Access to Peginterferon plus Ribavirin Therapy for Hepatitis C in Romania between 2002-2009

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Abstract

Background: An overall prevalence rate of HCV infection in Romanian adult population was recently estimated to be 3.23%. The proportion of treated patients with chronic hepatitis C in our country has never been assessed. Aims: 1) to analyze the quality and quantity of antiviral therapy delivery; 2) to determine the proportion of patients being annually and ever treated with antiviral therapy in Romania and 3) to identify barriers against treatment of HCV infected-population in Romania. Results: The number of annually treated patients remained relatively stable between 2002 and 2007 (1,813 patients treated with pegylated interferon and ribavirin in 2002 and 2,446 in 2007). There was a doubled increase in reimbursed treatment in 2008 and 2009 (4,503 and respectively 4,701 treated patients) due to a special campaign organized to increase awareness and prevention of HCV transmission. The median time to therapy approval varies from county to county; overall it is 10.23 months. A total number of 25,318 patients with chronic C hepatitis were treated between 2002-2009, corresponding to a cumulative proportion of 4.1% of the prevalent cases of HCV infection treated in Romania until 1st January 2010. The main limiting factor of access to antiviral therapy for hepatitis C in Romania remains the lack of funds. Conclusions: This is the first analysis of the nationwide practice for treatment of hepatitis C in Romania. Increased public health efforts are required to improve access to antiviral therapy for hepatitis C in Romania.

Key words

Hepatitis C – peginterferon – ribavirin – therapy.

Introduction

Affecting 170 million (3%) of world’s population, hepatitis C virus (HCV) infection remains a highly prevalent and burdensome disease worldwide [1, 2]. It has been identified as the leading cause of chronic hepatitis, end-stage liver disease [3], and liver transplantation [4], and has contributed to the significant rise in the incidence of hepatocellular carcinoma [5]. Prevalence of HCV infection in the countries of the WHO European region ranges between 0.1 and 4.5% [6]. A recent nationwide cross-sectional survey conducted between 2006-2008 by a population stratified random cluster sampling has shown a prevalence rate of 3.23% of HCV infection in the Romanian adult population [7]. About 20% of HCV infections progress to liver cirrhosis and end-stage liver disease within 10-20 years [8]. Although the incidence of new HCV infections has declined, the number of patients with end-stage liver disease and deaths will increase 2 to 4-fold over the next 20 years due to the prevalent cases with chronic HCV infection [9, 10].

Currently, only viral eradication by antiviral drug therapy can prevent progression and mitigate the future public health burden of HCV infection [9, 10]. In the last two decades, there have been dramatic improvements in treatment for hepatitis C. The state-of-the art combination therapy with pegylated interferon and ribavirin can now achieve sustained virological response (SVR) in 50% of patients in everyday practice [11]. Patients who eradicate the virus maintain long-term remission of the disease with liver-related mortality rates comparable to the general population [12]. Despite the dramatic improvement in antiviral therapy for hepatitis C, there are many reasons which limit the uptake of antiviral therapy and not all patients who are eligible for antiviral therapy will receive treatment. The proportion of patients treated for hepatitis C and the reasons for lack of treatment vary from country to country.

The aims of this study were: 1) to analyze the quality and quantity of antiviral therapy delivery; 2) to determine the proportion of patients being annually and ever treated with antiviral therapy in Romania, and 3) to identify barriers against treatment of HCV infected-population in Romania.
Methods

The antiviral therapy delivery in Romania

The hepatitis C treatment policy in Romania

The antiviral therapy in Romania is fully reimbursed. National Health Insurance Agency (NHIA) reimburses 100% of peginterferon costs and 25% of ribavirin costs and the pharmaceutical companies are currently supporting the remaining 75% of ribavirin costs. Patients are prioritized to receive reimbursed treatment on the following criteria: time spent on the waiting list (WL) for antiviral therapy, severity of the disease, professional exposure, age (children and adolescents), oncologic co-morbidities requiring chemotherapy. The diagnosis, recommendation for antiviral therapy, and follow-up are performed exclusively by specialists (gastroenterologists/infectious diseases specialists). Retreatment was not reimbursed for relapsers or non-responders until 2010, therefore only naïve patients have been treated until that date.

