Original Article

The management of patients positive to hepatitis C virus antibody in Malta

Anthea Brincat, Neville Azzopardi, Maria Deguara, Kelly Mifsud Taliana, Marilyn Rogers, James Pocock

Abstract

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease and hepatocellular carcinoma worldwide and is an important public health concern. A retrospective analysis of the demographics and management of patients who had a positive anti-HCV detected by enzyme immunoassay test done at Mater Dei Hospital was carried out to analyse the epidemiology of HCV infection in Malta and assess our management when compared to the European Association for the Study of the Liver (EASL) guidelines. 72% of patients were male. The majority of patients were aged 21-50 years. The main mode of infection was via intravenous drugs use, accounting for 68% of cases.

Only 56% of patients found to be HCV Ab positive had a scheduled appointment with an infectious diseases specialist or gastroenterologist documented on the MDH online appointment system. 58% of patients had HCV RNA testing done and 45% had genotype testing. 7.3% with HCV infection were given treatment, of which 43% had a Sustained Virological Response (SVR).

Anthea Brincat M.D. *
Department of Medicine,
Mater Dei Hospital
Msida
anthea.brincat@gov.mt

Neville Azzopardi M.D. MRCP(UK)
Department of Gastroenterology,
Mater Dei Hospital,
Msida

Maria Deguara M.D.
Affiliations: Department of Medicine,
Mater Dei Hospital,
Msida

Kelly Mifsud Taliana M.D. MRCP(UK)
Department of Oncology and Haematology,
Sir Paul Boffa Hospital

Marilyn Rogers M.D. MRCP(UK)
Affiliations: Department of Medicine,
Mater Dei Hospital,
Msida

James Pocock M.D. FRCP(UK)
Department of Gastroenterology,
Mater Dei Hospital,
Msida

**Corresponding author*

Keywords

Hepatitis C virus, EASL guidelines, management, treatment

Introduction

The Management of Patients Positive to Hepatitis C Virus Antibody in MaltaHepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.[1] WHO estimates that about 150 million people are chronically infected with HCV and that every year more than 350 000 people die from HCV-related liver diseases.[2]

HCV is a single-stranded enveloped RNA virus belonging to the Flaviviridae family. The outcome of HCV infection on the liver may range from minimal changes to acute or chronic hepatitis, cirrhosis and hepatocellular carcinoma. 75-85% of patients infected with HCV will not clear the virus by 6 months, thus developing chronic HCV infection. Cirrhosis develops in approximately 10- 15% of individuals with chronic HCV infection over twenty years.[3] The European Association for the Study of the Liver (EASL) has issued guidelines on the management of patients infected with HCV. In this study we have audited the management of chronic HCV with respect to the EASL guidelines.

Method

The audit is a retrospective analysis of the demographics and management of patients who had a positive HCV Antibody detected by EIA test done at the Virology Laboratory at Mater Dei Hospital. The time period studied was between January 2008 and May 2012, during which there were a total of 1,074 unique positive tests. Of these, 538 patients could not be identified as the tests were coded and 25 patients never had a file created or their file was misplaced. The remaining 506 files were viewed at medical records. This is a limiting factor of the study since not all the files could be traced. The following data pertains to these 506 patients.

Results

Demographics

72% (363) of patients were male. The age distribution of the patients with a positive HCV antibody test is shown in Graph 1. 77.7% of patients who tested positive were aged 21-50 years. This model of infection suggests that the risk for HCV infection was greatest in the relatively recent past and primarily affects young adults. Table 1 describes the nationality of individuals with a positive HCV antibody test, with 81% of patients being Maltese.

