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## A Government Sponsored Clinic for the Evaluation and Treatment of Chronic Hepatitis C in an Underinsured Population in Puerto Rico

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**Background:** Chronic hepatitis C (CHC) is a major health problem in Puerto Rico (PR). More than 50% of the population is insured by a government-sponsored managed care system that does not cover treatment for CHC. Lack of access to treatment will result in an increase in end-stage liver disease with its high socioeconomic impact in the future. In an attempt to identify strategies for the treatment of CHC in the publicly insured population, the PR Health Department and the University of Puerto Rico (UPR) Gastroenterology (GI) Division have developed a pilot clinic for the evaluation and treatment of CHC.

**Methods:** UPR and the PR Health Department negotiated a fee per patient to include all medical care and follow-up laboratories. Viral studies were covered by a grant to the Health Department. Medications were bought at a discount price by the government and dispensed at a government pharmacy. The Health Department allocated funds for 200 patients with government insurance. A dedicated clinic was established at the UPR, staffed by an internist under the supervision of the GI faculty. Patients with a positive HCV antibody were referred to this clinic. The public insurance covered the CBC, liver tests, metabolic panel, TSH, HBsAg, HIV, ultrasound and liver biopsy, which were required prior to evaluation for possible treatment. In the initial visit, patients underwent a medical evaluation, including assessment of suitability for therapy and counseling. Those deemed to be candidates who still needed a liver biopsy had it performed by the GI staff. Genotype and viral titers were ordered after the decision on treatment had been made. The clinic physician prescribed pegylated interferon and ribavirin, which were dispensed by the government pharmacy. Instruction on proper drug administration was given. Clinic visits were scheduled for 1, 3, 6 and 12 months but also allowed on demand. Laboratory

tests were done at the clinic and reviewed by the physician expeditiously to monitor for toxicity. Any medical problems or treatment for complications of therapy were covered by the primary insurer. Viral load was repeated at 12 weeks to discontinue therapy in those unlikely to respond. The budget per patient for medical visits and laboratory tests was \$1,500.00, HCV RNA titers plus genotype costs \$200.00, and HCV qualitative RNA costs \$123.00

**Results:** 405 patients have been referred between February 2002 and April 2003 (the number was increased at adjust for no-shows and those not treated). 30% are female, the major risk factor is IVDU, and 80% are unemployed. 101 have started treatment and 48 are awaiting biopsy. A support group has been established at the clinic.

**Conclusions:** The treatment for CHC in practice is not only costly but also resource consuming. Most gastroenterologists in our community refer these patients for treatment. The establishment of a dedicated clinic with a primary physician supervised by the specialists reduces costs and facilitates caring for a larger number of patients. The volume of services allows for negotiation of medical, laboratory and drug costs. In allocating funds for this project, the PR Health Department recognized the importance in reducing the potential spread in the community by treating infected patients as well as reducing the future medical and socioeconomic burden of end-stage liver disease. Although the outcome of this project is still unseen, we believe that this model may serve to establish other clinics for the treatment of CHC at lower costs with the same effectiveness.

*Key words:* HCV, Pegylated Interferon, Ribavirin, Puerto Rico, Publicly insured.

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**H**epatitis C is a common chronic infection with an estimated global prevalence of 2.5 % (1). Approximately 2% of the population in the USA is infected with the hepatitis C virus (HCV). The prevalence of infection is highest among groups with behaviors at risk that expose mucosal surfaces or the circulation to contaminated body fluids: intravenous drug use, sexual

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promiscuity, cocaine inhalation, body piercing, tattoos, and blood product transfusions before 1992. Prevalence at correctional facilities is particularly high due to the incidence of environmental risk factors.

Approximately 80% of infected patients will develop chronic liver inflammation and remain asymptomatic. Depending on the series studied, 4% - 24% of patients with chronic liver injury will develop cirrhosis, usually between 20 and 30 years after infection (2). Once cirrhosis is established, 1-4% will develop hepatocarcinoma and 3-5% will go on to decompensated cirrhosis (3) with a 2% risk mortality/year (4).

