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Optimising management of patients with hepatitis C virus in the age of direct-acting antivirals: results of a Delphi consensus

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Abstract. – OBJECTIVE: To optimize the management of patients with chronic hepatitis C virus (HCV).

MATERIALS AND METHODS: We developed two questionnaires to determine Italian healthcare professionals' opinions on the overall management of HCV chronic liver disease and the use of direct-acting antivirals (DAAs) in the treatment of HCV. A Delphi consensus method using the RAND/UCLA appropriateness method was used to determine opinions of an expert panel (EP) of specialists.

RESULTS: Overall 443 physicians from 167 Italian centres completed the two questionnaires. The EP confirmed the importance of collaboration with general practitioners (GPs) and HCV testing in high-risk groups, but did not agree on treating patients over 80 years of age with DAAs. Over 90% agreed that it was important to quantify HCV-RNA, determine genotype, and test for anti-HIV and HBsAg before starting DAAs. Transient elastography (FibroScan®) was used by >90% to evaluate the stage of liver fibrosis while serum biomarkers were used by <20%. Adherence to therapy, drug-drug interactions and the possibility of treating advanced liver disease were decisive factors in therapy choice. Monthly monitoring during therapy was considered appropriate and 80% were in favor of HCV-RNA testing 24 weeks after the end of the therapy to confirm sustained virological response (SVR). Over 80% agreed that it was necessary to continue follow-up of patients with advanced fibrosis/cirrhosis.

CONCLUSIONS: Scientific organizations should review their guideline recommendations to facilitate access to DAAs.

Key Words:
Hepatitis C Virus, Direct-acting antivirals, Delphi method, Consensus.

Abbreviations

DAA = Direct-acting antivirals; HCV = Hepatitis C virus, SVR = Sustained virological response; PWID = People who inject drugs; GPs: General practitioners; EP = Expert Panel.

Introduction

Chronic hepatitis C virus (HCV) infection, estimated to affect up to 71 million people worldwide, is a global health problem1. The introduction of the direct acting antivirals (DAAs) that achieves >90% rates of viral clearance in different stages of liver disease was a major step forward in the management of patients with HCV[2]. DAAs are effective and well tolerated and are now considered to be the gold standard of care for patien-

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ts with HCV infection. The sustained virological response (SVR) observed after treatment with DAAs, can induce regression of liver fibrosis, resolve virus-related extra hepatic manifestations and reduce liver disease complications as well as decreasing overall mortality[3,4]. In the next 10 years the increased availability of DAAs, means that the majority of patients with confirmed HCV liver disease can be treated. In order to meet this goal, new management models are however required to ensure that increased numbers of patients can be treated while containing costs to already over stretched healthcare systems. How do physicians treating patients with HCV chronic liver disease decide on the most appropriate therapy? Physicians make clinical decisions based on a range of factors including recommendations/guidelines from national and international scientific associations. It is, however, important that they also take into account regulations/constraints of local healthcare systems as well as the capabilities and capacities of the health structures where they work. Recommendations included in international guidelines such as those from the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) are widely used in clinical practice but there are areas where the quality of evidence is limited and the strength of the recommendations is low[5,6]. For example, there is still no universal consensus on the type and timing of virological tests and the non-invasive clinical assessments to perform before, during, and following treatment in patients achieving SVR. There is, therefore, an urgent unmet medical need to develop a more effective model to optimize referrals, diagnosis, access to therapy and centre capacity. We conducted a Delphi method consensus to assess scientific, clinical behavioral and organizational protocols and procedures to optimize patient referral and centre capacity in the management of HCV in Italy.

Materials and Methods

The Delphi method is a validated, consensus-building process to develop agreement and make group-based decisions in a variety of fields7-10. The method, traditionally based on the three fundamental concepts of anonymity, controlled feedback and statistical group response, is routinely used in healthcare research and in clinical challenges[11-13]. The RAND method for measuring the appropriateness of medical care uses a scale ranging from 1 (maximal disagreement) to 9 (maximal agreement), with 5 corresponding to a neutral opinion on a given statement. Scores given by experts are analyzed statistically to obtain an appropriate 'index of consensus'. The most recommended, according to 'the RAND/UCLA Appropriateness Method User's Manual', is the IPRAS (Interpercentile Range Adjusted for Symmetry)[14]. The first step in this process was to convene an Advisory Board of nine experts in the field. The first questionnaire (Q1) included sections on physician demographics, type/size of institutions where they worked, epidemiology/diagnosis, therapeutic choices and management aspects. The Advisory Board then met to discuss results of the Q1 survey and they then developed a second questionnaire (Q2) to resolve points that were not cleat from Q1 and to better assess the appropriateness of some diagnostic/therapeutic/management procedures. Q1 and Q2 were then administered (in two rounds) to an Expert Panel (EP) via a digital platform. Clinicians then completed Q1 and Q2 electronically and answers were stored remotely for analysis using specific statistical software to assess the level of agreement of the EP.

