Original Research Paper

Volume - 13 | Issue - 02 | February - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Gastroenterology

C-THRU: TRACKING OF HCV PATIENTS LOST TO FOLLOW UP IN A RETROSPECTIVE DATABASE REVIEW STUDY

M.G. Minissale*	RESIST-HCV Rete Sicilia Selezione Terapia – HCV, Ospedale Buccheri La Ferla Department of Internal Medicine – Palermo Medical Doctor *Corresponding Author
F. Cartabellotta	RESIST-HCV Rete Sicilia Selezione Terapia – HCV, Ospedale Buccheri La Ferla Department of Internal Medicine – Palermo Medical Doctor
V. Di Marco	RESIST-HCV Rete Sicilia Selezione Terapia – HCV, PROMISE University of Palermo Department of Internal Medicine – Palermo Medical Doctor
Stefania Grieco	Medical Affairs Infectious Disease MSD Italy (Medical Doctor)
Stella Grattacaso	Medical Affairs Infectious Disease MSD Italy (Medical Doctor)

ABSTRACT In Sicily over 30.000 people live with chronic C virus hepatitis (HCV). Despite the fact that Direct Antiviral Drugs (DAAs) achieve 95% SVR, there are still many patients who are lost to follow-up (LTFU) and there is a need to characterize them to develop measures or programs to link them back to care. The Sicily Region has activated a Network for the management of HCV infection through a web-oriented model (RESIST-HCV). This is a retrospective cohort study implemented through the regional HCV database. The primary objective is to assess the number/proportion of diagnosed chronic hepatitis C (CHC) patients who are not linked to care. The secondary objective is to assess the characteristics of the CHC patients who are not linked to care at last documented visit. **METHODS:** Our study evaluated retrospectively the demographic and virologic characteristics, the stage of liver disease and the co-morbidities of the patients with a diagnosis of CHC that are included in the RESIST-HCV and did not received treatment with DAAs during the study period March 2015-November 2020. Lack of linkage to care was defined as no follow-up visits 12 months or longer following CHC diagnosis. **RESULTS:** Among 19.825 patients included in RESIST-HCV from March 2015 to November 2020, 15.201 (76,7%) already received therapy, while 2.311 (11,7%) had not yet received therapy and were lost to follow-up. Patients LTFU were more frequently male (60.6%), more than 70 years old (45%%) and infected with genotypes 1b (51,3%). Cirrhosis was diagnosed in 30% of patients, over 55% had a chronic hepatitis. Diabetes and arterial hypertension were present in 15,4% and 24,6% respectively. **CONCLUSIONS:** we suggest to plan a more active and close follow-up for monitoring patients with the characteristics founded in our study.

KEYWORDS : HCV, therapy, eradication

INTRODUCTION

Chronic C virus infection (HCV), is a major public health problem worldwide, affecting more than 71 million people with a prevalence of 1%, that varies greatly by region of the world. It is responsible for 400,000 deaths per year (1).

After twenty years of antiviral therapy with Interferon (alfa2b and then PEG-IFN), associated with Ribavirin with a sustained virological response (SVR) < 50%, a revolution spread over several waves. The first one was observed in 2011 with the first DAAs (Direct Antiviral Agents), with SVR >75% but with clinically relevant side effects and increased the daily pill burden for patients (2,3). This was rapidly followed in 2014 by the second wave of oral regimes, increasing SVR rates to 90-98% (4-5-6-7). Finally, a third wave with the introduction of the so-called pan genotypic DAAs able to treat the whole HCV population (8,9,10,11). A short treatment duration (8-12 weeks) with the last available DAAs allows SVR in more than 95% of cases. These DAAs are very well tolerated and accessible to all patients, with minimal fibrosis and with advanced form of cirrhosis (12). The presence of comorbidities is not a barrier, and the choice of a specific molecule is based on potential drug interactions and renal function.

In the majority of patients SVR after therapy allows a decrease in inflammation and an improvement in the fibrosis score (13), however presence of cofactors (alcohol abuse, metabolic syndrome) may influence the expected beneficial effect of treatment on fibrosis. Thanks to the implementation of DAAs, even in the most advanced forms of cirrhosis, viral clearance has been shown to improve liver function at 6 months compared to untreated patients (12). SVR has also been associated with a reduction in portal hypertension and a reduction of the risk of liver decompensation (14). Finally, SVR has been linked to the reduction of HCV extrahepatic manifestations, such as cryoglobulinemia vasculitis, renal impairment, insulin resistance and type 2 diabetes, cardiovascular events. HCV viral clearance with DAAs lowers the risk of HCC occurrence even in advanced cases of cirrhosis (15). However, the risk of HCC development remains even after SVR (16) and justifies long-term follow-up in cirrhotic patients (17).

