Position paper on the role of Internal Medicine in the management of hepatitis C virus infection (screening, diagnosis, linkage-to-care, treatment)

Giorgio Ballardini,[1] Francesco Bandiera,[2] Luca Fontanella,[3] Antonio Mancini,[4] Giancarlo Parisi,[5] Paola Piccolo,[6] Claudio Puoti,[7] Giuseppe Zaccala,[8] Elisa Zagarrì,[9] Giovanni Pappagallo,[10] Andrea Fontanella[3]

[1]Internal Medicine Department, Ospedale degli Infermi, Rimini; [2]Internal Medicine Department, SS. Annunziata Hospital, Sassari; [3]Internal Medicine Department, Buonconsiglio Fatebenefratelli Hospital, Napoli; [4]Internal Medicine Department, Careggi Hospital, Firenze; [5]Internal Medicine Department, Feltre Hospital (BL); [6]Internal Medicine Department, Fatebenefratelli Hospital, Roma; [7]Epatology Center, INI Institute Grottaferrata (RM); [8]Internal Medicine Department, Ospedale Maggiore della Carità, Novara; [9]FADOI Study Center, Milano; [10]Epidemiology & Clinical Trials Office, General Hospital, Mirano (VE), Italy

ABSTRACT

Since Internal Medicine (IM) is the most frequent setting of hospitalization for both patients with advanced liver disease and those with comorbidities and risk factors for infection, through this position paper FADOI aims to promote and disseminates its vision regarding the current and potential role of IM in managing hepatitis C virus (HCV) infection (screening, diagnosis, linkage-to-care, treatment). The Internist plays an important role in identifying new cases, in selecting the appropriate diagnostic work-up for liver disease staging and prognosis, and in initiating antiviral therapy, coordinating care and communication with other specialists, the Hepatology outpatient clinic and General Practitioners.

Since the Internist is naturally accustomed to the management of multiple comorbidities, he has a fundamental role in the identification of extrahepatic diseases associated with HCV infection and in the diagnosis of comorbidities, some of which are potential factors of liver disease progression. Moreover, in the prescription of the antiviral therapy, it is important to consider the possible drug interactions, and this ideally fits the role of the Internist who can weigh the risk/benefit ratio of possible alternatives, by considering the patient's clinical situation, especially in case of multiple comorbidities.

Moreover, it seems appropriate that the ability to prescribe antiviral therapy is guaranteed to all IM hepatology clinics, favoring a spread of awareness as well as an increase in national coverage and therefore patient access to therapies. The network of IM can also contribute to homogenizing the management policies of HCV treatment, which sometimes differ between Italian Regions.

Correspondence: Elisa Zagarrì, FADOI Study Center, Piazza Cadorna 15, 20123 Milano, Italy.
E-mail: elisa.zagarri@fadoi.org

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Introduction

Internal Medicine is an excellent observational field for hepatitis C virus (HCV)-related liver diseases, because it is the most frequent site of hospitalization for both patients with advanced liver disease and patients with comorbidities and risk factors for infection. From an analysis carried out by FADOI [*Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti*/Federation of Associations of Hospital Doctors on Internal Medicine] on SDO data [*Scheda di Dimissione Ospedaliera*/Hospital Discharge Form] for the year 2016 of the Ministry of Health,[1] Internal Medicine (IM) wards in Italy are responsible for 14% of all hospital discharges (1,101,648 discharges out of a total of 7,875,074). Of all the hospital discharges with the initial diagnosis of *Hepatic Cirrhosis*, 46%, or 25,373 discharges, are from IM wards.[1] These figures alone explain the interest and the need for FADOI to express a Position Paper on its role in managing HCV infection, also by virtue of the fact that the national distribution of IM in all Italian hospitals, in a homogeneous

network, can contribute to standardizing the management policies for the treatment of HCV, which sometimes differ between Italian Regions. Moreover, also due to the fact that more than 95% of IM admissions occur directly from the emergency ward, an important role is played by identifying new cases and initiating treatment, as most of the hepatological centers are established within IM units; furthermore, the internist hepatologist is naturally accustomed to the management of associated comorbidities and drug interactions, conditions frequently encountered in cases of HCV infection.

Methods of research

Project aim and phases

The project aims to compile and disseminate FADOI's *vision* regarding the role of Internal Medicine in the management of HCV infection through three distinct phases: i) identification of the aspects most deserving of clarification and/or in-depth analysis; ii) building behavioral statements for each aspect mentioned in the previous point; iii) writing an organization position paper, with the input of ten subject matter experts.