Results

Q1 was dispatched on 11 January 2017, to 823 physicians working in 235 Italian HCV referral centres according to the official list supplied by the Italian Drug Agency (L'Agenzia Italiana del Farmaco, AIFA). In total, 167 centres (71%) participated in the survey with good geographical representativeness (North: 69%, Centre: 74%; South-Islands: 70%) (Figure 1). A total of 548 physicians (68.8%) provided responses to Q1. On 5 May 2017, Q2 was then sent to those physicians who had responded to Q1. A total of 443 (80%) physicians who responded to Q1 completed Q2.

Strategies to Increase the Access to Antiviral Therapy

Question 1: do you Agree with the Plan For a Screening Program In High-Risk Population to Identify Subjects with Chronic HCV infection?

Screening to identify people with chronic HCV infection is a major point of discussion among

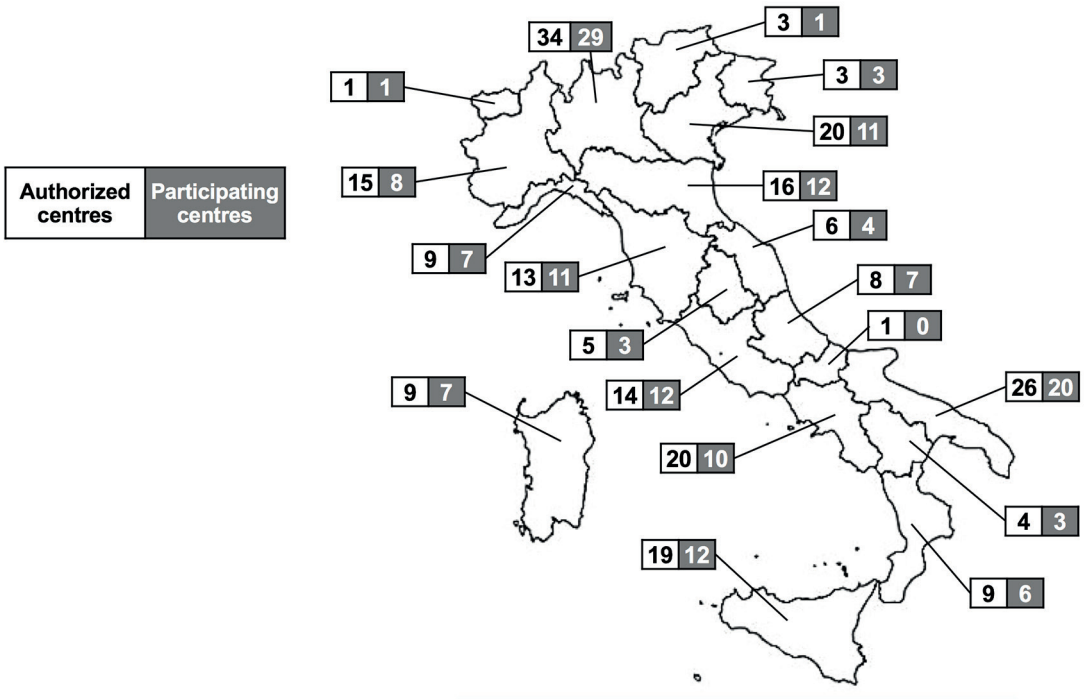

Figure 1. Distribution of the 167 structures participating in the survey.

the medical community and healthcare authorities worldwide. The AASLD recommends screening of people born between 1945 and 1965 as well as those at increased risk for HCV infection. The EASL recommends that screening strategies should be defined according to the local epidemiology of HCV infection[5,6]. Results of our questionnaire showed that 84% of responders felt it was appropriate to promote a screening programme the following groups: subjects at high risk of infection, people who inject drugs (PWID), prisoners and those who received blood transfusions before 1990.

Question 2. what are Possible Strategies to Increase the Access of Patients with Hcv Chronic Liver Disease to Antiviral Therapy?

Overall, 57% of the EP considered that the most appropriate strategy to facilitate access of patients with known HCV chronic liver disease to DAAs was collaboration with general practitioners (GPs). While 11% indicated that cooperation between specialist HCV centres and local healthcare providers was an appropriate strategy. Only 20% considered that a communication initiative managed by national scientific associations and patient groups was an appropriate way to increase numbers of patients treated.