Thanks to DAA treatments that brought optimism about potential eradication of HCV, WHO launched a program in May 2016 to "eradicate" viral hepatitis by the year 2030 (18). Unfortunately, this objective was too ambitious and WHO has therefore defined other eradication goals for 2030, among these 90% reduction in the incidence of new HCV infections, treatment of 80% of patients chronically infected with HCV. One of the main barriers to treatment access was their elevated cost, prompting many countries to establish access restrictions. However, the arrival of low-cost generic drugs has allowed a wide spread of this therapy even in resource-limited countries (19,20).

We described the reality of chronic C virus hepatitis (HCV) in Sicily, where there are over 30.000 people infected. The Sicily Region has activated, in 2015, a Network for the management of HCV infection through a web-oriented model (RESIST-HCV). The platform includes 30 centers that manage the diagnosis and treatment of HCV-related chronic hepatitis and cirrhosis and contains information regarding the staging of liver disease, basal virological evaluation, DAA regimens, adverse events and treatment outcomes. Even though DAAs achieve 95% of SVR, there are still many patients who are lost to follow-up (LTFU) and there is a need to characterize them to develop measures or programs to link them back to care.

This is a retrospective cohort study implemented through the regional HCV database, with two main objectives. The primary objective is to assess the number/proportion of diagnosed chronic hepatitis C (CHC) patients who are not linked to care. The secondary objective is to assess the characteristics of the CHC patients who are not linked to care at last documented visit.

METHODS

Our study includes the retrospective evaluation of demographic and virologic features of patients with a diagnosis of CHC, stage of their liver disease and co-morbidities. These patients were included in the RESIST-HCV during a period from March 2015 to November 2020 and did not received treatment with DAAs.

Clinical, bio-humoral and imaging evaluation

The database contains clinical and anthropometric parameters of the

patients such as sex, age, body mass index (BMI); bio humoral tests including blood count, liver and kidney function, coagulation, viral markers (HCV RNA, genotype HCV, coinfection: HBsAg, anti-HIV); the ultrasound study for the evaluation of steatosis, focal hepatic lesions, portal hypertension; hepatic elastometry for non-invasive evaluation of the stage of fibrosis; gastroscopy in cirrhotic patients searching sign of portal hypertension with research of esophageal varices and possible specific treatment. There is also the description of co-pathologies such as hypertension, diabetes mellitus, non-viral hepatological disease, hematological and oncological disease, and their associated therapies.

This, which represents the inceptive diagnostic definition of the patient, is preparatory to the next phase, which is identified with the start of therapy, then there are the follow up during and after therapy. However, we noted that a number of the patients in the database had no follow-up visits. Lack of linkage to care was defined as no follow-up visits 12 months or longer following CHC diagnosis.

We use a descriptive statistic to examine patient characteristics.

RESULTS

Among 19.825 patients included in RESIST-HCV from March 2015 to November 2020, 15.201 (76,7%) already received therapy, while 2.331 (11,7%) had not yet received therapy and were lost to follow-up, 2293 subjects were recorded but no other information were collected, so we don't know their real liver disease activity.

In table 1 we noted that patients LTFU were more frequently male 1413 (60.6%). The distribution for age showed: 418 patients (18%) with less than 50 years, 861 patients (37%) between 50 and 70 years, 1052 patients (45%) more than 70 year, and among these 26 were over 90 years. The genotypes more represented was 1b with 1196 patients (51,3%), followed by 1a-3 in 430 patients (18.4%). In 48 patients HCV RNA quantitative was negative, so they do not need any antiviral therapy. About the virological history 1424(61%) patients were naïve, while 795 (34%) were experienced or with previous intolerance. HBV and HIV coinfection were present in 35 (1,5%) and 111 (4.7%) patients respectively. Liver fibrosis was evaluated in 1262/2331 patients by Fibroscan, so that 46% had not a stiffness value in patients LTFU, while the stiffness value was 10 kPa, 7-10 kPa and <7 kPa in 21%, 14% and 19%, respectively. Regarding the liver disease stage: 730 patients (30%) were diagnosed as cirrhotic, 73 decompensated and 3 in waiting list for liver transplantation, while 1312 (56%) had a chronic hepatitis, the others were not well defined because of lack of data. Among co-pathologies, diabetes was present in 359 patients (15.4%), arterial hypertension in 574 pts (24.6%), nephropathy with renal impairment in 97 pts (4%), cardiopathy in 96 pts (4,1%), depression in 186 pts (8%).

