Observational Study

Attempt to calculate the prevalence and features of chronic hepatitis C infection in Tuscany using administrative data

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Abstract

AIM
To evaluate this prevalence in Tuscan populations that was known and unknown to the Tuscan Regional Health Service in 2015.

METHODS
Tuscan Health administrative data were used to evaluate hepatitis C virus (HCV) infected people known to the Regional Health Service. Residents in Tuscany with a HCV exemption code (070.54) were identified. Using the universal code attributed to each resident, these patients were matched with hospital admission codes identified by the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification, and with codes for dispensing drugs to patients by local and hospital pharmacies. Individuals were considered only once. Capture-recapture analysis was used to evaluate the HCV-infected population unknown to the Regional Health Service.

RESULTS
In total, 14526 individuals were living on 31/12/2015 with an exemption code for HCV. In total, 9524 patients were treated with pegylated interferon + ribavirin and/
or direct-acting antiviral drugs during the last 10 years, and 13879 total hospital admissions were noted in the last 15 years. After data linkage, the total number was 25918. After applying the Capture-Recapture analysis, the number of unknown HCV-infected people was 23497. Therefore, the total number of chronic HCV-infected people was 38643, excluding those achieved sustained virological response to previous treatment.

CONCLUSION

Our results show a prevalence of HCV infected people of 1%. Tuscan administrative data could be useful for calculating health care costs and health planning in the coming years.

Key words: Hepatitis C; Public health; Fibrosis; Antiviral treatment; Epidemiology

Core tip: Given the considerable differences among the world regions, the calculation of hepatitis C virus (HCV) prevalence through administrative flows seems to be essential for intervention policy strategies. Currently, these data are highly interesting given that the introduction of direct-acting antiviral drugs has highlighted the problem of sustainability due to the high costs of new drugs in low and middle income countries. Therefore, given the high number of chronic HCV-infected patients and the high costs of these drugs, the administrative data could be useful for calculating health care costs and health planning in the coming years.

INTRODUCTION

The screening of blood donors, which began in the early 1990s, has reduced the spread of hepatitis C virus (HCV) in the population. The most effective preventative measures for HCV include the screening and testing of blood and organ donors, the implementation of practices in healthcare settings and a strong education programme. Bruggmann et al[1] in a recent systematic review, show that in selected countries (Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Egypt, England, France, Germany, Portugal, Spain, Sweden, Switzerland, Turkey) the viremic prevalence varied widely between countries, ranging from 0.3% in Austria, England and Germany to 8.5% in Egypt. A subsequent systematic review[2], considering 15 countries (Argentina, Finland, Greece, India, Ireland, Israel, Luxemburg, Mexico, Mongolia, The Netherlands, New Zeland, Norway, Poland, Russia, South Africa), shows that a viremic prevalence ranged from 0.13% in the Netherlands to 2.91% in Russia. Gower et al[3] revealed a 1.6% (range 1.3%-2.1%) global prevalence of people who have been infected with HCV (presence of anti-HCV antibodies), and this value reaches 2.0% if we exclusively consider the population over 15 years of age.

In most cases, the test for anti-HCV antibodies remains positive even in people who have cleared the virus, while a minimum percentage of these may instead be falsely positive.

On the contrary, the true prevalence is defined as the presence of HCV-RNA in serum or plasma. In this case, the estimated global HCV prevalence is 1.1% (range 0.9%-1.4%), whereas the value is 1.4% if we exclusively consider people over 15 years of age.

The meta-analysis of Gower et al[3] reveals very different prevalences of anti-HCV and HCV-RNA in different regions of the world, highlighting the strong variability in different areas (the lowest prevalence of 0.1% was observed in Oceania, whereas the highest prevalence of 4.1% was observed in Sub-Saharan West Africa). The World Health Organization (WHO) estimates that 150 million people, approximately 3% of the world population, are HCV chronically infected and are at an increased risk of developing liver cirrhosis and hepatocellular carcinoma[4].

The WHO estimates that 15 million people are currently infected with HCV in European countries[5].

Ansaldi et al[6] observed a slightly different sero-prevalence in Italy. The authors used the national serological bank of the "European Sero-Epidemiology Network - ESEN" project testing samples for anti-HCV, HCV-RNA and genotypes from 18 Italian regions. The analysis, which was performed by age and geographic area, showed that 51.6% of anti-HCV-positive subjects were also HCV-RNA positive, with a north-south gradient ranging from 1.3% to 4.6% and a greater involvement in the population over 30 years of age. The analysis revealed an overall anti-HCV prevalence of 2.7%.