***Figure 1**: Age distribution of patients*

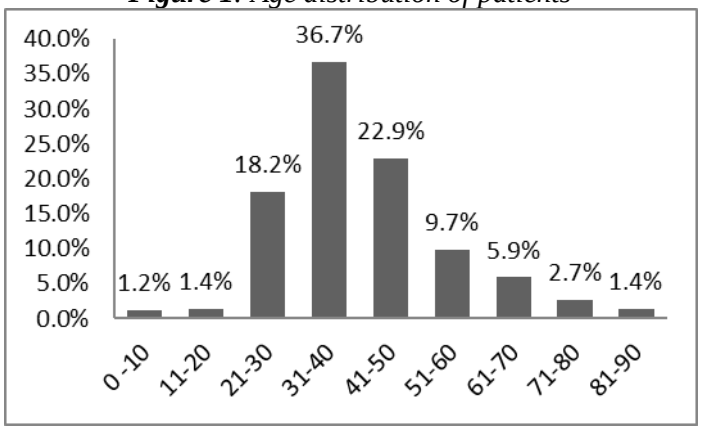


***Table 1**: Nationality of individuals with a positive HCV antibody test*

Nationality	Percentage
Maltese	81%
African & Eastern countries	11%
West Europe	6%
Other	2%

The residing locality of the patients was documented to analyze the distribution of HCV in Malta. The population estimate for each locality was obtained from The Malta Government Gazette (Number 18,789 published on Tuesday 9th August, 2011).[4] The number of patients infected with HCV living in a particular locality was multiplied by 10^6 and divided by the population living in that location thus allowing us to compare localities (Table2).

The highest ranking localities are mainly Harbour or Inner Harbour areas or localities associated with recreation.

***Table 2**: Highest Ranking Relative Prevalence Rates according to localities*

Rank	Locality	No. of people with HCV in the locality	Population[4]	Relative Prevalence No./Population X10^6
1	COSPICUA	30	5658	530
2	VALLETTA	23	6966	330
3	ST.VENERA	18	6939	259
4	FLORIANA	5	2335	214
5	ST.JULIANS	22	10573	208
6	HAMRUN	18	9649	187
7	VITTORIOSA	5	2758	181
8	GZIRA	15	8392	178
9	MSIDA	16	9227	173
10	KALKARA	5	2999	167

Mode of Infection

Chart 1 shows the alleged mode of infection. 68% of patients were known IVDU. In 2% of cases, the alleged mode of infection was via blood transfusions infected with HCV prior to the introduction of blood screening. In these cases, blood transfusions were the only risk factor documented in the notes. Vertical and sexual transmission accounted for 1% each whilst there was only one case (0.2%) of a needle stick injury resulting in infection. In 27% of cases, no risk factors were documented.

Investigations

Diagnosis of ongoing HCV infection requires the presence of HCV RNA, which is detected by molecular assays such as PCR. In our study, only 58% of patients had HCV RNA checked with 46% being positive and 11% negative. A negative HCV RNA in a patient who has a positive HCV Ab could be due to previous successful treatment, neonates who received the HCV Ab via transplacental transfer of the antibody, spontaneous clearance of the virus, a low viral load that is below the limit of detection of the laboratory or a false positive HCV Ab.

HCV is divided into six genotypes with numerous subtypes. Genotype 1, with subtypes 1a and 1b is the most prevalent genotype worldwide. Genotype 3a is highly prevalent among European IVDU[5] whilst genotype 1b is associated with blood transfusions.[6] In our study, it was shown that genotype testing was done in 20.5% of patients, with genotype 1a accounting for 45% of cases. (Chart 2). HCV genotype testing should be assessed in patients prior to starting antiviral therapy as it is important to decide treatment duration and dose of ribavirin.