FEATURES	PATIENTS LOST IN FOLLOW UP (pts n= 2331)
Sex	
Male/Female	1413/918
Age	
< 50 years	418
50-70 years	816
>70 years	1052
Genotype	
1b	1196
1a	220
2	176
3	210
4	69
Not determinable	48
Previous treatment	
Naïve	1423
Intolerance/Experienced	795
Stage liver disease	
Cirrhosis	704
Chronic hepatitis	1312
Not available	315
Associated diseases	
Arterial Hypertension	574
Diabetes mellitus	359
Depression	186
Cardiopathy	96
Renal Impairment	97
Cryoglobulinemia	27
Lymphoma	7

Tab.1 Characteristic of patients who are lost to follow-up

CONCLUSIONS

HCV infection represents a worldwide problem that has not been completely resolved yet; the WHO's goal is the eradication of the HCV infection by 2030, but there are many obstacles. Above all, the difficulty in reaching asymptomatic patients, positive patients unaware of being infected, the ability in unmasking the submerged that carries the infection and spreads it. For this reason, there are and will be many efforts for screening the general population as well as patients at high risk (drug addicts, homosexuals, etc.). However, an important step is also being able to reach people who have a known moderate-advanced pathology, who have also been treated with IFN-based regimens without response or who have never been treated, for co-pathologies or because with mild liver pathologies that in the past decades allowed to postpone the treatment. Our regional database allows us to find many of these positive subjects that have not yet been treated. In particular our study showed that the proportion of diagnosed CHC patients lost in the follow up (LTFU) was 11.7% of overall subject recorded in the database. Subjects aged>50 years, had moderate-advanced liver disease as revealed by fibroscan values or the presence of overt cirrhosis. They are mostly male subjects, infected with genotype 1 b and naïve to antiviral treatment. Our aim should be to prevent the worsening of the stage of liver disease of these patients turning into cirrhosis, or that the subjects already cirrhotic manifest complications. All this requires making a greater effort to treat and monitor these subjects, despite the current period of extreme difficulty related to the pandemic from Covid19, which inevitably slows down the global effort to eradicate HCV infection.