Since the advent of the HCV screening tests among blood donors, the incidence of HCV has decreased (5). However, the prevalence of chronic liver disease is expected to rise due to the presumably large number of undetected viral infections prior to the initiation of blood product screening in 1992 and significant lag time between acute infection and the development of signs and symptoms of cirrhosis (6). For example, from 1982 to 1999, there was a six-fold increase in the number of deaths attributable to viral hepatitis, and 77% of these cases had hepatitis C (7).

Antiviral treatment has a poor efficacy in advanced liver disease, and liver transplant is the only option to restore liver function at this stage. In fact, chronic hepatitis C (CHC) is the leading cause of liver transplantation in the USA. However, infection of the allograft with hepatitis C virus is almost universal and liver damage is accelerated. Therefore, the only real chance for cure, with the current therapies available, is detection and treatment before the infection becomes symptomatic.

The only approved therapy for the treatment of CHC, a combination of interferon injected subcutaneously and oral ribavirin, has significant drawbacks. In the first place, duration of therapy is prolonged (6 months - 1 year depending on genotype). Secondly, the medication is very expensive (approximately \$2500/ month). This cost does not include physician visits, follow up laboratory tests, or treatment of complications. Finally, antiviral therapy is plagued with side effects, such as anemia, leucopenia, thrombocytopenia, and depression, that are likely to require intervention and significantly increase cost.

Reliable data on the prevalence of hepatitis C in Puerto Rico are lacking. A study on volunteer blood donors in the island reported a 0.79% prevalence of hepatitis C antibodies (8). In 2002, a study by Pérez et al from the UPR School of Public Health evaluated the prevalence of HCV antibodies in adults living in San Juan. A total of 970 subjects were tested and 6.3% were HCV positive. The prevalence was highest among the 30-49 year old group, and injection drug use (IDU) was the most common risk

factor identified. This number may be overestimating true prevalence, since IDU appears to be more common in large metropolitan areas. Between January 2001 and March 2002, 3,576 cases of HCV infection were reported among patients under the government sponsored health insurance (Health Reform), mostly from San Juan, the rural area of La Montaña, and the East. The Puerto Rico Department of Health (DHPR) assumes that the overall prevalence of infection in PR is similar to the US, although there are no data to support this. Based on this assumption, there are 43,280 cases by the 2000 census.

The economic impact of this disease is substantial. As mentioned earlier, antiviral therapy is very expensive. Treatment of the side effects with hematopoietic stimulation factors and antidepressants is also costly.

Monitoring of viral loads, necessary to assess response of therapy and determine total duration, adds significantly to costs. Many patients are not able to work at least during part of the lengthy therapy, which increases indirect costs. Finally, liver transplantation for end stage liver disease has a high price tag. For example, in Puerto Rico from 1996-2002, 231 patients were referred for liver transplant at a cost of \$28.5 million. Although most patients are able to return to work after liver transplant, they are tied to life-long immunosuppression and its attendant complications.

