carcinoma after hepatitis C treatment by direct-acting antivirals: comparative analysis with non-direct-acting antivirals-treated patients. Eur J Gastroenterol Hepatol 2019;31:75–9.
[64] Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular Cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153, 996-1005.e1.