Question 3: Do you Agree with Treating all Patients Over 80 Years of age?

Age is not generally to be considered a criterion on which to base priority for DAAs therapy. Published data suggests high efficacy and safety of DAAs in patients in the range 65-70 years of age, but international guidelines do not make recommendations based on the age of patients15-19. The EP was divided on the use of DAAs in elderly patients (>80 years). The percentage of responders who were in agreement with treating elderly patients (>80 years) was almost equal to the percentage of EP who didn't have a clear opinion on the subject. The frequency distribution and RAND evaluation of appropriateness indicated that no consensus was reached for this point (Figure 2).

Virological and Clinical Assessments Necessary Before Starting Therapy with DAAs

Question 4: What do you Consider are the Virological tests that should be Conducted Before Starting Therapy?

EASL guidelines recommend that HCV-RNA quantification and HCV genotype should be carried before starting treatment. The AASLD/IDSA guidelines recommend that virological tests can

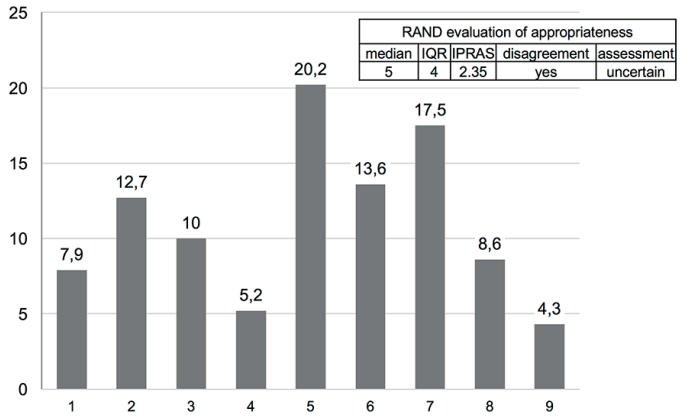

Figure 2. Question 3: Do you agree with treating all patients over 80 years of age?

be performed at any time before starting antiviral treatment. The AASLD/IDSA guidelines recommend that all patients initiating DAAs should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc. More than 90% of the EP agreed that it is necessary to quantify HCV-RNA, determine viral genotype, and test for anti-HIV and HBsAg before starting DAA therapy. About 80% of physicians thought it was useful to determine anti-HBc to evaluate a previous HBV infection.

Question 5: What Clinical Tests are Used in your Centre to Assess the Severity of Liver Disease?

Both the EASL and AALSD recommend that the severity of liver disease should be assessed before starting therapy. It is important to first identify patients with cirrhosis or advanced fibrosis in order to select the most appropriate treatment regimen and post-therapy surveillance. There is accumulating evidence that measurement of 'liver stiffness' and certain other biomarkers can be used to assess liver fibrosis thus reducing the need for liver biopsy. However, biopsy should be considered in patients exhibiting inconsistent test results. Over 90% of respondents reported that they use the FibroScan® (transient elastography) to determine the stage of fibrosis while 40% use liver biopsy to evaluate liver damage. Interestingly, serum biomarkers were used by <20% of physicians (Figure 3).

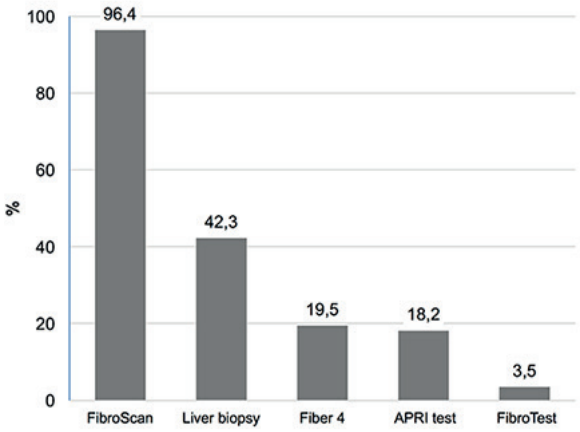

Figure 3. Question 5: What clinical tests are used in your centre to assess the severity of liver disease?

Management Strategies

Question 6: What Factors Influence the Choice of Therapeutic Regimens?