Limitations of *informal consent* and *formal consent*

Meetings that directly engage individuals asked to contribute to the knowledge-building and decision-making process are influenced by the socio-emotional dynamics that govern the functioning of the group.[2]

The options of the individual participants are governed by the power relations and the conflict-alliance dynamics that are created between the participants, rather than by the sharing of the analysis. This means that the ideas taken into consideration are limited and tend to reproduce the behaviors already present in the organization in a conformist manner, being careful to avoid undermining the power relations that govern its functioning.[3,4] The formal methods currently codified for consensus-building aim at controlling these factors by reducing the effects due to formal leadership dynamics, and maximizing autonomy and freedom of judgement.[5]

Identification of the aspects most deserving of clarification and/or in-depth analysis

In this first phase of the project, the nominal group technique (NGT)[6,7] was applied, which requires the presence of all the Experts involved in a face-to-face meeting, with the coordination of a facilitator method. The meeting was conducted based on the question: *What are the aspects that characterize the current role of Internal Medicine in the management of HCV infection, and how could this role be further enhanced?*

The NGT process was divided into 4 phases: i) generation of ideas (basic responses to the question) by each participant, individually and silently (without any interaction between them); ii) collection of ideas: the participants reported what was discussed, one idea at a time, in succession one after the other - round robin session - to compile a first list of ideas (on flip charts) without any debate yet being allowed; iii) discussion of ideas [General Practitioners (GP)-guided discussion]: participants were invited to comment on each of the ideas on the whiteboards, in this phase the ideas were subjected to refinement (textual and/or conceptual) and partially merged under a new name; iv) prioritization of ideas (rankings) to define the relative importance of what was presented (formal voting discussion). The meeting of the group of experts led to the identification of a list of 8 points worthy of clarification/expansion, and for each of them a systematic review of the Literature was subsequently carried out. The 8 aspects identified as critical for this task were: i) health policy; ii) impact of disease identification in IM; iii) methods for disease identification; iv) identification of the patient candidate for treatment; v) communication; vi) methods for disease management; vii) comorbidities; viii) pharmacological interactions;

Production of behavioral statements for each of the most important aspects

The Delphi method[8,9] was used for this phase, which is based on indirect and structured interaction between experts. Again, in this case, communication between experts was not free, but based on independent and autonomous work.

The task was then conducted as follows: i) each of the experts produced one statement (succinct, explicit sentence of a specific behavior) for each of the NGT ideas defined in the previous phase (1st Delphi phase); ii) the GP has arranged to harmonize the common points and subject the statements to expert judgement (even more than one for a single idea) resulting from the previous phase; iii) the experts had the power to modify and/or supplement what they received (2nd Delphi phase). At this point, a final meeting was convened, managed as a Consensus Conference,[10] in which statements derived from the 2nd Delphi phase were discussed to conduct the final formulation of statements.

Drafting of the company position paper

Once the final statements for each NGT idea were agreed, the tasks were assigned for the drafting of the position paper.

Health policy

The availability of drugs for the treatment of HCV infection, which are well tolerated and allow cure rates close to 100%, offers the ability to pass from a policy of disease control (to treat patients with the most advanced, most serious, most urgent disease) to a policy of eliminating the infection. Treating 80% of patients, with particular attention given to high-risk populations, and taking preventive measures to eliminate incident cases should make it possible to reduce the number of infected subjects by at least 90%, in the absence of new infections. The World Health Organization (WHO) aims to achieve the elimination of HCV infection by 2030.[11]

An obstacle to achieving this goal is the current uncertainty on the epidemiology of HCV infection in Italy. Data from around 20 years ago placed the number of anti-HCV positive subjects in Italy at approximately 3%, with greater prevalence in the south and in the elderly population. As for hepatitis B, the prevention campaigns following the appearance of the human immune deficiency virus (HIV) have significantly reduced incident cases through the decrease of risk behaviors; in 2016 incident HCV cases fell below 0.2/100,000 of the population, with no incidents under 14 years of age. The natural reduction in the number of the over-75 age cohort of 20 years ago, who had a high prevalence of infection, has brought current prevalence estimates between 0.6 and 1.7%, with a median of approximately 1%. What remains undefined with any certainty is the share of patients not yet diagnosed even if, currently, the estimates that were previously 50-60% appear to be around 20%.[12,13]