***Figure 2**: Alleged mode of Infection*

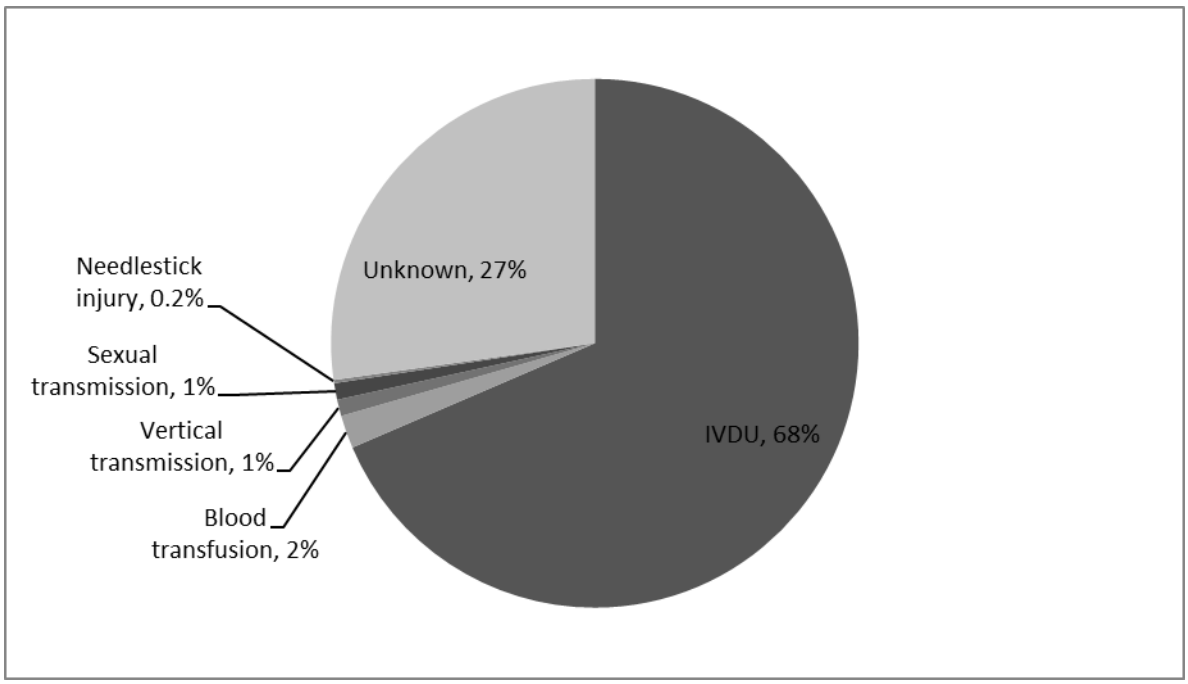
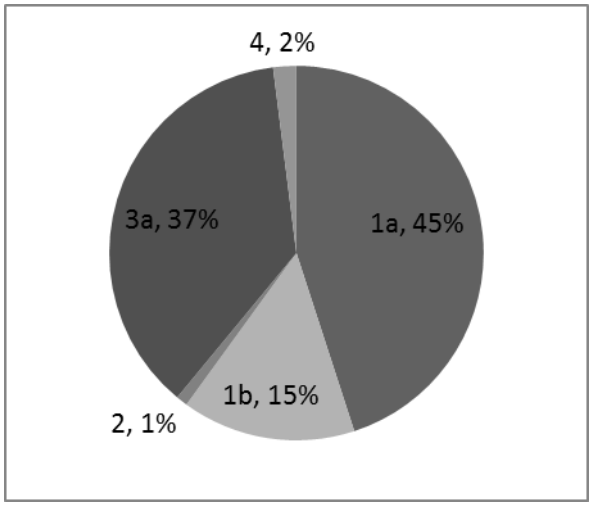


***Figure 3**: Distribution of Genotype*



EASL guidelines recommend that assessment of liver disease should include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, INR, albumin, gammaglobulins, full blood counts and an abdominal ultrasound.[1] Having low platelet counts, high INR, low albumin and high bilirubin is highly suggestive of underlying cirrhosis. (Table 3)

***Table 3**: Blood Tests*

Value	Percentage of patients	Number of patients tested
Platelets < 150 x10^9/L	21%	n=499
INR > 1.3	10.5%	n=416
Albumin < 35g/dL	14.5%	n=343
Bilirubin > 30µmol/L	10%	n=454

An ultrasound was done in 51% of patients. The finding of a nodular liver (suggestive of liver cirrhosis) was present in 9%. Ascites, which is indicative of liver failure, was found in 9%. Splenomegaly (suggestive of portal hypertension) was found in 18%.