Because of the large number of patients requiring antiviral therapy for hepatitis C against the limited funds of the National Program of Antiviral Therapy in Chronic Hepatitis (included in National Program for Therapy in Chronic Diseases), a percentage of patients are referred monthly from the local (county) WL, according to the above mentioned criteria, for national validation and access to therapy. After reviewing the indication, an Expert Committee of NHIA validates/approves the indication and patient’s entry into therapy. Within the National Program for Therapy in Chronic Diseases, chronic hepatitis competes with other chronic diseases such as psychiatric, rheumatologic, or dermatologic diseases for the same category of NHIA funds.

There is a central NHIA database allowing to register and follow-up the patients receiving reimbursed antiviral therapy in Romania. There are no bureaucratic hurdles in the reimbursement process apart from the existence of the WL.

Quantity of antiviral therapy delivery

The delivery of antiviral therapy for hepatitis C patients in Romania is limited by the restricted reimbursed quantity; this results in a relatively low annual treatment rate against the number of prescriptions, leading to WL for antiviral therapy. A variable number of reimbursed courses of therapy are negotiated annually between NHIA, professional associations and pharmaceutical companies. It represents the maximum number of paid prescriptions, although it is not mandatory to be fulfilled.

Responding to European commitments, in 2007 the academic community and authorities have joined their efforts in order to identify and treat more patients with hepatitis C. The first effective awareness and prevention campaign on hepatitis C „Find out why” (in Romanian language „why” sounds like „about C”) was conducted in 2007 by the professional associations and Patients Association with the support of industry. TV advertising, posters in medical units, schools and universities, flyers for the general population, a web site and toll-free number were all part of this campaign.

The authorities undertook their own action in order to increase the number of patients with chronic hepatitis detected and treated. In 2007, the Ministry of Health initiated a screening program for chronic diseases in the Romanian general population using basic laboratory tests scheduled to be completed on each individual in his/her month of birth. A huge proportion (65%) of subjects responded to this interventional program and, as a result, large numbers of patients with increased ALT were discovered and further referred to specialists for HCV and HBV screening. Additionally, screening programs in high risk groups were systematically applied.

Quality of antiviral therapy delivery

Only state-of-the-art therapy with pegylated interferons and ribavirin is currently prescribed in Romania for HCV-infected patients. A national panel of experts revises and updates the therapeutic recommendation (eligibility, doses, duration, etc.) according to national and international guidelines. Until March 2009 there was restricted access to therapy which prioritized advanced disease/fibrosis, younger patients, patients with high viral load and aminotransferases, professional exposure. These factors were comprised in an arbitrary, non-evidence-based scoring system. Patients with mild hepatitis (A1F1 on META VIR), compensated cirrhosis with small varices, and older than 65 years, irrespective of their biological condition, were not allowed to receive treatment. Beginning with March 2009, the quality of our program increased due to the activity of the Expert Committee of NHIA who updated the therapeutic protocol, allowing an unrestricted access to therapy for all eligible HCV-infected patients (positive HCV RNA, at least mild hepatitis, compensated disease). The selection prescription between peginterferon α-2a and peginterferon α-2b is at the physician’s decision. An adequate follow-up while on therapy is provided by gastroenterologists/infectious diseases (ID) specialists in order to avoid loss of resources in non-responders, critical adverse events or premature stop. All prescriptions, response during therapy, adherence, continuation/discontinuation are validated by the Experts Committee of the NHIA.

Proportion of patients treated for hepatitis C in Romania

Peginterferon α-2b was launched in Romania in late 2002 and peginterferon α-2a in 2003. Beginning with 2002, the Romanian Health Insurance System introduced a National Program for Antiviral Therapy in Chronic Hepatitis (within which antiviral therapy is fully reimbursed) covering the exceptional medical expenses for antiviral treatment of patients chronically infected with hepatitis C and B viruses, apart from hospital care, GP care and common drugs, covered by basic health insurance. In order to have a safeguard mechanism on Program expenses, a complex database has been introduced to register and follow-up during therapy every patient receiving paid antiviral therapy in Romania. It captures virtually all paid prescriptions nationwide. Every patient is encrypted by a personal card identity number in order to follow the therapeutic trail (type of therapy, dose,
naive/experienced, date of starting dose, therapeutic interval, EVR, completion of the therapy course). Demographics of subjects is also comprised in this database. Thus, to report the number of patients who received antiviral therapy against chronic hepatitis C in Romania, data on the number of new prescriptions of pegylated interferon products (α-2a and α-2b) each year from 2002 to 2010 were extracted from the NHIA database.