For this reason, policies are desirable that lead to treating diagnosed patients, starting with high-risk groups, and seeking out undiagnosed patients with active policies. In this context, given the ever-present high numbers of patients and the issue of available resources, the cost of drugs remains an important aspect and still represents one of the main limiting factors, along with access to care. To identify unknown cases, awareness campaigns aimed at high-risk groups, GP and hospital facilities that admit high-risk patients are required to help diagnose infection and put patients in contact with treatment-dedicated clinics. IM is an excellent observational field for HCV-related liver disease, because it is the most frequent site of hospitalization for both patients with advanced liver disease and patients with comorbidities and risk factors for infection. Internal Medicine can play an important role in identifying new cases and initiating treatment because most of the hepatological centers are established within IM units and the internist hepatologist is naturally accustomed to the management of associated comorbidities and pharmacological interactions, conditions frequently encountered in cases of HCV infection. Also, in view of this, it seems appropriate that the ability to prescribe antiviral therapy is guaranteed to all IM hepatology clinics, favoring a spread of awareness to this issue as well as an increase in national coverage, so that geographical distance from the prescribing centers does not hinder patient access. The network of IM can also contribute to homogenizing the management policies of HCV treatment, which sometimes differ between Italian Regions.

Impact of disease identification on internal medicine

Although the prevalence of HCV infection is in sharp decline in Italy, both due to the introduction of direct-acting antivirals (DAAs) and for physiologically generational reasons, the question remains whether or not to apply an extensive screening of HCV in departments such as those of IM who have significant volumes of care burden and manage a large number of patients in high-risk categories.[13,14]

Screening for HCV infection by detection of anti-HCV antibodies on admission to the IM ward should be indicated in all subjects born before 1978 - although disposable medical supplies have been produced since the early 1960s, their introduction in Europe and in Italy took place only at the end of the 1970s - as well as subjects presenting the following risk factors for HCV infection: i) active or prior intravenous drug use; ii) cosmetic treatments such as piercings and tattoos; iii) subjects with multiple sexual partners, men who have sex with men; iv) recipients of blood, plasma or derivative transfusions prior to 1992; v) organ transplant recipients; vi) dialysis patients; vii) patients undergoing multiple hospital admissions; viii) subjects living with HCV-infected patients; ix) HIV-positive patients; x) incarcerated subjects; xi) patients from countries with high prevalence of HCV infection; xii) patients with otherwise unexplained increase in serum alanine transaminase.

In past years, when only interferon±ribavirin-based therapies were available, in many cases the diagnosis of HCV infection was not followed by effective therapy; currently there are new issues to consider: i) oral therapies are practically free of side effects, are now low in cost and guarantee very high rates of virologic response; ii) even subjects with persistently normal alts may have relevant chronic liver damage; iii) the prevalence of HCV among patients admitted to IM departments, of advanced age, is higher than in the general population; iv) large-scale identification and treatment can lead to progressive control and containment of the spread of HCV, and therefore to a reduction in the prevalence of infection.

For these reasons, extensive testing for HCV in patients admitted to IM would be desirable, and not excessively expensive, with a possible/likely advantageous cost/benefit ratio.

Methods for disease identification

The diagnosis of HCV infection requires the presence of viremia (measurable HCV RNA in serum) with a protein C-reactive method (lower limit of detection 10-15 IU/mL) in the anti-HCV positive patient. The subsequent staging of HCV-related liver disease uses imaging methods (liver ultrasound), tests for non-invasive quantification of hepatic fibrosis (transient elastography), and biochemical tests (indices of hepatic cytolysis, cholestasis, liver synthesis, *etc.*). At the same time, other concurrent etiological causes must be sought and excluded. In some select cases, liver biopsy may be indicated. Further clinical-instrumental examinations are indicated in cases of HCV-related extra-hepatic disease. In anticipation of the antiviral treatment, virologic characterization can be indicated with research for viral genotype.[15,16]

During hospitalization in the IM ward, the anti-HCV positive patient can undergo some of the aforementioned examinations, depending on the clinical scenario and the reason for admission. The diagnostic work-up, which may require a length of stay that is not compatible with the hospital admission, can be completed in the Hepatology Outpatient Clinic (HOC) after discharge.

Patients in whom an initial anti-HCV positive result is detected, hepatic ultrasound and serum HCV RNA quantification are indicated during hospitalization; at discharge, patients will be sent to the HOC to complete the staging of the liver disease and to indicate antiviral therapy.

In patients with known HCV-related chronic liver disease, admitted to Internal Medicine due to complications of liver disease or extrahepatic diseases, it is not necessary to repeat the serum HCV RNA analysis. These patients will be referred to continued follow-up and antiviral treatment, if indicated, at the HOC.