Disclaimer: Funding for this research was provided by MSD, Italy

REFERENCES

1. Blach, S.; Zeuzem, S.; Manns, M.; Altraif, I.; Duberg, A.S.; Muljono, D.H.;Waked, I.; Alavian, S.M.; Lee, M.H.; Negro, F.; et al. Polaris Observatory HCV Collaborators Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. Lancet. Gastroenterol. Hepatol. 2017, 2, 161–176.
2. Poordad, F.; McCone, J.; Bacon, B.R.; Bruno, S.; Manns, M.P.; Sulkowski, M.S.; Jacobson, I.M.; Reddy, K.R.; Goodman, Z.D.; Boparai, N.; et al. SPRINT-2 Investigators Boceprevir for untreated chronic HCV genotype 1infection. N. Engl. J. Med. 2011, 364, 1195–1206.
3. Jacobson, I.M.; McHutchison, J.G.; Dusheiko, G.; Di Bisceglie, A.M.; Reddy, K.R.; Bzowej, N.H.; Marcellin, P.;Muir, A.J.; Ferenci, P.; Flisiak, R.; et al. Advance Study Team Telaprevir for previously untreated chronichepatitis C virus infection. N. Engl. J. Med. 2011, 364, 2405–2416.
4. Afdhal, N.; Zeuzem, S.; Kwo, P.; Chojkier, M.; Gitlin, N.; Puoti, M.; Romero-Gomez, M.; Zarski, J.-P.;Agarwal, K.; Buggisch, P.; et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection. N. Engl.J. Med. 2014, 370, 1889–1898.
5. Kowdley, K.V.; Gordon, S.C.; Reddy, K.R.; Rossaro, L.; Bernstein, D.E.; Lawitz, E.; Shiffman, M.L.; Schiff, E.;Ghalib, R.; Ryan, M.; et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis.N. Engl. J. Med. 2014, 370, 1879–1888.
6. Feld, J.J.; Kowdley, K.V.; Coakley, E.; Sigal, S.; Nelson, D.R.; Crawford, D.; Weiland, O.; Aguilar, H.; Xiong, J.;Pilot-Matias, T.; et al. Treatment of HCV with ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin. N. Engl.J. Med. 2014, 370, 1594–1603.
7. Zeuzem, S.; Jacobson, I.M.; Baykal, T.; Marinho, R.T.; Poordad, F.; Bourlière, M.; Sulkowski, M.S.;Wedemeyer, H.; Tam, E.; Desmond, P.; et al. Retreatment of HCV with ABT-450/r–Ombitasvir and Dasabuvirwith Ribavirin. N. Engl. J. Med. 2014, 370, 1604–1614.
8. Feld, J.J.; Jacobson, I.M.; Hézode, C.; Asselah, T.; Ruane, P.J.; Gruener, N.; Abergel, A.; Mangia, A.; Lai, C.-L.;Chan, H.L.Y.; et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N. Engl. J. Med.2015, 373, 2599–2607.
9. Foster, G.R.; Afdhal, N.; Roberts, S.K.; Bräu, N.; Gane, E.J.; Pianko, S.; Lawitz, E.; Thompson, A.;Shiffman, M.L.; Cooper, C.; et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N. Engl. J.Med. 2015, 373, 2608–2617.
10. Forns, X.; Lee, S.S.; Valdes, J.; Lens, S.; Ghalib, R.; Aguilar, H.; Felizarta, F.; Hassanein, T.; Hinrichsen, H.;Rincon, D.; et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (Expedition-1): A single-arm, open-label, multicentre phase 3 trial.Lancet Infect. Dis. 2017, 17, 1062–1068.
11. Zeuzem, S.; Foster, G.R.; Wang, S.; Asatryan, A.; Gane, E.; Feld, J.J.; Asselah, T.; Bourlière, M.; Ruane, P.J.;Wedemeyer, H.; et al. Glecaprevir–Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. N. Engl.J. Med. 2018, 378, 354–369.
12. Poynard, T.; Moussalli, J.; Munteanu, M.; Thabut, D.; Lebray, P.; Rudler, M.; Ngo, Y.; Thibault, V.; Mkada, H.;Charlotte, F.; et al. FibroFrance-GHPS group Slow regression of liver fibrosis presumed by repeatedbiomarkers after virological cure in patients with chronic hepatitis C. J. Hepatol. 2013, 59, 675–683.
13. Foster, G.R.; Irving, W.L.; Cheung, M.C.M.; Walker, A.J.; Hudson, B.E.; Verma, S.; McLauchlan, J.;Mutimer, D.J.; Brown, A.; Gelson, W.T.H.; et al. HCV Research, UK Impact of direct acting antiviraltherapy in patients with chronic hepatitis C and decompensated cirrhosis. J. Hepatol. 2016, 64, 1224–1231.
14. Backus, L.I.; Boothroyd, D.B.; Phillips, B.R.; Belperio, P.; Halloran, J.; Mole, L.A. A sustained virologicresponse reduces risk of all-cause mortality in patients with hepatitis C. Clin. Gastroenterol. Hepatol. 2011, 9,509–516.
15. Calvaruso, V.; Cabibbo, G.; Cacciola, I.; Petta, S.; Madonia, S.; Bellia, A.; Tinè, F.; Distefano, M.; Licata, A.;Giannitrapani, L.; et al. Rete Sicilia Selezione Terapia–HCV (RESIST-HCV) Incidence of HepatocellularCarcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents.Gastroenterology 2018, 155, 411–421.
16. Van der Meer, A.J.; Veldt, B.J.; Feld, J.J.; Wedemeyer, H.; Dufour, J.-F.; Lammert, F.; Duarte-Rojo, A.;Heathcote, E.J.; Manns, M.P.; Kuske, L.; et al. Association between sustained virological response andall-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012, 308,2584–2593.
17. Galle, P.R.; Forner, A.; Llovet, J.M.; Mazzaferro, V.; Piscaglia, F.; Raoul, J.L.;

Schirmacher, P.; Vilgrain, V.European Association for the Study of the Liver EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J. Hepatol. 2018, 69, 182–236.
18. WHO. Combating Hepatitis B and C to Reach Elimination; WHO: Geneva, Switzerland, 2030.
19. Elsharkawy, A.; El-Raziky, M.; El-Akel, W.; El-Saeed, K.; Eletreby, R.; Hassany, M.; El-Sayed, M.H.; Kabil, K.;Ismail, S.A.; El-Serafy, M.; et al. Planning and prioritizing direct-acting antivirals treatment for HCV patientsin countries with limited resources: Lessons from the Egyptian experience. J. Hepatol. 2017.
20. Gupta, S.; Rout, G.; Patel, A.H.; Mahanta, M.; Kalra, N.; Sahu, P.; Sethia, R.; Agarwal, A.; Ranjan, G.;Kedia, S.; et al. Efficacy of generic oral directly acting agents in patients with hepatitis C virus infection. J.Viral Hepat. 2018, 25, 771–778.