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REVIEW

Hepatitis C in Argentina: epidemiology and treatment

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Abstract: Hepatitis C is the leading cause of chronic hepatitis, cirrhosis, and liver cancer in Argentina, where from 1.5% to 2.5% of adults are infected. Most of the infections were acquired 30–50 years ago. It is estimated that more than half of infected individuals are not aware of their infection. Even though the prevalence in blood donors has decreased to 0.45% at present, many high-prevalence populations still exist, where the reported prevalence ranges from 2.2% to 7.1%. Therapy is recommended for patients with fibrosis, in order to prevent disease progression, hepatic decompensation, and hepatocellular carcinoma. Great advances were achieved in the treatment of genotype 1 infection since the development and release of boceprevir and telaprevir. When either of these protease inhibitors is associated with peginterferon plus ribavirin, the sustained virological response (SVR) rate improves from 40%–50% to 67%–75%. For genotype 2 and 3 infection, treatment with peginterferon plus ribavirin is still the standard of care, with SVR rates of 70%–90%. There are significant new antivirals in development, and some of them are close to being released. These drugs will most likely be the future standard of care for all genotypes, and will be incorporated in better-tolerated and highly effective all-oral regimes. The impact that these new therapies might have in health-related economics is unpredictable, especially in developing countries. Each country must carefully evaluate the local situation in order to implement proper screening and treatment programs. Difficult-to-treat patients, such as those with decompensated cirrhosis, patients in hemodialysis, and those with other significant comorbidities, might not be able to receive these new therapeutic approaches and their management will remain challenging.

Keywords: hepatitis C, prevalence, transmission, therapeutics, genotype, Latin America

Introduction

Hepatitis C virus (HCV) infection is a major public health matter of concern to both industrialized and developing countries. It is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), as well as the most common indication for liver transplantation in Argentina and many other countries.[1,2] It is estimated that 180 million people are infected worldwide,[3] and more than half of them are not aware of their infection.[4]

Hepatitis C virus is a ribonucleic acid (RNA)-enveloped flavivirus, and there are at least six major HCV genotypes whose prevalence varies geographically. This virus is mainly transmitted by a parenteral route, being the most efficient means of transmission. There are several factors influencing interactions between the host and the HCV; therefore, the clinical picture and natural history are variable for both acute and chronic hepatitis. After acute infection, 75%–85% of patients develop chronic disease.[5]

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Chronic HCV infection often follows a progressive course, and may ultimately result in cirrhosis, HCC, and the need for liver transplantation.[6]

The HCV genotype determines the treatment selection and is one of the main therapy-response predictors. Some studies suggest that the HCV genotype could have an impact on the natural history of HCV infection. However, this has not been confirmed.[7–9]

The study of pathogenic mechanisms and natural history of the disease is hampered by the absence of adequate animal or cell-culture models. Therefore, most of the studies have been based on observations of infected patients, with different clinical settings and significant geographical heterogeneity. Successful treatment of HCV eradicates infection, reduces hepatic fibrosis and inflammation, and precludes hepatic decompensation.[10–12] This article focuses on the epidemiology and treatment of HCV in Argentina.

HCV epidemiology in Argentina

HCV-prevalence estimation

The global estimate for the actual prevalence of HCV infection is still associated with some degree of uncertainty. The available data suggest that HCV-infection prevalence is approximately 2.2%–3.0% worldwide (130–170 million people).[13] Important efforts are being made throughout specific regions to ascertain HCV prevalence in high-risk populations, blood donors, and healthy volunteers.

Because there are no large-scale general population studies on HCV prevalence in Argentina, available data are based mainly on spontaneous demand studies, blood donors, and specific small communities where seroprevalence was suspected to be high. The main difficulties in obtaining demographic data are related to Argentina's sociocultural, geographic, and economic aspects. Ninety percent of the country's 40 million population is concentrated in a few principal cities, whereas the overall population density is 15 inhabitants/km^2.