The reasons for the selected interval were: 1) the launch of new pegylated molecules, 2) the start of the reimbursed National Program and 3) the implementation of the NHIA database.

Reasons for lack of antiviral treatment for chronic HCV infection

Treatment decisions were investigated using data from the Hepatitis B & C Treatment Questionnaire delivered to patients during an epidemiological study [7]. The 425 participants tested positive for hepatitis C were sent a letter informing them of their test results and counselling them to contact their GP for further recommendations. Between 2 and 6 months later they received a follow-up questionnaire containing several questions about further testing: GP recommendations, referral to a specialist, treatment recommendation, follow-up. Responses allowed placement of responders into the following categories: 1) unaware of diagnosis; 2) aware of diagnosis but did not seek further medical attention; 3) GPs did not refer the patient to the specialist; 4) specialist did not recommend treatment; 5) specialist did recommend treatment but subject refused treatment; 6) treatment recommended; 7) treatment already started.

Results

The antiviral therapy delivery in Romania

The quantity of antiviral therapy delivery

The quantity of reimbursed therapy represents the main limiting factor of access to antiviral therapy against hepatitis C in Romania. This is the consequence of the limited funds allocated to the National Program against the rising number of prescriptions. During the 2002–2007 interval these funds and, as a consequence, the number of patients treated annually remained stable in spite of the increasing number of the prescriptions. This resulted in the increasing number of patients on the WL, as well as in prolongation of the time on the WL (Table I).

Since April 2007, as a result of the awareness and prevention campaign on hepatitis C, more than 150 articles were released/spread in press, more than 35 TV news about hepatitis C were broadcasted, more than 10 million people saw the TV advertising at least once (the advertisement was seen 44 million times), 12 pages of references on “hepatitis C” “find out why” were posted on Google in Romanian language, more than 27,000 people visited www.afladec.ro, and more than 1,000 people called the toll-free number.

On the other hand, a high number of individuals responded to the interventional program of screening for chronic diseases initiated by the Ministry of Health (65% participation rate), and as a result, a large number of patients with increased ALT were discovered and further referred to the specialist for HCV and HBV screening.

As a consequence, the detection, evaluation and decision for treatment tremendously increased during 2007, leading to the highest rate of patients awaiting for antiviral therapy and the longest waiting time at the end of 2008 (Table I). The WL increased by 2,500 patients in the first trimester of 2008, as compared to a number of 800 treatment courses expected to begin in a 3-month interval. This put an enormous pressure on the NHIA system of funds allocation and, a double number (5,200) of annually reimbursed treatment courses were negotiated between the NHIA, professional associations, patients’ associations and industry companies. The number of patients treated, awaiting for treatment and the waiting time had a favorable trend in 2008 and 2009 and continues to maintain this course in 2010, although a discrepancy continues to exist between the number of new detected cases and prescriptions for therapy on one hand, and the number of the approved courses of treatment on the other.

Unfortunately this favorable course is not a homogeneous process across the country. In some counties, the regional allocated funds of the National Program for Therapy in Chronic Diseases are straighten to other chronic diseases, without taking into account the huge number of patients and the waiting time on the local WL and, as a result, these counties have longer WLs and waiting time for antiviral therapy (marked on the map in Fig. 1).

In the last year 4,645 new treatment courses for hepatitis C were approved and 4,184 initiated (461 patients were validated but did not start the therapy because of lack of local funds).