HCV infection is associated with a 15 to 20-fold increase in hepatocellular carcinoma (HCC). The rate of HCC among patients with HCV infection ranges from 1-3% over 30 years.[7] In our study, HCC was found in 4% of patients who underwent an US abdomen, 80% of who were male.

A liver biopsy is done locally to assess the severity of liver disease, unless the patient is already has established liver cirrhosis. EASL guidelines state that a liver biopsy is regarded as the reference method to assess the degree of inflammation and fibrosis.[1] A standardized scoring system is used to report the grade, which is the

degree of inflammation and stage, which is the degree of fibrosis. Both values range from 0 being no inflammation or fibrosis, progressively worsening with a higher grade or stage until 4 is severe inflammation or fibrosis (termed liver cirrhosis). Assessment of the severity of hepatic disease is important in decision making with regards to treatment as patients with cirrhosis are less likely to respond to therapy and have a worse prognosis post-treatment[1]. In this study, 47 patients (9%) underwent a liver biopsy (Charts 3 and 4). 80% of patients have either no, minimal or mild inflammation and fibrosis which a good prognostic factor for treatment. Alternative non-invasive methods such as transient elastography can also be used to assess liver fibrosis in patients with chronic HCV[1]; however this non-invasive test is not available locally.

***Figure 4**: Distribution of Grade of liver biopsies*

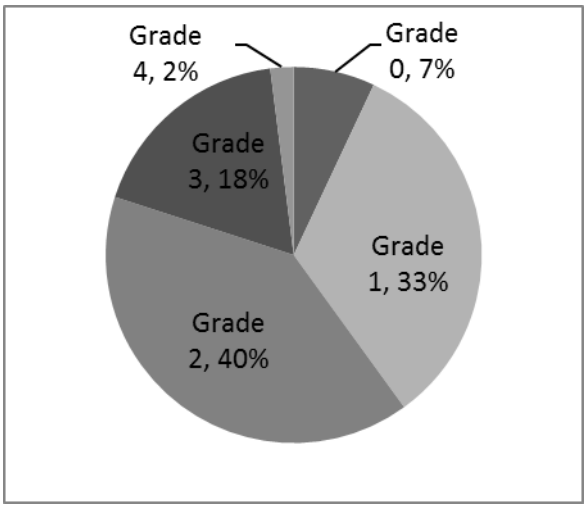
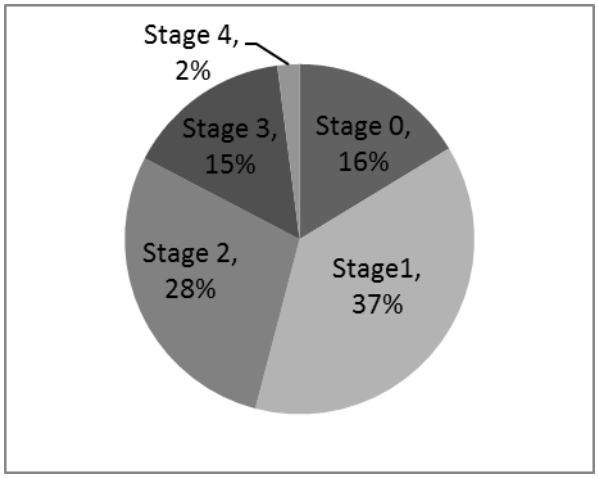