In general populations and in studies done on spontaneous demand population, the estimated prevalence is from 1.5% to 2%–2.5% in adults.[14,15] Another study showed a prevalence of 0%–0.6% in 18- to 24-year-old adults, which is congruent with a lower incidence transmission in young adults.[16]

Some studies performed on specific populations showed much higher prevalence, ranging from 2.2% to 7.1%.[17–20] It is suspected that the transmission pattern in these small communities involved injectable material misuse in health community centers, as aggregation of subgenotype clusters was observed (Table 1).

Table 1 Hepatitis C virus (HCV) prevalence in specific population studies in Argentina

Study	n	Prevalence	HCV genotype distribution
Picchio et al[18]	1,817	5.6%	1b: 100%
Golemba et al[17]	1,814	4.9%	1a: 7%; 1b: 89%; 2a: 4%
Ramadan[19]	452	2.2%	1b: 66.6% 2a: 33.3%
Mengarelli[20]	2,008	7.1%	1: 9%; 2: 90%

HCV prevalence in blood donors

Blood donors in our country represent a select group. They are mainly men (65%), do not report risk factors for blood-borne infections, and are mainly young adults. Consequently, they do not represent the general population.[21] The prevalence of HCV among blood donors is decreasing (Table 2),[21,22] and is probably associated with better donor selection, the known lower HCV prevalence in the younger population, and improvements in diagnostic equipment. With regard to serological tools, new technologies applied in the last few years have contributed to improving detection, thus lowering false-positive results.

HCV prevalence in high-risk populations

Intravenous drug users

Most patients infected with HCV worldwide acquired the disease through intravenous drug use (IDU).[3] In Argentina, the prevalence of HCV in this group is reported to be 54.6%, with a high rate of human immunodeficiency virus (HIV)/HCV coinfection (88%).[23] In the cited study, patients' average age was 30 years, and most of them were male. The IDU incidence is reported to be decreasing because of harm-reduction programs.

HCV/HIV coinfection

Since the introduction of antiretroviral therapy in HIV$^+$ patients, HCV infection has gained relevance as a cause of morbidity and mortality in this population. In coinfected patients, accelerated fibrosis progression was observed, leading to cirrhosis and its complications in a shorter period compared to HCV-monoinfected patients.[24]

Table 2 Hepatitis C virus (HCV) prevalence in blood donors by year in Argentina

Year	HCV prevalence	Total blood donors
1997	1.16%	No data
2000	0.78%	444,182
2004	0.67%	147,475
2006	0.69%	442,916
2008	0.66%	387,361
2010	0.43%	462,141

Different reports on the HIV+ population in our country show a 12%–60% HCV prevalence.[25–27] Risk factors for infection and genotype distribution are slightly different than in HCV-monoinfected patients. In Argentina, when the route of transmission was studied, IDU was described in 90% of those coinfected. On the other hand, sexual exposure was reported as the main risk factor in 49% of women.[28] Genotype distribution varies in coinfected patients, being HCV genotype 1a/c (HCV-G1a/c) responsible for 50% of all infections, mixed infections in 15.3%, genotype 3 (HCV-G3) in 11.8%, and HCV-G1b in 10.6%.[29,30] This trend toward an increased rate of G1a and G3 versus G1b is consistent with a previous study by Findor et al denoting a presumed increase in transmission by IDU in our country.[31]

Furthermore, a 2005 Argentine study showed a 15% false negative rate of HCV enzyme-linked immunosorbent assays (ELISAs) in positive HCV polymerase chain reaction (PCR) RT (real time) patients, remarking on the importance of high-sensitivity techniques, such as PCR RT or third-generation ELISA, for HCV screening in this group.[27]

Hemodialysis

The HCV-infection incidence among hemodialysis patients is steadily declining. This is in part due to the decrease in post-transfusion HCV-infection rates, as well as the implementation of transmission-reduction policies in dialysis units.