The quality of antiviral therapy delivery

The state-of the art therapy with peginterferon and ribavirin for 48 weeks (almost exclusively genotype 1 HCV-infected population) [13] continues to be the standard therapy for chronic hepatitis C in Romania. The quality of therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients starting therapy</th>
<th>Number of patients on WLs</th>
<th>Median waiting time at 31st Dec (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>1,813</td>
<td>2,017</td>
<td>4</td>
</tr>
<tr>
<td>2003</td>
<td>2,189</td>
<td>2,435</td>
<td>14</td>
</tr>
<tr>
<td>2004</td>
<td>3,701</td>
<td>4,117</td>
<td>15</td>
</tr>
<tr>
<td>2005</td>
<td>3,149</td>
<td>3,503</td>
<td>20</td>
</tr>
<tr>
<td>2006</td>
<td>2,816</td>
<td>3,132</td>
<td>24</td>
</tr>
<tr>
<td>2007</td>
<td>2,446</td>
<td>2,721</td>
<td>25</td>
</tr>
<tr>
<td>2008</td>
<td>4,503</td>
<td>5,009</td>
<td>27</td>
</tr>
<tr>
<td>2009</td>
<td>4,701</td>
<td>5,229</td>
<td>15</td>
</tr>
<tr>
<td>2010</td>
<td>1521/1st trimester</td>
<td>4645/1st trimester</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25,318</td>
<td>26,839</td>
<td></td>
</tr>
</tbody>
</table>
delivery increased by up-dating the therapeutic protocols. There is now an unrestricted access to therapy for those eligible irrespective of age, the presence of mild hepatitis (≥A1/F1 on METAVIR scoring system) or compensated cirrhosis, HBV/HBV-HDV/HIV coinfected patients and i.v. drug users (stable on methadone), haemophiliacs, haemodynamised patients and patients with controlled co-morbidities.

During the analyzed interval, the preference of the Romanian prescriptors changed from peginterferon α2b in 2002 and 2003 to peginterferon α2a from 2004 till 2009.

**Proportion of treated patients out of the prevalent cases of hepatitis C**

There was an increase in the number of new prescriptions for pegylated interferon and ribavirin regimen from 1,813 in 2002 to 4,701 in 2009 (Table I). A total number of 25,318 patients with chronic VHC hepatitis/compensated cirrhosis were treated between 2002-2009.

Considering the estimated number of 633,080 HCV-infected subjects in Romania according to the 3.23 % prevalence rate of HCV infection in adult population [7] and the results of the last Census, a cumulative proportion of 4.1% of the prevalent cases of HCV infection were treated in Romania until 1st January 2010 (Fig. 2).

### Reasons for lack of treatment / Barriers against antiviral therapy for chronic HCV infection

Only 177 out of the 425 HCV positive subjects (41%) responded to the Hepatitis B & C Treatment Questionnaire. The placement into the 7 categories of the questionnaire is shown in Table II.

**Table II. Reasons of lack of treatment for hepatitis C as revealed by patients’ questionnaire.**

<table>
<thead>
<tr>
<th>Reasons for lack of treatment</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaware of diagnosis</td>
<td>27 (18.7%)</td>
</tr>
<tr>
<td>Did not seek medical attention due to various reasons (lack of time, stigmatization etc)</td>
<td>26 (18%)</td>
</tr>
<tr>
<td>GP did not refer the patient to gastroenterologist/infectionist</td>
<td>25 (17.3%)</td>
</tr>
<tr>
<td>Specialist did not recommend treatment (not eligible, etc)</td>
<td>22 (15.2%)</td>
</tr>
<tr>
<td>Specialist recommended antiviral therapy but subject refused/delayed treatment</td>
<td>12 (8.3%)</td>
</tr>
<tr>
<td>Specialist recommended antiviral therapy</td>
<td>45</td>
</tr>
<tr>
<td>Treatment already started</td>
<td>20</td>
</tr>
</tbody>
</table>

### Discussion

Our study is the first systematic assessment of data regarding access to reimbursed peginterferon and ribavirin combination therapy for hepatitis C in Romania. We performed an analysis of the antiviral therapy delivery in Romania, highlighting its strengths and weak points, as well as its constant improvement over time. Additionally, we calculated the proportion of patients annually treated from the prevalent cases of hepatitis C and assessed the main reasons for lack of treatment.

