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Linkage to care strategy for the micro-elimination of hepatitis C among parenteral drug users on methadone replacement therapy in Gipuzkoa

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ABSTRACT

Introduction: parenteral drug users (PDUs) are a population with a high prevalence of infection with the hepatitis C virus (HCV) and significant difficulties to access to treatment. Opioid replacement therapy programs regularly monitor these individuals.

Objective: to effectively treat this population using a directly observed therapy (DOT) and bringing resources closer to the methadone dispensing center in Gipuzkoa (Bitarte).

Methods: all methadone users that were positive for anti-HCV antibodies were included in the study. Using a simplified circuit, a hepatologist visits the center with a

Fibroscan® device and requests treatment following assessment. Treatment is dispensed at the addict center, under the supervision of a psychiatrist and nursing staff. Prevalence, population characteristics and circuit effectiveness were assessed.

Results: Bitarte monitors 660 individuals. Of these, 73.6 % were positive for antibodies against HCV. The prevalence of viremic infection is 62.5 %. The predominant genotype was 1a, followed by 3. A total of 38.5 % had advanced fibrosis (F3 and F4) and 38 % of users admitted to active heroin use. In all, 82.07 % (174/212) of the population received treatment and 97 % had sustained viral response (SVR) after 12 weeks. No re-infections were recorded.

Conclusions: the prevalence of viremic HCV infection among PDUs under treatment with methadone is 62 %. The linkage to care strategy was effective and > 80 % of the population with an active infection have been treated so far.

Keywords: Hepatitis C virus (HCV). Parenteral drug users (PDUs). Opioids. Methadone.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is a highly relevant condition from an epidemiological standpoint and affects 118 million people worldwide (1). One of the most common transmission routes of HCV is injected drug use and parenteral drug users (PDUs) constitute a risk group responsible for most of the transmissions in developed countries (2,3). The prevalence of infection with HCV among PDUs is heterogeneous amongst countries, but estimates suggest that between 60 % and 80 % of the population are positive for antibodies against HCV (4). In 2008, an estimated 16 million people might have been using injected drugs around the world (5).

The prevalence of HCV remains high, despite the effectiveness of damage and risk reduction interventions (such as opioid replacement therapy and syringe exchange programs) to decrease the individual risk of HCV infection. This population is considered as a significant reservoir for HCV. The treatment of individuals with a high transmission risk, such as PDUs, is deemed a priority, as it represents a tool to diminish prevalence, transmission and reinfection (6-8). Furthermore, direct acting antivirals (DAAs) have proven safe and cost-effective (11) in this group of patients, with cure

rates above 95 % (9,10). However, access to treatment remains low in this population (12). This is partly due to a lack of awareness regarding the actual prevalence in this setting, as well as the difficulties encountered in the follow-up of these patients. There are damage reduction programs where methadone is dispensed as a replacement therapy concentrate to a large proportion of PDUs and monitoring is both regular and effective (13). Furthermore, they allow the administration of directly observed therapies, which have shown their ability to improve adherence (14).

The primary goal of this study was the startup of a new care circuit for this population, bringing resources closer to the methadone dispensing center, with the aim of effectively treating infection. The prevalence of HCV infection among methadone users in our region (Gipuzkoa) was estimated, as well as the population characteristics.

METHODS

A descriptive, observational, population-based study was performed in a group of individuals at risk for HCV infection. Namely, people assigned to the intermediate outcome program with opioid replacement therapy (methadone or buprenorphine), called Bitarte in Gipuzkoa. The Bitarte program covers people under a detoxification regimen with methadone from a total population of around 630,000 inhabitants and is contingent on the Gipuzkoan mental health network. All individuals who gained access to the program from June 2017 to February 2020 were evaluated.

Inclusion criteria included age over 18 years, diagnosis with opioid dependence, under replacement therapy with methadone (ICD 10 F11.22) and positive for antibodies against HCV (anti-HCV). Individuals with a coinfection with human immunodeficiency virus (HIV), those who did not consent to participate in the study and individuals lost to follow-up in the methadone program within one year before study start were excluded (Fig. 1).

Resources are brought closer to the center via a new care circuit, in an attempt to foster adherence. The main figurehead is the psychiatrist responsible for the damage reduction program. The psychiatrist is in charge of requesting laboratory tests for subjects with anti-HCV antibodies. These tests included a general chemistry panel with liver function parameters, anti-HCV antibodies, HCV RNA and serology for HIV and

hepatitis B. After evaluating the results obtained, a hepatologist visits the center to assess patients with an active infection. This assessment included a Fibroscan®, a clinical interview and a prescription of treatment (type and duration).