In Argentina, according to the Chronic Dialysis Registry, HCV-ELISA+ reactions in individuals entering hemodialysis have decreased from 2.0% in 2004 to 1.0% in 2011. The global HCV prevalence in 2011 was reported to be 4.9%. The risk of infection rises with time on hemodialysis, being about 38% HCV+ in those hemodialysis patients undergoing 16 or more years of treatment.[32]

Routes of transmission

HCV infection may spread by several routes: blood transfusions, IDU, nosocomial infections, non-IDU forms of injections, dental procedures, tattooing, and other procedures that involve contact with contaminated blood being the most infective. The routes of transmission vary according to different geographic areas and periods.

The available epidemiological data in Argentina are consistent with most people acquiring HCV infection approximately 30–50 years ago through blood transfusions or by using non-IDU forms of injections with inadequately sterilized glass syringes.[17–20] A government registry report on 1,011 HCV-infected patients showed different means of transmission in separated age-distributed cohorts. Among people who were born before 1945, the main risk factors for HCV infection were previous surgery (34%) and transfusion (36%). For the cohort born after 1965, IDU was the main risk factor.[33] At present, post-transfusion HCV infection has decreased significantly, and IDU is the main means of transmission in both the HCV-monoinfected and HCV/HIV-coinfected population.[22,23,28]

Less infective sources, such as non-IDU, sexual routes, and household transmission, have been studied in Argentina. A study reported that 8.9% of the patients had most likely acquired the infection through intranasal drug use. In the same study, 18.3% of women and 1.7% of men had most likely become exposed to HCV through sexual contact.[28] In a retrospective study performed in 219 infected patients, 25% reported intranasal drug use, 7% had had an HCV+ sexual partner, and 0.5% reported household contact as the most probable means of transmission. Of note, 19% had no identifiable risk factor.[34]

With regard to vertical transmission of HCV infection, the main risk factors for HCV transmission to children are maternal HCV infection and blood-product transfusion. It has been reported that vertical HCV-infection transmission occurs at birth in about 5% of children born to an infected mother.[35] This rate rises in highly viremic patients, as it happens in HIV/HCV coinfection, shifting the transmission rate to 19.4%.[36] A cohort study in Argentina analyzed 48 children under HCV risk, and described that pediatric HCV infection was characterized by high viral loads and was independent of both age and route of transmission. It also stated that among 17 perinatal infected children, 16 (94%) were born to HCV/HIV-coinfected mothers.[37]

Health care workers are at risk of HCV infection by percutaneous injuries with disposable syringes, suture needles, and scalpels; the risk of infection after a needlestick accident is 1.8%.[38] A single-center study on 402 health care workers in Argentina found HCV-ELISA+ prevalence of 0.5%.[39]

Screening for hepatitis C

The following groups of persons are considered to be at risk of HCV infection, and must be tested:[40,41]

- persons who have injected or inhaled illicit drugs at least once in their life
- persons with conditions associated with a high prevalence of HCV infection, including:
  - persons with HIV infection
  - persons with hemophilia
  - persons who have ever been on hemodialysis

  - persons with unexplained abnormal aminotransferase levels
  - prior recipients of transfusions or organ transplants prior to 1992
- children born to HCV-infected mothers
- health care workers after needlestick injury or mucosal exposure to HCV+ blood
- current sexual partners of HCV-infected persons.

The following groups of persons might benefit from HCV screening:

- health care workers
- persons exposed to invasive medical interventions
- those who have undergone unsafe piercing or tattooing practices
- men who have sex with men
- those with multiple sexual partners
- household contacts of patients with HCV.

Universal screening is not formally recommended. However, testing every person at least once could increase the number of undiagnosed patients who might benefit from treatment.

Treatment of HCV

The natural history of HCV shows that the majority of patients may become chronically infected and will not spontaneously resolve the infection.[5] About 20% of chronically infected patients will evolve to cirrhosis within 25–30 years, with an increased risk of hepatic decompensation and HCC. A natural history study on the transfused population performed in our country showed that 21% of HCV+ patients evolved to severe fibrosis 24 years posttransfusion.[42] Another study from a high-HCV-prevalence population in Argentina showed that during a 5-year follow-up period, 40% of HCV cirrhotic patients developed hepatic-associated decompensation or HCC.[18]

The goal of HCV treatment is to eradicate the virus and prevent the complications of chronic liver disease. Attaining SVR (sustained viral response) has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, HCC, and liver-related complications.[10–12] Selecting patients for antiviral therapy is based upon various factors. Patient factors include fibrosis stage, probability of adverse events of therapy, and comorbidities, such as chronic kidney disease or psychiatric disease, that may preclude or modify therapy options. Virological factors include mainly the HCV genotype, which determines the treatment strategy: drug selection and treatment duration.