The availability of second- and third-generation DAAs has changed many aspects of antiviral therapy. In particular, the duration of therapy is reduced and administration is easier. Importantly, newer therapeutic regimens can be given to patients with advanced liver disease and certain regimens do not require the administration of ribavirin. There were statistical differences in how the EP rated the importance of factors in their therapeutic decision making process with adherence to therapy, lack of drug-drug interactions and the possibility of treating patients with advanced liver disease, rated as decisive factors in their choice of therapy (Friedman test, $p<0.001$ and Wilcoxon paired test after Bonferroni correction, $p<0.001$). A small number also reported that the use of ribavirin and duration of therapy were important in their choice of therapeutic regimen ($p=0.830$) while disease severity and pharmacological inte-

Table I. RAND evaluation of appropriateness.

Statement	Median	IQR	IPRAS	Disagreement	Assessment
27.b. Methods to accurately identify F2 stage do exist	5	3	3.1	No	Uncertain
27.a. It is still correct to distinguish patients on the basis of stages of liver fibrosis.	7	4	4.6	No	Appropriate
10.a. Agree to treat all patients aged more than 80 years	5	4	2.35	Yes	Uncertain
31.a. Monthly control during therapy, at the end of therapy and 12 weeks after the end of therapy	7	4	4.6	No	Appropriate
31.b. Control at the start of therapy, at the end of therapy and 12 weeks after the end of therapy	5	5	3.1	No	Uncertain
31.c. Control at the start of therapy and 12 weeks after the end of therapy	2	3	6.1	No	Inappropriate
15.a Verify therapy adherence	9	1	7.6	No	Appropriate
15.b Repeat research of genotype	8	2	6.85	No	Appropriate
15.c Perform a test for viral resistance	9	2	7.6	No	Appropriate
15.d Keep serum for future analyses	8.5	2	6.85	No	Appropriate

IQR = Inter Quartile Range; IPRAS = Inter Percentile Range Adjusted for Symmetry.

ractions showed the lowest scores (p=0.948) (Figure 4).

Question 7: When is the Optimal Time to Evaluate Virological Response with the New Pangenotypic Daas?

The new pangenotypic therapeutic regimens allow the time to evaluate virological response and the number of clinical controls to be reduced. The EP considered three clinical scenarios to determine SVR. The first involved monthly check-ups during therapy, at the end of therapy and 12 weeks post-therapy. The second included a check-up at the start of therapy, one at the end of the therapy, and one after 12 weeks. The third involved a clinical and virological check-up at the start of therapy and another 12 weeks post-therapy. The EP agreed that the first scenario was the most appropriate (median=7 without disagreement, RAND assessment: 'appropriate'), the second obtained a median=5 (RAND assessment: 'uncertain') while the third was considered not to be practical (median=2 without disagreement, RAND assessment: 'inappropriate') (Table I).

Follow-Up Strategies After Sustained Virological Response (SVR)

Question 8: What is the Appropriate Time to Evaluate SVR After the End of DAA Therapy?

The virological endpoint of DAA therapy is undetectable serum HCV-RNA using a sensitive assay 12 weeks after the end of therapy (SVR12). EASL and AASLD guidelines recommend that quantitative HCV viral load testing could be considered at the end of treatment and 24 weeks (or longer) post-therapy. Although the definition of SVR is universally accepted, the guidelines are unclear on the need to repeat the HCV-RNA test after confirmation of SVR. Feedback from EP confirmed this point with only 4% of physicians confirming a 12-week HCV-RNA test was adequate in determining SVR. In contrast, 80% of physicians confirmed that they thought it was necessary to repeat the test 24 weeks post-therapy to confirm the SVR. Furthermore, 45% of physicians considered it necessary to repeat serum HCV-RNA test after 48 weeks with 34% stating that it was useful to repeat HCV-RNA testing annually.

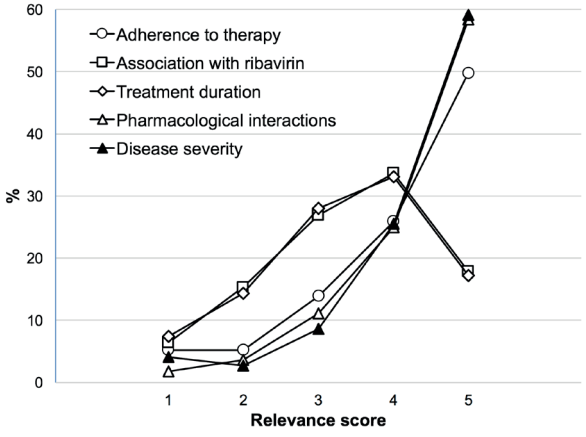

Figure 4. Question 6: What factors influence the choice of therapeutic regimens?

Question 9: Which Patients with SVR Require Continued Clinical Surveillance?