Treatment choice is made according to the action plan for the management of hepatitis C established by the Osakidetza (Basque public health service). G lecaprevir/pibrentasvir (GLE/PIB) was the regimen of choice from November 2017 to the end of 2019. Previously, the prioritized drug combination was o mbitasvir/paritaprevir/ritonavir + dasabuvir (OBV/PTV/r + DSV) +/- ribavirin (RBV). The agreed upon medication is sent to Bitarte from the hospital pharmacy along the same path as the methadone, and from there it is dispensed following the directly observed treatment (DOT) strategy. Administration intervals (daily, weekly and monthly) for DAAs are individualized according to each subject's characteristics and dispensing is arranged to coincide with methadone collection. These intervals are established by the center's healthcare staff. Drugs are delivered on previously agreed dates by the mental health nurses previously trained in the management of antivirals and their potential adverse effects.

The previous follow-up in specialist clinics, adherence and access to prior therapies for HCV is reviewed using a clinical interview and medical records. The prevalence of active infection with HCV among our population and its related rate of spontaneous cure were estimated by reviewing the recent and previous laboratory results. Drug (heroin, cocaine, amphetamines and cannabis) use was measured regularly in the urine at the same addiction center, before methadone dispensation. Genotype and Fibroscan®-determined fibrosis stage were evaluated in cases of viremic infection. Viral load (VL) was assessed in all treated patients at 12 weeks post-therapy (cure rate) and one-year post-therapy (reinfection rate).

Statistics

An access database was set up for prospective data recording. The above variables were independently analyzed according to their qualitative or quantitative nature. The SPSS software package was used for statistical analysis. Continuous variables were described as the mean, median, standard deviation and maximum and minimum

observed values. Categorical variables were described as patient numbers and percentages by response category.

Ethical considerations

All subjects were duly informed and signed an informed consent form before inclusion into the study. The study received a positive opinion from the Basque Country Research Ethics Committee.

RESULTS

Bitarte monitors 660 methadone users. All underwent serology tests for anti-HCV and HIV as a requirement for inclusion into the program. The rate of anti-VHC seropositivity was 73.63 % (486/660); 343 subjects were eventually included after excluding 143 patients due to coinfection with HIV (113), refusal to participate (3), recent demise (4) or loss of contact with Bitarte (23).

Viral load information was up-to-date for 339 subjects (98.83 %) as of February 2020, with an estimated prevalence of viremic infection of 62.54 % (212/339). Viral load was negative in 127 subjects (37.46 %), of whom 49 exhibit a sustained viral response (SVR) to therapies received before study onset and 78 were cases of spontaneous virus clearance. The rate of spontaneous virus clearance was 23 % (78/339).

The mean age of the population was 50 years (range, 23-70) and 83.38 % (286/343) were male. In all, 41.39 % (142/343) had never been previously assessed at a Gastroenterology clinic and of the 58.60 % (201/343) who had occasionally been evaluated, 58.20 % (117/201) were lost to follow-up. The most common cause of loss to follow-up was failure to attend the clinic, which accounted for 82.05 % (96/117).

Treatment was administered to 82.07 % (174/212) of the population with an active infection. Patients under prior regular follow-up at Hepatology clinics and prison inmates (54/174) remained within the original circuit and were treated from outpatient clinics or in prison for inmates. A total of 68.96 % (120/174) received treatment in Bitarte. Of the remaining patients with a confirmed positive viral load, 20 are still waiting for treatment, four did not want to be treated, eight were lost to follow-up at Bitarte and six died before receiving therapy. The causes of death

included were liver cancer (1/6), sepsis (1/6) and unattended death (4/6).

The most commonly observed genotypes were 1a (45.5 %) and 3 (26.1 %); 38.5 % had fibrosis equal or greater than 9.5 kPA, as measured by elastography. Following Osakidetza prioritizations, 79.3 % (138/174) were treated with GLE/PIB and 10.9 % (19/174) received sofosbuvir/velpatasvir (SOF/VEL). The reasons for indicating this combination was drug interactions in 73.7 % (14/19) and advanced liver disease at risk of decompensation in 26.3 % (5/19) of cases. Drug-drug interactions that advised an indication of SOF/VEL included quetiapine, paliperidone, clotiapine, clozapine, aripiprazole and dienogest/ethinylestradiol (in order of frequency). A total of 9.7 % (17/164) of cases were treated with different drug combinations, all in the second half of 2017. No adverse effects that required treatment discontinuation were recorded.