The European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines on HCV management have suggested that identifying individuals at risk for progressive HCV disease by assessing fibrosis stage should prompt an indication of therapy.[44] Beyond that, any patient who is willing and able to receive therapy should be treated; therapy may be considered in patients after a biopsy proving moderate fibrosis (METAVIR score F2), and mandatory for advanced fibrosis (METAVIR score F3–F4). These are also the stated recommendations on local guidelines.[43,44] Assessment of fibrosis stage can be achieved either on liver biopsy or noninvasive methods, including transient elastography or serological markers.

For years, the standard of care (SOC) for HCV treatment has been the use of pegylated interferon (PEG) plus ribavirin (RBV). Recently, the SOC on HCV-G1 infection changed, including the addition of protease inhibitor (PI) therapy to the PEG-RBV scheme, with improvements in SVR increasing from 40%–50% to 67%–75%.[45,46] For HCV-G2 and HCV-G3, PEG plus RBV still remains the SOC, with SVR of about 70%–90%.[40,47]

Argentina's health care system is composed of three main groups:

- patients without any health insurance (they are assisted by the public health system)
- patients with private health insurance
- patients assisted by social security.

HCV treatment-related costs are always the responsibility of the public health system, which ultimately reimburses private insurance and the social security system. However, since this has been recently implemented, logistic barriers exist that make accessibility to treatment of patients without any health insurance difficult. The national program of viral hepatitis is actively working to improve this issue.

In our country, treatment indication of HCV follows our local guidelines, which are in line with the AASLD and EASL ones. However, real-life studies reflecting how patients are ultimately treated are lacking.

Predicting treatment response

The HCV genotype is the main therapy-response predictor, with HCV-G2 the most sensitive to PEG-RBV therapy. HCV-G3 and HCV-G1 follow in order of SVR rate. With a new SOC for HCV-G1 therapy, HCV-G1 and HCV-G3 could achieve similar SVR rates.[8] Other predictive factors of response are useful to estimate SVR, and are different according to the genotype.

Genotype 1

Pretreatment response predictors for HCV-G1 infection include low basal viral load, absence of fibrosis, and

Caucasian race. The relationship between *IFNL3* (previously interleukin [IL]-28B) polymorphism and response to treatment was reviewed recently.[48] A retrospective study on 102 Latin American patients treated with PEG-RBV in Argentina found that *IFNL3* rs12979860-CC and rs8099917-TT genotypes were associated with SVR rates of 64% and 55%, respectively, marking its use as an important tool for planning therapy.[49] Other factors such as age, sex, presence of steatosis, obesity, and diabetes mellitus follow in order of importance.

With regard to PI-based therapy, on-treatment main predictors of response are virological: rapid virologic response (RVR) and extended RVR. In addition, SVR rate is reported to be 7%–10% higher for HCV-G1b than HCV-G1a, explained by differences in genetic barriers to the PI.

Genotype 2

As reported in other genotypes, fibrosis stage decreases with SVR rate. It has been reported in a real-life study on HCV-G2 patients that the presence of cirrhosis decreased SVR rates by 11% and increased virological relapse by 5%.[50] On the other hand, steatosis and basal viral load do not strongly predict SVR in this group of patients.[51] In HCV-G2, the *IFNL3* polymorphism seems to only predict SVR in patients who do not achieve RVR.[52]