The AASLD recommends that follow-up should be the same in patients who do not have advanced fibrosis as those who have never been infected with HCV. Surveillance for HCC with ultrasound examination every six months is however recommended for patients with advanced fibrosis with a SVR. Assessment of other causes of liver disease is also recommended in patients with persistently abnormal liver test results following a SVR. The majority of the EP (>80%) agreed with the need for continued follow-up in patients with advanced hepatic fibrosis/cirrhosis and those with causes of chronic liver injury. Only 35% considered that clinical follow-up of all patients who were treated with DAAs is indicated.

A Proposed Model to Improve/Optimise Patient Referral and Centre Capacity in the Management of HCV Patients

An objective of this study was to develop a model to improve patient referral and centre capacity in HCV management. Adequate centre capacity is fundamental in any strategy to rationalise HCV management. The EP were almost unanimous in the belief that adequate numbers of healthcare professionals (medical and nursing staff), particularly in the outpatient setting, are fundamental in providing an accessible and efficient service for patients and their curers. In addition, the role of support staff — data managers, administrative and computer staff — should not be underestimated as they can have a significant effect on centre capacity. Likewise the number and frequency of follow-up visits have a significant effect on centre capacity. Patients who have already been treated take up a large portion of resources (up to 40%). If adequate numbers and type of healthcare professionals are not available the ability to effectively treat and manage new patients may be sub-optimal. One possibility to reallocate time and resources is to consider reducing follow-up activities in line with the EASL and ASLD recommendations (Figure 5).

Discussion

The Delphi consensus method — combining the knowledge and expertise of healthcare professionals with that available in the scientific literature — helps to standardize care, provides guidance on diagnosis and treatment and assists clinical decision-making for healthcare professionals. The Delphi methodology has a number of important advantages in the assessing the use of DAAs in the management of HCV hepatitis. Our study has two important advantages. First, we enrolled a large number of physicians from all centres in Italy authorized to prescribe DAAs for the treatment of hepatitis C infection. Second we reduced the possible uncertainties of this approach by selecting questions not resolved by the current international guidelines. The results confirmed that among Italian experts while there was a general consensus on the diagnostic procedures (instrumental, haematochemical and virological tests) and therapeutic regimens. However, there was a lack of consensus on a number of points: how best to identify patients infected with HCV; optimal management of elderly patients (>80 years) and the ideal follow-up procedures post-therapy. Screening for HCV infection in the general population is not advisable due to organizational difficulties and low cost-benefit ratios. In contrast, screening populations at high risk of HCV infection is relatively straightforward and has a high cost-benefit ratio. In Italy, people > 60 years of age have a high risk of having HCV chronic infection and should therefore be screened, in particular if they have physical or laboratory signs suggesting chronic liver disease. Other high-risk categories such as prison inmates and people who inject drugs (PWIDs) should also be routinely screened for HCV infection. The EASL recommends that screening strategies should be defined according to the local epidemiology of HCV infection. The majority of the EP stated that they believed the most appropriate strategy for first detecting people with HCV infection in Italy and then starting them on antiviral treatment is to work in close partnership with general practitioners (GPs)6. The GP should recommend HCV serum markers to people at high risk and direct patients with chronic infection to hub centers that have the resources to evaluate the stage of liver disease and to manage antiviral therapy. The EP was divided on the use of DAA in elderly patients (>80 years of age). EASL and AASLD/IDSA guidelines do not provide recommendations for this group but reports confirm their efficacy and safety in older patients15-19. It is necessary however to evaluate the prognosis of hepatic disease in elderly patients. It may not be appropriate to treat elderly patients with mild hepatic fibrosis or those with advanced/decompensated liver disease and severe co-morbidities. The EP was more in agre-