A cure rate of 97 % (137/141) was recorded with the currently available data and no reinfections were identified after one year (0/45). All four therapy failures were reported with the GLE/PIB combination. Genotypes included were genotype 3 (2/4), genotype 2 (1/4) and genotype 4 (1/4). Fifty percent (2/4) of cases recognized poor adherence to treatment.

Among the methadone users who were treated, 81.7 % consumed alcohol on a regular basis and up to 38.7 % were actively using heroin. Drug use was measured in urine during treatment or within six months before treatment. Five additional deaths have been reported in treated patients and the causes included lung cancer (1/5), intestinal obstruction (1/5) and unattended death (3/5). The remaining characteristics of treated patients are listed in table 1.

DISCUSSION

With the advent of DAAs and the possibility to treat all infected people, both effectively and safely, the World Health Organization (WHO) set the ambitious goal of hepatitis C elimination by 2030 (WHO, 2017). In order to achieve this goal, it is crucial that patients capable of reinfection have access to treatment. PDUs are a key group in pursuing these goals. Nevertheless, when we initiated this study in 2017, access to therapy was low for methadone-using PDUs, mainly due to barriers to health care and treatment. Follow-up at specialist clinics was rare and adherence thereto was lost in

most cases. This was particularly due to unawareness of available options to access the newer therapies, low perception of disease and fear of adverse effects.

With regard to the implementation of this new liaison strategy where the key pillar and doctor of reference is a psychiatrist, we managed to screen most of this population, to inform them about available therapies and to follow them up with a higher adherence level than previously. Thus, we have established the prevalence of both anti-HCV serology and active viremic infection in our setting, which does not differ from expectations according to available reports. With regard to treatment dispensation, we use the DOT approach, which is well known in other infectious conditions such as HIV or tuberculosis (TBC). This attempts to strengthen adherence and monitor adequate therapy compliance (15) and we believe this may have enhanced response rates in our population. Mathew J. Akiyama et al. (14) compared the DOT approach with individual self-administered treatment in a population similar to ours. This study found an SVR rate of 98 % in the DOT group *versus* 90 % in the control group, although it was not significant ($p = 0.152$). Our SVR rate was 97 %, which is comparable to that seen in the DOT group.

Despite the measures taken, this population remains challenging, mainly due to their active use of substances such as heroin, which might result in reinfection. Although the expected reinfection rate was not recorded in our series (16,17), this may be due to the fact that to date, we only have yearly VL values available for 27.5 % of the sample. Furthermore, as we have learned from patient interviews, heroin use seems to be changing and smoking is now the most frequent administration route.

With regard to the HCV micro-elimination goal, it must be highlighted the fact that some patients refused to participate and others refused treatment despite undergoing lab tests. This was a major limitation of our study. Furthermore, it was observed that, given their particularly vulnerable social situation (non-residents, frequent committals to prison and severe addictions), this population is less accessible. Therefore, their assessment and treatment is even more challenging, and insisting and informing on treatment advantages becomes crucial. In addition, we should not forget about people who used injected substances in the past and no longer require replacement therapy, as they may be underdiagnosed and not included in the sample.

Therefore, despite great advances towards hepatitis C elimination, there is still a need to develop treatment strategies for the more difficult cases. All of this, in association with a population screening plan, focuses on patients at risk for infection with hepatitis C.

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Table 1.

Characteristics of methadone users treated with DAAs	n*	(%)
Alcohol consumption	170	
Active use		139 (81.7 %)
Prior use		15 (8.8 %)
No use		16 (9.4 %)
HBcAb +	172	88 (51.1 %)
Active drug use[†]		
Heroin	155	60 (38.7 %)
Cocaine	154	51 (33.1 %)
Amphetamines	155	28 (18 %)
Cannabis	135	86 (63.7 %)
Genotype	172	
1a		80 (46.5 %)
1b		18 (10.4 %)
2		2 (1.1 %)
3		45 (26.1 %)
4		26 (15.1 %)
Mixed (3 + 4)		1 (0.5 %)
Fibrosis	174	
F1-2 (< 9.5 kPa)		96 (55.1 %)
F3-4 (≥ 9.5 kPa)		67 (38.5 %)
Unknown or no window		11 (6.3 %)
Prior therapy failure	174	
IFN therapy		5 (2.8 %)
DAA		3 (1.7 %)
Treatment regimen	174	
GLE/PIB		138 (79.3 %)