Genotype 3

There is enough evidence to consider HCV-G3 separately from HCV-G2 when evaluating treatment-related aspects.[8,53] Pretreatment variables that predict SVR in HCV-G3 patients are fibrosis stage (≤ F2), age less than 40 years, white ethnicity, female sex, basal viral load below 400,000 IU/mL, weight less than 85 kg, coffee consumption, and absence of steatosis. As in G2, the *IFNL3* polymorphism seems to only predict RVS in patients who do not achieve RVR.[52,54]

Genotype 1 treatment

The recent development of direct-acting antiviral agents changed the current treatment of HCV-G1.[55] Furthermore, a large number of compounds are being studied, including five distinct drug classes. These are NS3 PIs, NS5B polymerase inhibitors, NS5A replication-complex inhibitors, and interferon and host-target agents, including microRNA-122 and cyclophilin inhibitors.[56] These pharmacological developments provide the motivation to move novel treatments into clinical investigation. As a result, a large number of drugs are to become available in clinical practice in the next few years, bringing changes to current therapeutic regimens. Until these new treatments are released, the decision to treat patients infected with HCV-G1 with the currently approved drugs or to wait for future options has to be made, taking into account fibrosis stage, the patient's wish to be treated, and individual patient characteristics.

According to recent guidelines, patients with HCV-G1 infection should be treated with PEG, RBV, and either boceprevir (BOC) or telaprevir (TVR).[55] With this approach, SVR rates increase from 40% to 67%–75%.[45,46] Despite their clear benefits on SVR, these schemes have increased the rates of adverse events and costs substantially. Real-life studies report discontinuation rates of up to 6%–12%.[57,58] With regard to BOC- or TVR-based therapy cost-effectiveness, some studies remark that treating patients with BOC or TVR therapy is cost-effective in years of life gained.[59,60] Definitely, these first-generation PIs will be replaced by simpler ones and better-tolerated and even interferon-free strategies. In the meantime, it is of crucial importance to understand the optimal use of these drugs. Unlike PEG-RBV therapy, these drugs may induce resistance.[61,62] Therefore on-therapy viral kinetics must be carefully determined, and when indicated, therapy should be stopped (Table 3).[44,55]

BOC and TVR therapy are indicated for both naïve and experienced patients. SVR rates from registry studies showed more benefits on relapse and naïve patients treated, and lower efficacy on partial and null responders. Partial and null responders with advanced METAVIR-F4 fibrosis had the lowest chance of SVR (about 35%) in these studies.[63,64]

In July 2012, in Argentina, the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica drug-regulatory authority formally approved BOC and TVR for HCV-G1 therapy. Since then, the Asociación Argentina para el Estudio de las Enfermedades del Hígado has updated the local guidelines on HCV-G1 treatment.[44] These local guidelines, in line with the EASL and AASLD ones, state that first-line therapy in HCV-G1 patients is BOC or TVR in combination with PEG-RBV.

Table 3 Telaprevir and boceprevir stopping rules

	HCV-RNA-PCR	Action
Telaprevir (TVR)		
Week 4	>1,000 IU/mL	Discontinue TVR and PEG-RBV
Week 12	>1,000 IU/mL	Discontinue TVR and PEG-RBV
Week 24	Detectable	Discontinue PEG-RBV
Boceprevir (BOC)		
Week 12	≥100 IU/mL	Discontinue BOC and PEG-RBV
Week 24	Detectable	Discontinue BOC and PEG-RBV

Note: Data from Silva et al[45] and Ghany et al.[56]
Abbreviations: HCV-RNA-PCR, hepatitis C virus ribonucleic acid polymerase chain reaction; PEG, pegylated interferon; RBV, ribavirin.

Even though BOC/TVR + PEG-RBV has not been formally approved for use, some specific HCV-G1-infected patients, such as those co-infected with hepatitis B and/or HIV and transplant recipients, might benefit from this triple therapy.[65–70] On the other hand, in patients with advanced cirrhosis, on hemodialysis replacement therapy, or with other significant comorbidities, these therapeutic schemes are contraindicated. Finally PEG-RBV without BOC or TVR could be considered in a limited number of patients with favorable predictors of response.