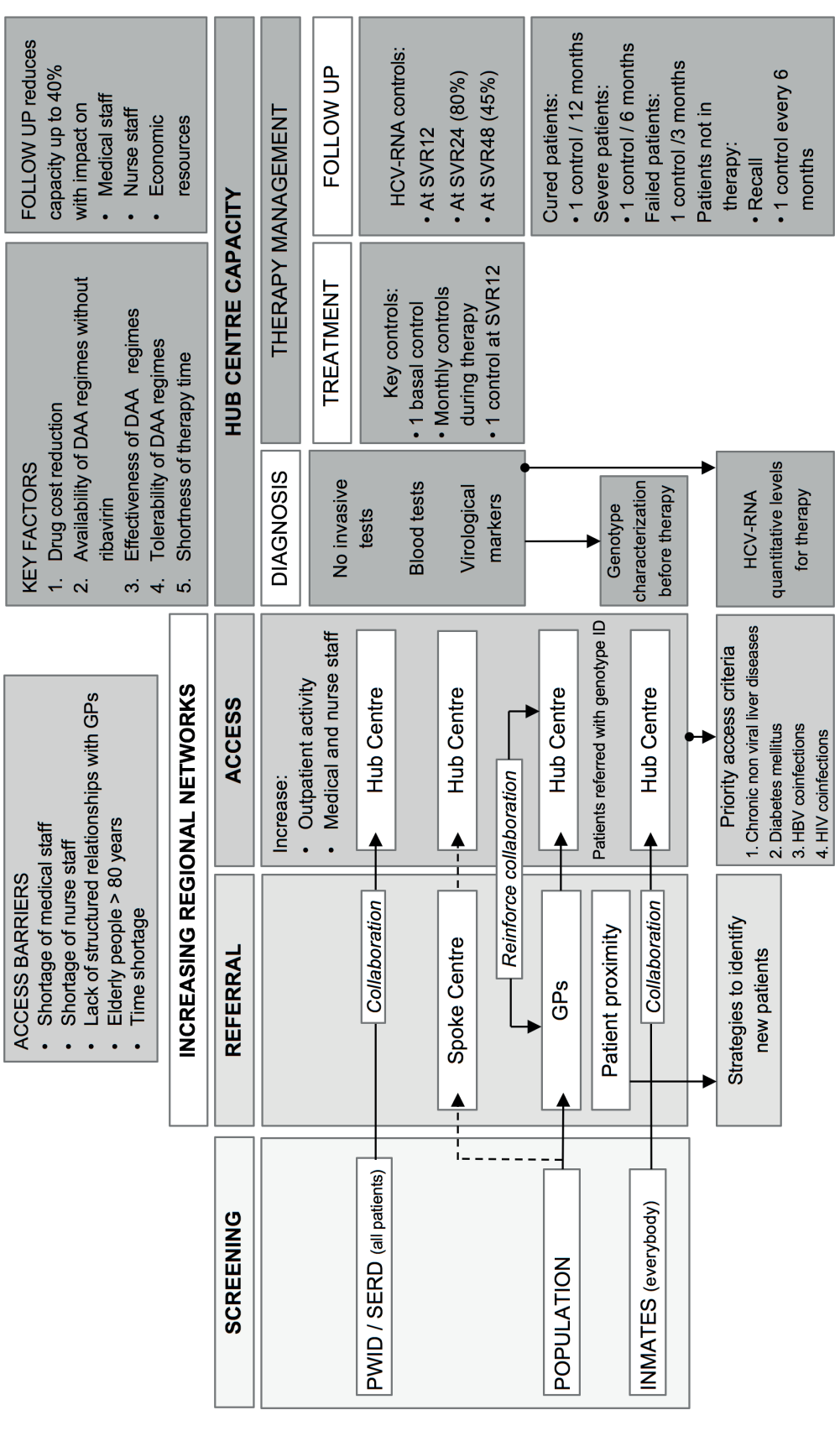

Figure 5. HCV Management Model: key aspects that may enhance patient referral and centre capacity.

ement on the strategies to define the virological pattern of patients with chronic HCV infection and to evaluate the stage of chronic liver disease. All physicians answered that a quantitative test of serum HCV-RNA and determination of viral genotype are mandatory to define the pattern of viral infection. Over 90% agreed that it is also necessary to carry out HIV and HBV testing. The EP confirmed that viral genotype continues to be important even if the new generation of DAAs have pangenotypic efficacy. Around 80% of physicians thought was useful to determine anti-HBc into order to evaluate a previous HBV infection. This response is justified by data showing that >30% of DAA-treated Italian patients have positivity for anti-HBc20. Hepatitis B virus reactivation was identified as a safety concern in patients with HBV-HCV co-infection treated with DAAs21. Patients meeting the criteria for treatment of active HBV infection should be started on nucleos(t)ide analogues (NUCs) at the same time as HCV DAA therapy is initiated5. Most members of the EP said that their centers used the FibroScan to define the stage of liver disease, while <20% of physicians use non-invasive serum tests for the definition of liver fibrosis. This is in line with international scientific bodies that recommend transient elastography as it shows better diagnostic performance in the detection of liver cirrhosis compared to APRI and FIB-422. The EP agreed that adherence to therapy, lack of drug-drug interactions and the possibility of treating patients with advanced liver disease, were factors instrumental in their choice of therapy. Treatment duration and association with ribavirin were cited as being less important. In general it has emerged that physicians prefer therapeutic regimens that they can offer to all patients regardless of the stage of liver disease and the presence of comorbidities that need treatment with other drugs. Interestingly the EP was not convinced that the time to evaluation of virological response and the number of clinical controls can be reduced with the new pangenotypic therapeutic regimens. They confirmed the need for monthly virological and clinical check-ups during therapy and only 4% felt that a12-week HCV-RNA test was adequate to determine a SVR. While 80% considered that it was useful to check HCV-RNA after 24 weeks. Although the definition of SVR is universally accepted, guidelines are unclear on the need to repeat the HCV-RNA serum test after confirmation of SVR4,5. Over 80% of the EP were in agreement with the need to continue follow-up of patients with advanced hepatic fibrosis/cirrhosis and patients who have chronic liver injury from other causes. An important objective of this study was to develop a model to enhance patient referral and center capacity in HCV management. The EP indicated that adequate numbers of healthcare professionals and efficient support staff are key to increase the capacity of centers. Creating structured partnerships with GPs may also significantly increase center capacity. Likewise, timely characterization of patients may reduce the time to starting therapy and increase the number of patients who have access to DAAs.