According to our analysis, the main limiting factor of access to antiviral therapy for hepatitis C in Romania remains the lack of funds. Therefore, a limited number of reimbursed courses of therapy are covered by NHIA annually. This number is negotiated every year between authorities (NHIA), professional associations, patients groups and industry. To our knowledge, this is a unique delivery system of antiviral
therapy in Europe resulting from the combination of high prevalence of hepatitis C and limited financial resources. Aware of the high prevalence of HCV infection in Romania [7], the Ministry of Health, professional associations and pharmaceutical companies developed a joint strategy aimed to increase public awareness and access to therapy of patients with hepatitis C. As a result of the first effective awareness and prevention campaign on hepatitis C "Find out why" and the screening program for chronic diseases initiated by the Ministry of Health, beginning with 2007, an increasing number of HCV-infected patients were detected and prescribed therapy. This resulted in the elongation of WL and increase of waiting time for antiviral therapy delivery. The increasing number of patients awaiting therapy, the academic world (by epidemiologic studies showing high prevalence of HCV infection and cost-efﬁcacy studies showing increased costs with advanced disease) and the community have generated a positive pressure on NHIA funds allocation policy claiming for more reimbursed courses of antiviral therapy. As a result, NHIA has doubled the number of reimbursed courses of therapy for patients with chronic hepatitis C.

The strength of the Romanian system of antiviral therapy delivery is the high quality of care for hepatitis C in Romania, which resulted from the continuous improvement in last years. This quality is reﬂected in the following characteristics: 1) it provides state-of-the-art therapy with pegylated interferon and ribavirin for genotype 1-infected patients (full dose, full duration); 2) the prescription and follow-up during therapy is provided by gastroenterologists/ID specialists; 3) in order to avoid dose reduction and maximize the chance of SVR, erythropoietin therapy is reimbursed for patients who develop critical anemia, while GCSF is reimbursed only for immunosuppressed patients who develop critical neutropenia during therapy; 4) national experts update the therapeutic guideline periodically; 5) there is an unrestricted access to therapy irrespective of age, stage of the disease, co-infections or controlled co-morbidities; 6) the therapy is fully reimbursed; 7) there are no bureaucratic hurdles of the reimbursement process except the WL; 8) there is a centralized database of NHIA comprising information about patients ever treated for hepatitis C in Romania.

Treatment policies for hepatitis C vary substantially across European countries. In some countries, access to state-of-the-art combination therapy is limited due to the lack of financial resources, inadequate knowledge, and limited access to specialists experienced in hepatitis C therapy or outdated national guidelines [6]. The exclusion from therapy of patients with mild disease, normal ALT, co-morbidities, with low hemoglobin or hepatic dysfunction, older than 60-65 years should be considered not only a limitation of the number of treated patients, but also a low quality, restricted policy [14, 15]. Limiting the access to optimal therapy or the access to therapy of deﬁned groups of patients will translate into a higher number of patients progressing to end-stage liver disease and liver cancer, resulting in additional losses of life years and quality of life, and increasing the demand for liver transplantation. Confronted with some of these problems in the former years, the Romanian policy of antiviral therapy delivery has improved steadily in the last years by increasing public and academic efforts in order to facilitate the unrestricted access to therapy for patients with hepatitis C.

The annual number of patients treated with peginterferon and ribavirin combination therapy for hepatitis C in Romania and detailed data about them and treatment courses are comprised in the centralized NHIA database. Therefore, the number of patients receiving reimbursed therapy here reported in our paper is correct. In contrast to our work, previous publications estimated country-speciﬁc hepatitis C treatment rates from sales data or using an algorithm to convert sales into patients’ numbers. However, this calculation introduces important biases resulting in under- or over-estimated number of treated patients, due to some highly uncertain parameters: 1) the use of an average genotype distribution to estimate dose and duration of therapy; 2) the use of an average body weight for a deﬁned population in order to extract the number of patients treated with weight-based regimens; 3) modiﬁcation of the treatment regimen (dose, duration) due to adverse events or comorbidities; 4) the proportion of therapy-experienced patients (patients receiving more than one course of therapy).