SOF/VEL		19 (10.9 %)
OBV/PTV/r + DSV +/- RBV		11 (6.3 %)
Other combinations		6 (3.4 %)
VL 12 weeks after	141	
SVR		137 (97.1 %)
Therapy failure		4 (2.8 %)
VL positive at 1 year - Reinfection	48	0 (0 %)

DAA: direct acting antivirals; IFN: interferon; GLE/PIB: glecaprevir/pibrentasvir; SOF/VEL: sofosbuvir/velpatasvir; OBV/PTV/r + DSV +/- RBV: o mbitasvir/paritaprevir/ritonavir + dasabuvir +/- ribavirin; VL: viral load; SVR: sustained viral response. *n estimated based on available data for each variable. †Measured in urine. Considered active in cases of established use within six months before or during treatment.

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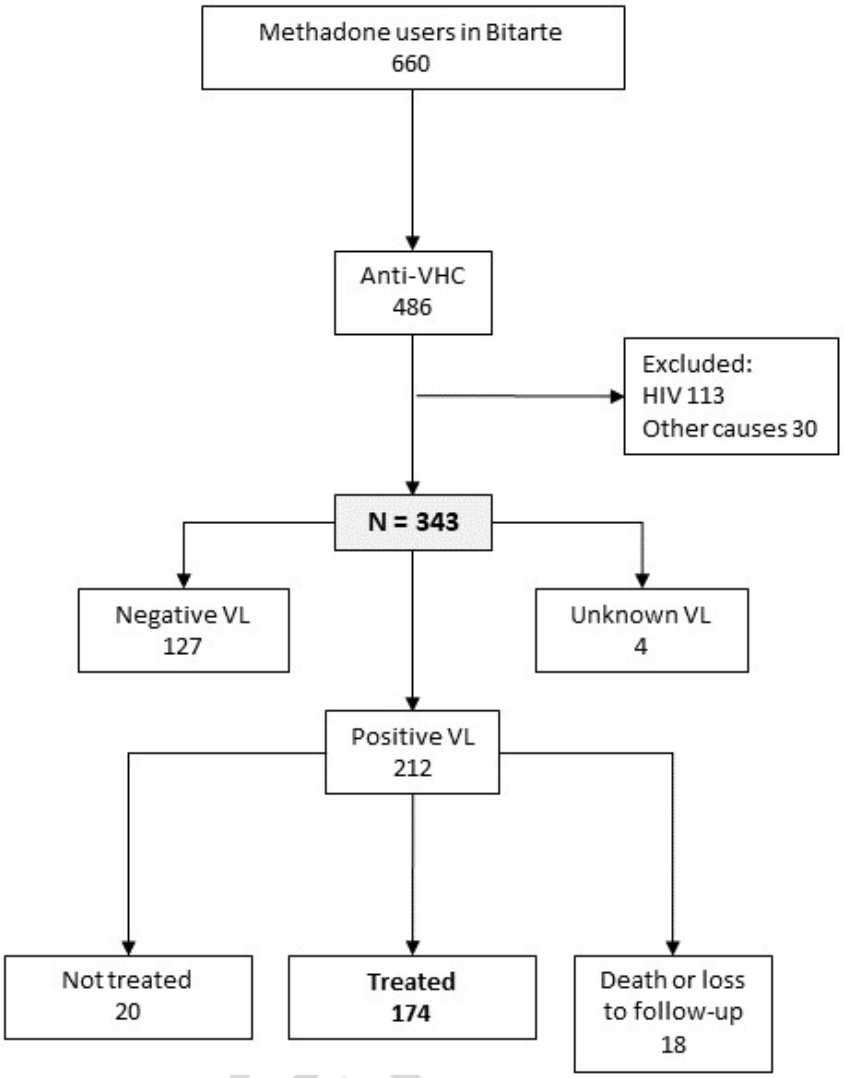

Fig. 1. The current status of the population monitored by the intermediate outcome program, Bitarte, who use methadone: serological update and therapies as of March 2020.

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