One of the main features of HCV is its genetic variability. Seven genotypes are currently known and divided into subtypes. In Italy, four genotypes are the most common. As observed in the most of Europe, the most frequent is the 1b genotype, which has a prevalence of 60%, followed by 2c (20%), 1a (6%) and 4a/d (8%)[6]. Based on this premises, the aims of this study were to assess the prevalence and features of HCV infected patients through both data reported in research studies and administrative data and to calculate the number of patients eligible for treatment according to some of the Italian Medicines Agency prioritization’s criteria.

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MATERIALS AND METHODS

Calculation of prevalence
A first analysis was performed by applying the prevalence data reported by Ansaldi et al[6] on HCV-RNA-positive residents in Italy. National Statistical Institute (ISTAT) data were used for this calculation. A subsequent analysis was performed using prevalence data of Ansaldi et al[6] on the resident population in Tuscany (data of Regional Health Agency of Tuscany). Using the universal identification code (IDUNI) attributed by the Region Tuscany to every citizen residing in its territory, we identified people who were assigned a code (in each information flow - transmission of information from one “place” to another).

Therefore, the calculation of people with HCV infection known to the Regional Health System was performed using the current main sanitary flows of the Regional Health Agency of Tuscany. Through the universal code attributed by Region Tuscany to each person, these patients were matched with hospital admission codes identified by the International Classification of Diseases, Ninth Revision (ICD-9) Clinical Modification (such as acute hepatitis: ICD9-CM: 070.41 e 070.51; chronic hepatitis: 070.44 and 070.54; hepatocellular carcinoma: 155.0; cirrhosis: 571.5) and codes for dispensing drugs to patients by local and hospital pharmacies (ribavirin J05AB04, daclatasvir J05AX14, sofosbuvir J05AX15, simeprevir J05AE14, dasabuvir J05AX16, viekirax J05AX67, peginteron L03AB10, pegasis L03AB11, sofosbuvir and ledipasvir J05AX65). Each individual was considered only once. In the most part of cases in Tuscany the detection of anti-HCV was performed using the 3rd generation of anti HCV tests, while for the detection of HCV-RNA was used the real time PCR.

Calculation of comorbidity score
Charlson Comorbidity Index was applied to calculate the comorbidity score of these patients. This method includes 19 categories of comorbidity and predicts ten-year mortality for those patients who may have a range of co-morbid conditions. A score of 1, 2, 3 or 6 is assigned to each co-morbid condition, depending on the risk of dying associated with the condition. For a physician, this information is helpful to know how aggressively a condition must be treated. Highest scores indicate greatest comorbidities. For example, a score of > 3 is associated with a survival probability of 45% in 10 years[7].

Sustained virological responders
A number of patients treated with pegylated interferon (PEGINF) + ribavirin (RBV) achieved sustained virological response (SVR); therefore, the overall prevalence was calculated excluding such patients from our cohort.

For the computation of the prevalence without sustained virological responders, the different responses to drug treatment according to viral genotype were taken into account using percentages of sustained virological responders observed by Marcellin et al[9].

According to the authors, previous treatment led to a SVR 24 wk after the end of treatment in 41.8% of patients with genotype 1, 71.4% of those with genotype 2, and 60.6% of those with genotypes 3 and 4.

Therefore, based on the genotypic subdivision in Italy of patients treated with PEGINF + RBV, the prevalence of HCV patients was calculated excluding those patients who benefited from the treatment.

Patients unknown to the regional health service
To estimate the number of people with HCV who are unknown to the Regional Health System, Capture-Recapture analysis was used. This method is most useful to count all of the individuals in the population. A major application of this method is epidemiology, where the method is used to estimate the completeness of disease registers. In the basic formulation (in the case of two capture sources) the sample of HCV patients from a target population is captured, marked and released, and a second sample captured at some later time. Therefore, the number of HCV patients observed in each sample is noted, and it is possible to estimate the size of the total population. Log-linear model allows to extend this method to more than two sources and to treat dependence among the sources. It is one of the most used method to estimate the total population size. Backwards stepwise regression was used to find a model which adequately described the data with the least number of parameters and the final model was chosen according to Akaike Information Criteria (AIC). The final model include all the two-way interaction terms. The data were analysed using STATA12.