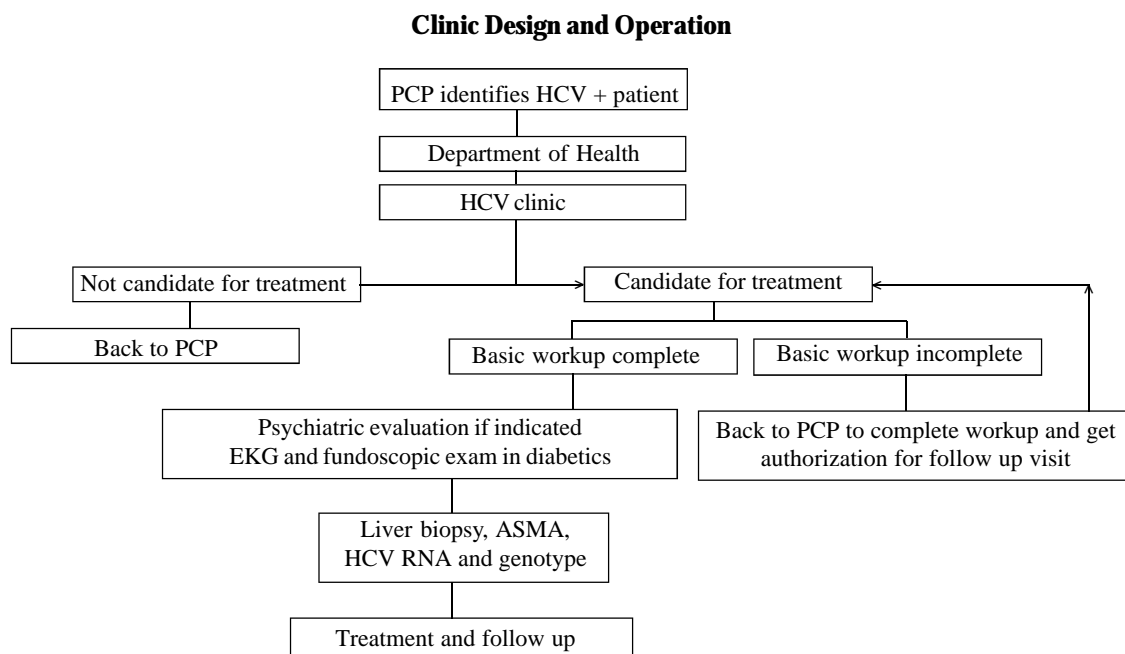
The problem is compounded because at the present time the Health Reform does not pay treatment for CHC, even though the cost of therapy is reduced to about \$2,000/month with a government discount. Approximately 30% of the population has Health Reform as their primary medical insurance. Other private insurers cover only 60-80% of the cost of treatment, if at all. The DHPR, recognizing the social and economic impact that CHC infection represents if left untreated, approached the University of Puerto Rico School of Medicine to assist in the creation and implementation of a pilot clinic for the evaluation and treatment of patients with CHC and Health Reform as their primary health insurance. The clinic started operations one year ago and is still running. A total of 400 patients were referred by the DHPR.

We will present the clinic design and operation, including patient entry and treatment protocol. Other operational aspects such as funding, personnel, and drug dispensing will also be addressed. Finally, the discussion will focus on the difficulties encountered and suggestions on how to resolve them.

## Methods

**Clinic Design and Operation.** Patients identified with HCV positive antibody were identified by the primary care provider (PCP) and referred to the DHPR (See Figure 1). A non health-related professional recorded basic patient data

**Figure 1.** Patient Entry Algorithm



and referred him or her to the hepatitis C clinic at our facility. The DHPR issued the patient a letter authorizing entry into the clinic and kept a register of how many patients were referred until the predetermined number was reached.

At the initial visit to the clinic, a thorough history and physical examination were performed. The history emphasized risk factors for infection, past or current IDU, social support, history of depression, suicidal ideations or attempts, and complications of chronic liver disease such as ascites, gastrointestinal bleeding, or encephalopathy. A history of chest pain or coronary artery disease was also elicited. The physical examination emphasized on signs of chronic liver disease. If the patient presented signs or symptoms of decompensated cirrhosis, significant thrombocytopenia (Plt < 80,000/ml), active IDU, HIV or HbsAg positivity, history of suicidal attempts, or normal ALT, he was considered not a candidate for the treatment protocol and was sent back to the PCP with recommendations. A history of major psychiatric illness or active use of psychotropic medications required psychiatric evaluation and a written consultation stating whether patient could receive antiviral treatment from a psychiatric standpoint. If patient was considered a good candidate, but the initial workup was incomplete, he or she was asked to return after workup was completed. All of the patient visits prior to recommending liver biopsy, except the initial visit, required PCP referrals and were not covered by the clinic.