Relatively few patients with chronic hepatitis C received reimbursed antiviral treatment in Romania between 2002-2010, although the treatment rates deﬁnitely increased annually, as a result of increasing public awareness in a country with a high prevalence of HCV infection. This is in contradiction with recent studies from Europe and United States where these rates appear to decline [16]. The inadequate access to antiviral therapy is evident especially when compared to the actual need. In a recently published market analysis of the state-of-the-art treatment for hepatitis C across 21 countries in Europe through 2005, Romania held the third lowest place (after Russia and Italy) in a rank order of discrepancy between prevalence rates and the number of patients ever treated [6]. Updating this calculation with the new prevalence rate of 3.23% [7, 17], which resulted in 633,080 infected patients and 26,000 treated patients, a proportion of 4.1% of prevalent cases was obtained, placing Romania in an intermediate position among European countries in a rank order of discrepancy between prevalence rates and the number of patients treated.

A number of barriers precluded therapy in treatable patients. The main reasons for lack of therapy were analyzed in a questionnaire addressed to subjects diagnosed with hepatitis C in a recent nationwide cross-sectional survey. In a French study published in 2005, 16.1% of the patients were not followed and treated after diagnosis of HCV infection and a quarter of patients with a Metavir score >A1F1 did not receive treatment [18]. The median delay between diagnosis and antiviral therapy was 8.4 months, relatively similar to the median waiting time for therapy approval in our country.

In our study, one of the reasons for patients not being treated was unawareness of diagnosis (18.7%). Thus, there
is an increased need of public education about the high prevalence of hepatitis C in Romania, as well as about the negative health impact of the lack of antiviral therapy. Secondly, even if all patients with hepatitis C were aware of their diagnosis, some barriers to treatment would still remain. Because hepatitis C is usually asymptomatic, and sometimes with normal ALT levels, patients may not seek medical attention (18%) because of lack of time, fear of becoming stigmatized or of treatment side-effects impairing their quality of life. To date, there is insufficient evidence to recommend screening for hepatitis C (high costs, logistic difficulties, impossible access to therapy for all positives). Therefore, many primary care physicians may not realize the importance of diagnosing hepatitis C by identification of risk factors and testing for HCV infection. Thirdly, there is a lack of referral of patients by the primary care physician to a specialist who prescribes antiviral therapy (17.3%). Although prior studies have suggested that lack of referral is the major barrier to treatment access [18-20], this is not the case in our study. This is probably because the primary care physicians targeted by the third question of the questionnaire were the primary care physicians involved in the national survey study, thus aware and well trained in this regard. In a recent Canadian study [20] it was shown that facilitating self referral (up to 21.5% of patients) to a hepatology clinic in comparison to a health care professional referral, can improve access to care, including risk reduction and HCV treatment. Fourthly, patients were not eligible for therapy because of decompensated liver disease, untreated co-morbidities or other reasons (15.2% in our study). The fifth reason of lack of therapy is the patient’s refusal or delayed therapy (8.3%). Because of the high prevalence of hepatitis C in Romania, costs and limited access to therapy, there are fewer patients than expected who refuse or delay therapy. Romanian patients with hepatitis C assume easier than other Europeans the impairment in quality of life related to therapy.

Although this study is the first to examine the antiviral therapy delivery for hepatitis C in Romania, it does have several limitations. First, the NHIA database does not include patients treated in clinical trials or by their own resources, thus it is possible that the true number of patients treated for hepatitis C in Romania is underestimated. As only few patients have been included in clinical trials in our country, this factor does not impact significantly the true number of treated patients. Conversely, the prevalence of hepatitis C may be underestimated due to the increased prevalence in homeless, institutionalized individuals and those who lack health insurance and, therefore, are not included in a GP list of patients (the GP list represented the instrument for the national epidemiologic survey).

Conclusions

The strength of this study is that it provides the first look and critical analysis of the nationwide practice for treatment of hepatitis C in Romania. Increased public health efforts are needed to improve access to antiviral therapy for hepatitis C in Romania. As the limited number of reimbursed courses of therapy represents the most important barrier of access to therapy, we suggest the cyclic strategy of increasing public awareness (limited funds → awareness campaign → improvement of detection → increased prescriptions → positive pressure on authority → increased number of reimbursed therapy) as the principal instrument leading to increasing access to therapy in any system with limited resources and increased needs (high HCV prevalence).

Aknowledgements

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Conflicts of interest

None to declare.

References


13. Grigorescu M; Romanian Society of Gastroenterology and Hepatology. HCV genotype 1 is almost exclusively present in