Calculation of patients eligible for treatment
In Italy, the Italian Drug Agency (AIFA) has identified a number of criteria for the prescription of second-generation DAAs to patients with HCV-related chronic disease. Among these, the 4 criteria provide the treatment of patients with chronic hepatitis with fibrosis stage METAVIR ≥ F3 (or corresponding ISHAK or corresponding liver stiffness ≥ 10 kPa).

Therefore, a liver stiffness ≥ 10 kPa can be a useful indicator to estimate how many people could be treated with DAAs along this criteria. For the Tuscan cohort, we used the study of Arena et al[8] and unpublished data of the Regional Health Agency of Tuscany. Out of 150 patients, 94 had a fibrosis stage ≤ F3, and 56 patients had a fibrosis stage ≥ F3.

RESULTS

Calculation of HCV prevalence
Tables 1 and 2 summarize the results obtained using
The characterization by gender and age revealed an increased prevalence in males compared with females (males: 56%; females: 44%), and the highest involvement was noted in individuals over 45 years of age (83.6%) (Table 3).

**Calculation of comorbidity score**
Applying the Charlson Comorbidity Index to our cohort, 14% of known patients had a score ≥ 5 (Table 4).

**Sustained virological responders**
Applying the prevalence of SVR observed by Marcellin et al. on the Tuscan population, 9524 individuals with chronic HCV infection treated with either PEGINF + RBV or DAAs were living as of 31/12/2015. Of these, the number of patients who benefited from the therapy and therefore did not need further treatment was 5652 (Table 5).

**Patients unknown to the regional health service**
Applying the Capture-Recapture analysis, it was estimated that 23497 people with chronic HCV infection living in Tuscany were unknown to the Regional Health Service. Therefore, by adding the 25918 people who had an exemption code for HCV were living in Tuscany were unknown to the Regional Health Service. Therefore, by adding the 25918 people...
with chronic HCV infection known to the Regional Health Service and the 23497 people unknown to the Regional Health Service, a total of 49415 people with chronic HCV infection were identified in Tuscany.

**Calculation of patients eligible to treatment**
According to literature data, approximately 40% of Tuscan patients with chronic HCV have a liver stiffness $>10$ kPa. Therefore, considering this value as a parameter for eligibility to DAAs along the 4 criteria, it is possible to assume that out of the 20266 chronic HCV-infected patients known to the Regional Health Service (25918 people with HCV infection known to Regional Health Service - 5652 who had SVR to previous treatment with PEGINF + RBV and DAAs). 8106 are potentially eligible for the 4 criteria that provide the treatment of HCV patients with fibrosis stage METAVIR $\geq F3$.

The same calculation was applied to patients to unknown to the Regional Health Service. Therefore, the total number of unknown patients to Regional Health Service was 18377.

Therefore, out of 38643 patients who were unknown and known to the Regional Health Service, 15457 are eligible for DAAs.

**DISCUSSION**
In 2010, a WHO resolution recognised viral hepatitis as a global health problem and stressed the need to implement measures for its prevention, diagnosis and treatment[10]. In May 24, 2014, a follow-up resolution urged WHO Member States to develop and implement a national strategy based on epidemiological data[11]. Given the considerable differences among Italian regions, the calculation of HCV prevalence through administrative flows seems to be essential for intervention policy strategies. Currently, these data are highly interesting given the introduction of DAAs, which allow the eradication of the virus. In addition, these data have highlighted the problem of sustainability due to the high costs of new drugs in low and middle income countries. Intervention strategies are directed both towards the eradication of cases known and unknown to Regional Health Services, especially in the population at risk of contracting infection. There are various statistical methods to calculate all the individuals in the population that include both subjects who are known and subjects who are unknown to Regional Health Services. In this study, we used the log-linear model that allows correction for any covariates (such as sex and age). The total prevalence calculated for the prevalence observed in previous studies and that of administrative data are 1.7 vs 1.3 %. Currently, based on the calculation of patients with SVR to previous treatment with PEGINF + RBV and DAAs, a fraction of patients (10772) out of these 49,415 were sustained virological responders; therefore, the prevalence was 1%.

The recommendations of the European Association for the Study of the Liver[12] outline that the goal of treatment is to cure HCV infected patients in order to prevent hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death. However, because not every HCV-infected patient can be treated within the next year or so, the EASL suggest prioritization of the treatment based on fibrosis stage, risk of progression towards more advanced disease, presence of HCV-associated extra-hepatic manifestations and risk of HCV transmission (active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and inmates). Along some of these recommendations, treatment should be prioritized in patients with advanced fibrosis (METAVIR score F3 to F4), including patients with decompensated cirrhosis who have a contra-indication to the use of IFN-a but can be safely treated with IFN-free regimens.