Genotype 2 treatment

HCV genotype 2 has a worldwide distribution, being the third-most prevalent genotype in most countries. It is particularly prevalent in some Latin American countries, like Argentina and Venezuela, where its prevalence ranges from 25% to 34%.[14] The SOC treatment with PEG-RBV for 24 weeks achieves SVR in up to 95% of chronic HCV genotype 2-infected patients, as this is the easiest genotype to treat with the current approved agents.[43]

Assessment of RVR at week 4 could identify candidates to shorten therapy. Chronic HCV genotype 2 patients with favorable basal and on-treatment predictors of response to PEG plus RBV could be treated for shorter periods, thus reducing costs and toxicity.[71] In this instance, weight-based RBV dosing is crucial to achieve similar SVR rates in short (16-week) regimens.[50] On the other hand, even though slow responders not achieving RVR but with early virologicalresponse at week 12 are infrequent, they still could benefit from prolonging the treatment to 48 or even 72 weeks.[43]

Genotype 3 treatment

According to recent guidelines, PEG-RBV therapy for 24 weeks is the established SOC for chronic HCV-G3 infection.[15,37,43,40,72] However, difficulties in treating HCV-G3 still exist. Recently, SVR rates with this approach were shown to be lower in HCV-G3 in relation to HCV-G2.[73] Furthermore, optimal duration and dosage have not been clearly established for those rapid and slow responders. A recent meta-analysis in response-guided treatment demonstrated that treatment with PEG plus RBV (weight-based) during 16 weeks in patients with RVR resulted in SVR rates of 76.3% in HCV-G3 infection.[74] Weight-based RBV dosing and close on-treatment viral kinetics are crucial to achieve the best results. It is not recommended to reduce the treatment duration in a fixed way, and it should be individualized. Some patients who do not achieve RVR would benefit from extending therapy for 48 weeks or even longer periods.[75]

Future perspectives

Great advances have been achieved in the last few years in the treatment of HCV-G1. Moreover, highly effective all-oral regimens will be available in the near future for all genotypes.[76–78]

The most promising drugs that might be released in forthcoming years are sofosbuvir, daclatasvir, asunaprevir, and simeprevir, among others.[76,79–81] The impact that these new therapies might have on health-related economics is unpredictable, especially in developing countries. Difficult-to-treat patients, such as those with decompensated cirrhosis, on hemodialysis, and with significant comorbidities, might not be able to receive these new therapeutic approaches, and their management will still be challenging.

Discussion

Global efforts to control HCV disease are being made. HCV infection is a major cause of liver disease worldwide, and will be a potential cause of substantial morbidity and mortality in the future. Overall, 25% of chronically infected patients will develop cirrhosis, and a significant proportion could develop hepatocellular carcinoma.[6] Robust epidemiological data in Latin America is missing. In Argentina, HCV prevalence is reported to be around 2%.[82] However, small samples of specific populations show higher prevalence ranging from 2% to 7%. In intravenous drug users, sexual workers, and patients on hemodialysis, prevalence is between 5% to 50%. It is of major concern that most HCV-positive patients might be unaware of their infection.

Significant improvement in SVR rates for HCV-G1 therapy has been observed since the approval of BOC and TVR. Response-guided therapy results in shortening treatment duration to 24–28 weeks in a substantial proportion of patients. However, this strategy has limitations in previous partial and null responders, patients with advanced fibrosis, and difficult-to-treat patients, such as transplant recipients, HIV/HCV-coinfected patients, or patients on hemodialysis.

For HCV-G2 and HCV-G3 infection, acceptable SVR rates with PEG-RBV are being achieved. However, a proportion of patients would benefit from new therapeutic strategies, particularly difficult-to-treat patients and prior nonresponders. Great expectation exists for the approval of new therapeutic strategies, with greater SVR rates and better safety profiles.

Chronic HCV will most likely turn into an easier-to-treat disease. This could have a significantly favorable impact on patients, but also an unpredictable impact on physicians and on health-related economics. Each country must carefully

evaluate the situation in order to implement proper screening and treatment programs.

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