Conclusions

The capacity of the centers treating patients with HCV chronic hepatitis or cirrhosis is still conditioned by frequent virological and clinical check-ups both during and post treatment. Registration studies and real-life cohort reports, confirm the high efficacy and good tolerability of current therapeutic regimens. These regimens may make it possible to reduce and simplify the number of virological and clinical controls during therapy[2,23-25]. Follow-up after SVR testing could be simplified for patients with mild/moderate liver fibrosis. But adequate clinical surveillance after SVR in patients with cirrhosis remains mandatory. Italy has one of the highest prevalence of HCV-infected patients in Europe and the highest rate of deaths from cirrhosis and HCC[26,27]. In order to effectively identify, diagnosis and manage these large numbers patients it is vital that an effective, cost-effective approach, which best utilizes resources of the health service is put in place28. Our results indicate that national and international scientific organizations need to continuously review and update recommendations in their guidelines to facilitate access of patients with HCV chronic hepatitis to DAA regimens, to increase the capacity of treatment centers, and to simplify post-therapy follow-up.

Conflict of Interest

V. Di Marco is a consultant for AbbVie, Gilead Science, Merck, BMS; A. Alberti is a consultant for AbbVie, Gilead Science, Merck, BMS; G. Angarano is a consultant for AbbVie, Gilead Science, Merck, BMS; M. Colombo is a consultant for Merck, Roche, Novartis, BMS, Gilead Sciences, Tibotec, Vertex, Janssen Cilag, Achillion, AbbVie; G. Di Perri is a consultant for AbbVie, Gilead Science, Merck, BMS; G.B. Gaeta is a consultant for AbbVie, Gilead Science, Mer-

ck, BMS; G. Ippolito has no conflicts of interest to declare; A. Mangia is a consultant for AbbVie, Gilead Science, Merck, BMS; P. Pasqualetti has no conflicts of interest to declare; A. Craxì is a consultant for Merck, BMS, Gilead Sciences, Janssen Cilag, Achillion, AbbVi.

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Authors contributions
All authors contributed to the research, development and writing of the manuscript. VDM acted as manuscript coordinator. All authors read and approved the final manuscript.