The Italian Drug Agency published the prioritization’s criteria for the therapy restricting DAAs treatment to groups of patients[13]. Some of these criteria include the stage of fibrosis, which is one of the most important predictors of progression of the disease that affects treatment decisions.

Currently, treatment is reimbursed for patients with post-liver transplantation (LT) recurrent HCV and

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**Table 5 Patients known to the Regional Health Agency of Tuscany treated with pegylated interferon + ribavirin and/or direct-acting antiviral drugs**

| Genotypes | HCV patients treated with PEGINF + Rib | Sustained virological responders to PEGINF + Rib | Eligible patients to DAAs | HCV patients treated with DAAs | Sustained virological responders to DAAs |
|-----------|----------------------------------------|-----------------------------------------------|--------------------------|-------------------------------|----------------------------------------|
| 1b (60%)  | 4516                                   | 2075                                          | 2445                     | 1996                          | 1896                                   |
| 1a (6%)   | 452                                    |                                               |                          |                               |                                        |
| 2c (20%)  | 1505                                   | 1075                                          | 364                      | 151                           | (about 95% SVR)                        |
| 3a (6%)   | 452                                    | 271                                           |                          |                               |                                        |
| 4a/d (8%) | 603                                    | 247                                           | 300                      |                               |                                        |
| Totale    | 7528                                   | 3668                                          | 3260                     |                               |                                        |

1 HCV is considered regardless of genotypes. Sustained virological responders and total number of patients based on genotype - Source: Regional Health Agency of Tuscany and prevalence data by Marcellin et al[8], PEGINF: Pegylated Interferon; RBV: Ribavirin; DAAs: Direct-acting antiviral drugs.
advanced graft fibrosis; patients with chronic HCV and cryoglobulinaemic syndrome or non-Hodgkin lymphoma; patients with chronic HCV and advanced fibrosis (METAVIR ≥ F3, corresponding to liver stiffness ≥ 10 kPa); patients with decompensated cirrhosis listed for LT with MELD < 25 or with HCC within Milan criteria and an expected time on the list of at least 2 mo; and patients with any (non-liver) organ transplantation and chronic HCV, with METAVIR ≥ 2; and patients with METAVIR F0–F2 (only for Simeprevir) [13]. When we consider the eligibility criteria, 34,164 patients were eligible for DAAs based on the criteria, including HCV infected patients with advanced fibrosis (METAVIR ≥ F3, corresponding to liver stiffness ≥ 10 kPa). A large number of studies have suggested that liver stiffness measurement by transient elastography is a useful technique for diagnosing severe fibrosis and cirrhosis and for excluding significant fibrosis in hepatitis C virus patients [14,15].

In the entire cohort of patients Charlson Comorbidity score of > 3, which was associated with a survival probability of 45% over 10 years, was observed in 14% of people.

For drug prescription, clinicians also considered comorbidities to exclude an interaction between DAAs and other drugs prescribed for comorbidities. However, interferon- and ribavirin-treatment free regimens are available and require shorter treatment periods (3 mo). These regimens do not have substantial side effects and are also effective in patients with decompensated cirrhosis [16].

Recently, Wedemeyer et al. [17] and Gane et al. [18] used a mathematical model to forecast HCV disease burden. The results of these analyses suggest that the largest reduction in HCV-related morbidity and mortality occurs when increased treatment is combined with higher efficacy therapies, generally in combination with increased diagnosis. However, for most countries, this will require a 3-5 fold increase in diagnosis and/or treatment. Using today’s treatment paradigm, HCV-related mortality and morbidity is expected to increase in all countries with the exception of France, which has had a high treatment rate [17]. The analysis of Wedemeyer et al. [17] and Gane et al. [18] also demonstrated that with a treatment rate of approximately 10%, it is possible to achieve elimination of HCV (> 90% decline in total infections by 2030). However, treatment of F0–F1 patients was necessary if the goal of the strategy is to eliminate HCV.

In conclusion, Tuscan administrative data reveal a prevalence of chronic HCV infection of approximately 1%. Given the high number of chronic HCV-infected patients and the high costs of these drugs, the new regimens will probably remain inaccessible to many patients throughout the world. Therefore, these data could be useful for calculating health care costs and health planning in the coming years.

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