***Figure 5**: Distribution of the Stage of liver biopsies*



Referrals

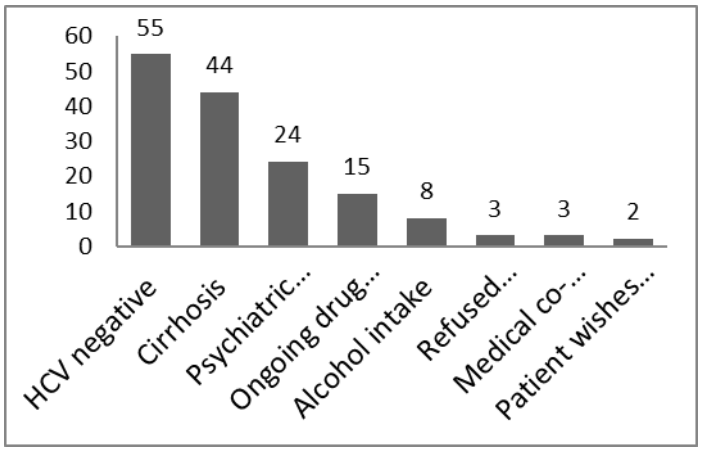
56% of patients found to be HCV Ab positive had a scheduled appointment with an infectious diseases specialist or gastroenterologist documented on the MDH online appointment system.

Treatment

Prior to the introduction of combination therapy, monotherapy with alpha interferon (IFN) was used. When combination therapy of pegylated interferon IFN-α (PEG IFN) and ribavirin was introduced, it became the standard treatment. Single therapy is nowadays only used if the patient cannot tolerate dual therapy due to side-effects.

37 out of the 506 patients audited (7.3%) were treated with either both PEG IFN and ribavirin or else with IFN alone. 55 patients (10.9%) were HCV RNA negative, and therefore treatment was not needed whilst 44 patients (8.7%) were in liver cirrhosis, so treatment was not given due to the risk of decompensation. 24 patients had an uncontrolled psychiatric condition and thus treatment was contraindicated. Chart 5 describes all patients who were deemed ineligible for treatment.

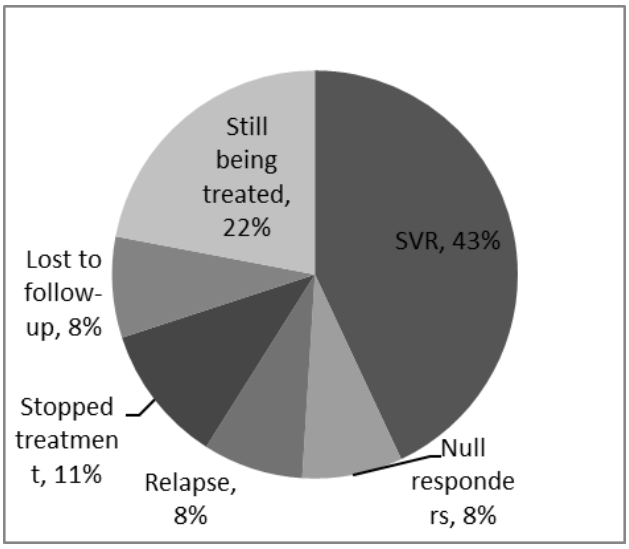
***Figure 6**: Ineligibility for treatment*



Sustained virological response (SVR) is defined as an undetectable HCV RNA level (<50 IU/mL) 24 weeks after cessation of treatment. Null response is defined as failure to achieve a decline of 2 logs HCV RNA IU/mL after 12 weeks of treatment or failure to achieve undetectable HCV RNA during treatment of a minimum duration of 24 weeks. Relapse is defined as having achieved undetectable HCV RNA at the end of treatment but HCV RNA is detected after stopping treatment[1].

Out of the 37 patients who were treated with either PEG IFN and ribavirin or IFN alone, 43% went into SVR, 8% were Null responders, 8% relapsed, 8% were lost to follow-up and 11% had to stop treatment due to side-effects (Chart 6).