In patients with liver cirrhosis as well as in patients with stage F3 fibrosis, whether or not treated with antivirals, hepatic ultrasound is indicated if not performed in the previous 6 months.

Upon discharge from the IM ward, the diagnosis containing the available data (genotype, fibrosis stage, histological data, previous antiviral therapies, extra-hepatic disease, *etc.*) will be reported in the medical record and on the discharge letter; the patient will be referred to the HOC for antiviral treatment (if indicated), prevention of complications, and monitoring for hepatocellular carcinoma, as per international guidelines.[15,16]

Identification of the patient candidate for treatment

Today, access to new treatments with DAAs is possible for all patients with HCV infection, with few exceptions [*i.e.*, active hepatocellular carcinoma (HCC)]. Even patients who do not have evidence of advanced liver damage can receive antiviral treatment, and there is no specified age limit for treatment. Over the last few years, the cost of therapy has been reduced, but it is still associated with a relevant health expenditure. Furthermore, although there are no official protocols regarding laboratory monitoring during DAA therapy, the expense of repeated testing, at the discretion of each prescribing center, should also be taken into consideration. It is therefore appropriate to set guidelines regarding the appropriate indication for antiviral treatment for an effective cost/benefit assessment.

Patients with biochemical or ultrasound evidence of liver damage, or advanced F2 to F4 fibrosis, require priority to treatment; pre-treatment staging will include viremia and genotype, as well as exclusion of alternative causes of liver damage.

In case of confirmed normal biochemical, ultrasound and stiffness values compatible with fibrosis F0/F1, the decision whether to treat with DAAs or not should take into account the following variables: i) age; ii) co-morbidities; iii) life expectancy; iv) ongoing drug therapies; v) risk of infection transmission; vi) patient motivation.

Communication

In managing the HCV-infected patient, the Internist must communicate effectively with the patient (and related caregivers), the GP, the specialist Hepatologist and the Transplant Centre.

Information can be provided by the Internist during admission to IM or by the Hepatologist specialist during subsequent outpatient care.

In case of initial diagnosis during IM admission, the anti-HCV positive patient must be informed of the need to perform second-level tests to confirm the infection, and to perform a specialist Hepatological work-up for disease staging. Ideally the Internist should be able to refer the patient directly to a HOC of the IM Department, or through direct contact with the appropriate HOC.

At the time of diagnosis of chronic HCV infection, the patient and caregiver must be informed on: i) modes of transmission in order to prevent the spread of infection; ii) the need for cohabitants to screen for HCV.

Upon completion of disease staging, the patient and caregiver must be informed on: i) stage of the disease and its prognosis; ii) indications for antiviral treatment,

how to take antiviral drugs, their benefits and side effects; iii) the need to perform imaging and laboratory follow-up after the completion of antiviral therapy.

The patient with HCV-related chronic liver disease identified during IM admission must be referred to the HOC to complete the staging and for antiviral therapy indication. The GP should be informed of the clinical and laboratory tests scheduled during the post-therapy follow-up.[17]

The patient with HCV-related liver cirrhosis discharged from the IM ward must be referred to the HOC for antiviral treatment (if indicated), prevention of cirrhosis complications and monitoring for HCC. The GP should be informed of the clinical and laboratory tests scheduled during this follow-up. The Internist and the specialist Hepatologist will coordinate the referral of the patient with cirrhosis to the Transplant Centre when indicated.[18]

The GP should be informed about the diagnosis, disease stage, the prescribed therapy, and the planned follow-up through the discharge letter from the IM Department, or through the outpatient medical report.[17,18] Patients who have completed antiviral therapy achieving HCV eradication must receive a certification of the outcome of their treatment in relation to the long-term persistence of anti-HCV positivity.

Methods for disease management

The management of HCV infection must be split into two different areas: i) therapeutic management (to cure); ii) clinical management (to care).

In the non-viremic patient (=anti-HCV positive/HCV RNA negative) following a spontaneous clearance that occurred in the past (often misdiagnosed), management can end, subject to the usual routine checks based on patient age and comorbidities.

In the non-viremic patient who cleared HCV following antiviral therapy, it is appropriate to continue the follow-up, even for years, although there are no clear guidelines in this regard.[19]

In the HCV RNA positive patient with abnormal liver functions tests, it is appropriate to perform a complete work-up (see above) to determine disease stage and prognosis. This can be arranged following hospital discharge, and referring the patient to the IM outpatient clinic. In selected cases (*e.g.*, hepatic comorbidities) an indication may be given to perform a liver biopsy.