After basic workup was completed, the patient

underwent liver biopsy. The gastroenterologist performs this procedure at our institution, but the patient has the choice of doing it elsewhere. An authorization for this procedure is required from the PCP, as liver biopsies are part of the diagnostic evaluation of patients with CHC and thus are not paid by the pilot clinic. At the time of scheduling the biopsy, the specialized labs ASMA and HCV RNA and genotype are ordered. These are paid by the clinic. The ASMA is an antibody which is used as a marker of autoimmune hepatitis, and its presence in an HCV + patients mandates careful evaluation for the coexistence of autoimmune hepatitis, which needs to be treated first. The HCV RNA quantitative test is a useful tool to monitor treatment response and determine early viral response at 12 weeks into treatment. A fail in reduction of at least 2 logs from pretreatment levels indicates a poor response and treatment can be discontinued. The HCV genotype dictates duration of treatment: genotypes 1 and 4 are treated for 48 weeks, whereas genotypes 2 and 3 are treated for 24 weeks.

**Treatment and monitoring.** The Gastroenterology and Liver Diseases Section of the Department of Internal Medicine developed a treatment and monitoring protocol according to accepted standards as validated by the NIH National Consensus on hepatitis C (see Table 1)\*.

According to current guidelines, peginterferon  $\alpha$ -2b is started at a dose of 1.5 $\mu$ g/kg SQ weekly and oral ribavirin is given at a dose of 10.6 mg/kg. Although the FDA-approved dose of ribavirin is different, many experts

**Table 1.** Laboratories and evaluation performed at each protocol visit. HbsAg- hepatitis B surface antigen, TSH- thyroid stimulating hormone, ASMA- anti smooth muscle antibodies, AST/ALT- aspartate aminotransferase/alanine aminotransferase, CBC- complete blood count, HCV RNA by PCR- polymerase chain reaction, quantitative assay.

Baseline labs	0 weeks	2 weeks	3 mo	4 mo	6 mo	9 mo	12 mo
CBC,PT/PTT, liver panel	Start treatment <sup>†</sup>		HCV RNA by PCR, quant	Treatment continues? <sup>‡</sup>			
HbsAg, HIV	HCV RNA by PCR and genotype <sup>**</sup>	CBC	CBC		CBC	CBC	CBC
TSH	Counsel about contraception		AST ALT		AST ALT	AST ALT	AST ALT
ASMA					TSH		TSH
Liver biopsy							

\* Other visits are allowed according to development of side effects and clinician judgment

<sup>†</sup> Peginterferon 4-2b 1.51g/kg SQ weekly and oral ribavirin 10.6 mg/kg

<sup>‡</sup> Treatment continues only if there is a 2 log reduction in the viral load compared to 0 weeks. For genotypes 2 and 3, this step is omitted and treatment continued for a total of 6 mos

\*\* Samples taken before treatment begins

recognize that the original studies on combination therapy used a suboptimal dose of ribavirin. Treatment is given for 3 months and then early viral response is assessed with a follow up viral load. This assessment is not necessary for genotypes 2 and 3 as response is very favorable and treatment is continued for 6 months. If the viral load does not show a 2 log reduction when compared to pretreatment values, this predicts non response to treatment, and therapy can be stopped. If there is such a reduction, then treatment is continued for a total of 48 weeks.

Adjustment of dosage is very frequent due to side effects. Hematologic side effects are the most frequent cause of dose reduction. Hemoglobin levels less than 10 gm/dl require ribavirin dose to be decreased by 200 mg daily. Likewise, neutropenia is a common side effect of interferon, and an absolute neutrophil count of less than 750/mm<sup>3</sup> mandates reduction to 50% interferon dose. Finally, platelet counts need to be monitored as well, and levels less than 80,000/mm<sup>3</sup> require interferon reduction to 50%. These modifications will have an impact on treatment response. Erythropoietin and filgrastim are used to control reductions in hemoglobin and neutrophil counts, thus allowing higher doses of antiviral medications and enhancing chance for cure, but these medications are very expensive and not likely to be covered by primary insurer. At the end of treatment, the patient is discharged from the clinic with the recommendation to repeat the viral load at 6 mos after end of treatment to determine if he or she has a sustained viral response and possibly cured of infection.