***Figure 7**: Response to Treatment*



Discussion

HCV is one of the leading causes of liver disease, cirrhosis and HCC and one of the most common indications for liver transplantation.[3] It is estimated that the prevalence of HCV infection is approximately 2.2-3% worldwide.[9]

Presently the main mode of transmission of HCV is via sharing of devices used for illegal drug use. These include both IVDU and nasal drug use. Measures have been instituted to attempt to decrease the risk of HCV transmission by providing free new syringes from health centres. It is of utmost importance to draw attention of the risks of sharing needles and apparatus to drug users at every visit and to educate the general public via national education campaigns. This study indicated the highest ranking localities where patients resided and these areas should be particularly targeted.

Some of the reasons for shortcomings in HCV management in Malta are due to the fact that the patient population can be difficult to work with as most patients are IVDU and there is stigma associated with both drug use and HCV infection. The disease is also clinically silent and so patients will present late unless the infection is picked up by screening blood tests. Inadequate referrals to appropriate specialists may occur because of lack of awareness amongst doctors of the rapid advances in management of HCV over the past years and the current success rates. Patients should also be encouraged by their GPs to attend Outpatients appointments and undergo the necessary investigations. In order to receive treatment patients frequently depend on funding from NGOs since the medications are not available on the NHS and are relatively expensive. This might also partly account of the small percentage of patients who were treated.

Once a patient is then referred to the appropriate specialist, the management is then of high standards and success rates are good. In clinical trials, SVR was achieved in 40-54% of patients infected with HCV genotype 1 who were given PEG IFN and ribavirin combination therapy and in 65-82% of patients infected with genotype 2 or 3.[1] SVR rates with monotherapy are lower. In the study population, 43% of patients (all genotypes included) went into SVR when treated with either combination therapy or IFN alone. IFN was used prior to the introduction of combination therapy. Thus, especially taking into account that both monotherapy and combination therapy are included, SVR rates for patients with HCV in Malta are favourable when compared to SVR rates in clinical trials.

Trials have shown that relapse rate after treatment with combination therapy varies between 15-25%.[1] In our study, 8% of patients relapsed on either monotherapy or combination therapy. In clinical trials, 32-53% of patients who relapsed after being given IFN alone then responded to combination therapy with PEG IFN and ribavirin.[1] Thus, patients who relapsed should be reassessed with an aim to give combination therapy.

4-14% of treated patients will not respond to combination therapy.[1] In our study population, 8% of patients treated with monotherapy or combination therapy were non-responders.

Recent studies have shown that boceprevir or telaprevir in combination with PEG IFN and ribavirin (triple therapy) result in substantially higher sustained virological response rates in both treatment-naïve as well as in previous non responders with genotype 1 HCV chronic hepatitis. Triple therapy is however associated with increased side effects, increased drug interactions, increased cost and reduced cost effectiveness.[8]

This article highlights the need to refer all patients with positive HCV antibody tests to a gastroenterologist or an infectious disease physician for assessment of hepatic function and suitability for treatment. Management of these patients at Mater Dei Hospital mirrors the results obtained from international studies and therefore this treatment offers the best hope of a cure for these patients.

References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. Journal of Hepatology. 2011;55(1):245-64.
2. Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat*. 1999 Jan;6(1):35–47.
3. Chen SL, Morgan TR. The Natural History of Hepatitis C Virus (HCV) Infection. Int J Med Sci. 2006;3(2):47–52.
4. Estimated Population by Locality 31st March 2001. Article 73 of Part VII of the Local Councils Act. Malta Government Gazette. 2011 Aug 9;18789:9657.

5. Muhlberger M, Schwarzer R, Lettmeier B, Scroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. DMC Public Health. 2009 Jan;34(9).
6. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol. 2008 Jan;48(1):148-62.
7. El-Seraq HB. Epidemiology of Viral Hepatitis and Hepatocellular Carcinoma. Gastroenterology. 2012 May;142(6):1264-1273.
8. Perlman BL. Protease inhibitors for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care. Lancet Infect Dis. 2012 Sept;12(9):717-28.