A particular scenario is represented by patients with normal biochemical, ultrasound and liver stiffness results. In these cases, the decision to treat with the second generation DAAs, which moreover are generally very well tolerated, will depend on different variables, such as: patient age, co-morbidities, life expectancy, interactions with any existing drug therapies.

Comorbidities

Chronic HCV infection can evolve into systemic disease, in which the severity of multiple extrahepatic manifestations is often not directly proportional to liver damage, and the presence of non-HCV-related liver or extrahepatic disorders may lead to significant interactions with the viral disease.

The main HCV-related extrahepatic diseases include: i) lymphomas;[20] ii) mixed cryoglobulinemia;[21] iii) non-cryoglobulinemic central and peripheral neuropathies;[22] iv) rheumatic disorders (Sjogren's syndrome, arthralgia/myalgia).[23]

Furthermore, the presence of HCV infection seems to increase the risk of developing: i) extrahepatic neoplasms;[24] ii) cardiovascular diseases;[25] iii) diabetes mellitus.[26]

The Internist has a fundamental role in the identification of extrahepatic diseases associated with HCV infection and in the diagnosis of any comorbidities, some of which are potential factors of liver disease progression [*i.e.*, alcohol abuse, obesity, diabetes mellitus, hepatitis B virus (HBV) co-infection].

Some situations involve specific treatment strategies: i) the evolution towards advanced chronic nephropathy requires shared management with the Dialysis Centre;[27] ii) in the presence or suspicion of HCC, after staging of both liver and any extrahepatic disease, the patient must be assessed in an interdisciplinary manner (by interdisciplinary or equivalent teams of care) and, if required, referred to the Transplant Centre.

The presence of comorbidity[28] on the one hand may hinder antiviral treatment (due to pharmacological interactions and side effects of antivirals); however, this is an indication not to delay treatment, due to the favorable effect that the continued virologic response produces on both evolution of the extrahepatic HCV-related disease, and on mortality from non-HCV related diseases.

For these reasons, an adequate profile of the HCV-infected patient, necessary for evaluation of antiviral treatment and/or monitoring, must include: i) complete definition of liver disease stage (for cirrhotics Child-Pugh and MELD score, evaluation of portal hypertension), both for the HCV component and for any other associated hepatic disorders; ii) screening for possible co-infections related to specific HCV-infected groups (*e.g.*, in intravenous drug users testing for HBV, syphilis, HIV; in migrants with tuberculosis, testing for HIV); iii) research and definition of any related or independent extrahepatic HCV disease.

Drug interactions

In the prescription and management of the antiviral therapy, it is important to consider the possible drug interactions:[29,30] i) with drugs prescribed (chronically or cyclically) for liver disease or other comorbid conditions; ii) with drugs prescribed for any other conditions occurring during the period of antiviral treatment.

Interactions between drugs, when significant, can be a source of: i) antiviral treatment failure; ii) toxicity, mediated by both pharmacokinetic and pharmacodynamic mechanisms;[31,32] iii) reduced therapeutic efficacy for concomitant disease(s).

The possibility of interaction should always be suspected and investigated, possibly with appropriate databases (*e.g.*, www.hep-druginteractions.org), given the dynamics of new drugs availability and continuous update of available data: considering the severity of possible interactions, the most appropriate antiviral approach will be chosen. It is important to record the result of the drug interaction verification on the treatment medical record, to explain the choice of the prescribed medication and any consequent temporary variations of the pre-existing drugs regimens.

The management of these issues ideally fits the role of the Internist, who must weigh the risk/benefit ratio of possible alternatives, considering the various aspects of the patient's clinical situation;[33] in particularly complex cases of pharmacotherapy the prescriber can coordinate with other specialists in charge of the patient's care (*i.e.*, antiarrhythmics, antiretrovirals,[34] antiepileptics[35]).

Especially in patients with multiple comorbidities, who are at higher risk of pharmacological interactions, a greater continuity in the doctor-patient relationship, achievable through an increase in the number of HOCs qualified for the prescription direct antivirals, would facilitate therapeutic individualization, with obvious positive effects on effectiveness and safety.

It is also important that all documentation of the aforementioned information and decisions be made available to the GP, who often coordinates care with other specialists, and is the first point of contact in case of adverse events; the importance and the methods of communication are described in section 7 of this document.

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