References

1) Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. http://apps.who.int/iris/bitstream/10665/255017/1/WHO-HIV-2017.06-eng.pdf. Accessed June 21, 2018.
2) Sacks HS. Review: in chronic hepatitis C virus infection, oral direct-acting antivirals have high sustained virologic response. Ann Intern Med 2017; 167: JC3.
3) van der Meer AJ, Wedemeyer H, Feld JJ, Dufour JF, Zeuzem S, Hansen BE, Janssen HL. Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. JAMA 2014; 312: 1927-1928.
4) Bruno S, Di Marco V, Iavarone M, Roffi L, Crosignani A, Calvaruso V, Aghemo A, Cabibbo G, Viganò M, Boccaccio V, Craxí A, Colombo M, Maisonneuve P. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol 2016; 64: 1217-1223.
5) AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. www.hcvguidelines.org. Accessed June 21, 2018.
6) EASL recommendations on treatment of hepatitis C 2016.https://www.easl.eu/medias/cpg/issue4/English-report.pdf. Accessed June 21, 2018.
7) Linstone H, Turoff M, eds. The Delphi Method. Techniques and applications. Reading, MA: Addison-Wesley Publishing Company 1995; pp. 1-616.
8) Jones J, Hunter D Consensus methods for medical and health services research. BMJ 1995; 311: 376-380.
9) Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, Wales PW. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014; 67: 401-409.
10) Rowe G, Wright G. The Delphi technique as a forecasting tool: issues and analysis. Int J Forecast 1999; 15: 353-375.
11) Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. J Clin Epidemiol 2003; 56: 1150-1156.
12) Kong LN, Guo Y, Qin B, Peng X, Zhu WF. Development of self-management indicators for chronic hepatitis B patients on antiviral therapy: results of a Chinese Delphi Panel Survey. PLoS One 2015; 10: e0134125.
13) Ho CK, Boscardin CK, Gleason N, Collado D, Terdiman J, Terrault NA, Gonzales R. Optimizing the pre-referral workup for gastroenterology and hepatology specialty care: consensus using the Delphi method. J Eval Clin Pract 2016; 22: 46-52.
14) Fitch, K, Bernstein SJ, Aguilar MD et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND Corporation, 2001. https://www.rand.org/pubs/monograph_reports/MR1269.html. Accessed June 21, 2018.
15) Conti F, Brillanti S, Buonfiglioli F, Vukotic R, Morelli MC, Lalanne C, Massari M, Foschi FG, Bernabucci V, Serio I, Prati GM, Negri E, Badia L, Caraceni P, Muratori P, Vitale G, Porro A, Morotti M, Mazzella G, Andreone P. Safety and efficacy of direct-acting antivirals for the treatment of chronic hepatitis C in a real-world population aged 65 years and older. J Viral Hepat 2017; 24: 454-463.
16) Snyder HS, Ali B, Gonzalez HC, Nair S, Satapathy SK. Efficacy and safety of sofosbuvir-based direct acting antivirals for hepatitis C in septuagenarians and octogenarians. J Clin Exp Hepatol 2017; 7: 93-96.
17) Su F, Beste LA, Green PK, Berry K, Ioannou GN. Direct-acting antivirals are effective for chronic hepatitis C treatment in elderly patients: a real-world study of 17 487 patients. Eur J Gastroenterol Hepatol 2017; 29: 686-693.
18) Sherigar JM, Gayam V, Khan A, Mukhtar O, Arefiev Y, Khalid M, Siddiqui I, Rangaraju AM, Budhathoki N, Mansour M, Guss D, Mohanty SR. Clinical efficacy and tolerability of direct-acting antivirals in elderly patients with chronic hepatitis C. Eur J Gastroenterol Hepatol 2017; 29: 767-776.
19) Fabrizio C, Saracino A, Scudeller L, Milano E, Dell'Acqua R, Bruno G, Lo Caputo S, Monno L, Milella M, Angarano G. The elderly and direct antiviral agents: constraint or challenge? Dig Liver Dis 2017; 49: 1036-1042.
20) Calvaruso V, Ferraro D, Licata A, Bavetta MG, Petta S, Bronte F, Colomba G, Craxì A, Di Marco V. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct-acting antivirals. J Viral Hepat 2018; 25: 72-79.

21) Bersoff-Matcha SJ, Cao K, Jason M, Ajao A, Jones SC, Meyer T, Brinker A. Hepatitis B virus reactivation associated with direct-acting antiviral therapy for chronic hepatitis C virus: a review of cases reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Ann Intern Med 2017; 166: 792-798.

22) Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute Technical Review on the role of elastography in chronic liver diseases. Gastroenterology 2017; 152: 1544-1577.

23) Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis C genotype-1 patients. Antivir Ther 2017; 22: 481-493.

24) Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. Hepatology 2016; 64: 405-414.

25) Aghemo A, Bruno R, Colombo M, Medagli M, Puoti M, Rizzardini G, Fagiuoli S; Lombardia Hepatitis Network. Treatment of patients with chronic hepatitis C infection in Lombardia: a report by the Lombardia Hepatitis Network. Eur Rev Med Pharmacol Sci 2016; 20: 17-19.

26) Croce D, Bonfanti M, Restelli U. Financial and feasibility implications of the treatment of hepatitis C virus in Italy: scenarios and perspectives. Clinicoecon Outcomes Res 2016; 8: 377-385.

27) Gardini I, Bartoli M, Conforti M, Mennini FS, Marcellusi A, Lanati E. HCV - Estimation of the number of diagnosed patients eligible to the new anti-HCV therapies in Italy. Eur Rev Med Pharmacol Sci 2016; 20: 7-10.

28) Marcellusi A, Viti R, Capone A, Mennini FS. The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model. Eur Rev Med Pharmacol Sci 2015; 19: 1610-1620.