**Funding.** The DHPR allocated funds for 200 patients, but this number was later increased due to the large number of dropouts and patients with contraindications for treatment.

The operational costs were divided as follows:

1. The DHPR would pay for physician fees, ASMA titers, CBC, AST/ALT and TSH during the treatment period, and the medication
2. The health plan, through its referral process, would pay for the liver biopsy, and baseline laboratories except ASMA, HbsAg, and HIV (see below). Other baseline evaluation, such as EKG, fundoscopic exams, and psychiatric evaluations, as well as medications for the treatment of complications of antiviral therapy, also mediated through referrals from the PCP.
3. A grant from a pharmaceutical company would pay for the PCR and genotype tests at 0 weeks and 3 months

The total cost of treatment was calculated as follows:

1. Physician fee: \$150/ initial visit + \$100/ follow up x 6 visits = \$750
2. Laboratories:
  - a. HCV genotype and PCR at \$465 x 2 = \$930
  - b. CBC at \$8 x 5 = \$40
  - c. AST/ALT at \$13.60 x 4 = \$54.40
  - d. ASMA at \$25
  - e. TSH at \$30 x 3 = \$90
  - f. HbsAg and HIV performed free of charge at the Centro Latinoamericano de Enfermedades Sexualmente Transmitidas (CLETS) located in the Puerto Rico Medical Center
3. Liver biopsy: cost covered by the Health Reform since deemed part of the diagnostic evaluation = \$120
4. Medications: peginterferon Alpha-2-b weight

based at 1.5 mcg/kg SQ weekly in combination with oral ribavirin 10.6 mg/kg = \$800 interferon + \$1200 ribavirin per month per patient

5. Cost of management of side effects, such as antidepressant medications, erythropoietin for ribavirin induced anemia, and granulocyte colony stimulating factor for neutropenia, were the responsibility of the Health Reform.

The DHPR made serial deposits to a University of Puerto Rico special account to which participating physicians billed medical visits and the participating laboratory (physically located in the same area where the clinics were held) billed laboratory tests. To avoid billing of patients from other clinics, an ink stamp was designed which identified the laboratory orders that could be billed. The same ink stamp was used to identify prescriptions which could be dispensed from a designated government pharmacy. The stamp consisted of the letters "PGI" to avoid unnecessary divulgence of the patient condition (PGI stands for piloto gastrointestinal).

The DHPR acquired the medication directly from the pharmaceutical company, while the specialized HCV PCR and genotype laboratories were paid directly to the laboratory by the pharmaceutical company.

**Personnel.** Two gastroenterologists and an internal medicine specialist supervised by a gastroenterologist conducted the clinics 4 times/week. A specially trained registered nurse was provided by the pharmaceutical company free of charge to educate patients regarding medication administration and side effects. This training was conducted at the drug dispensing site. She also conducted support group sessions near the clinic premises.

**Drug dispensing.** The health department designated a government owned local health center as the medication dispensing site. One morning per week, the health center was available for protocol patients to pick up their medications. The pharmacist verified the prescription, making sure it had the ink stamp which identified the protocol. A trained registered nurse at the site oriented patients on dose calculation, mixing, and injection.

## Discussion

We have presented the design of a pilot clinic for treatment of chronic hepatitis C in a medically underinsured population. Several difficulties were encountered during its operation which need to be considered during the planning of future clinics. The areas of concern were: patient screening, drug availability, management of side effects, and data collection.

Patient screening prior to entry to the clinic was nonexistent. The patient only needed to present a positive

antibody test to the clerk at the appropriate DHPR office in order to receive authorization for entry into the hepatitis C clinic. The patient was then instructed to call for an appointment. As a result, approximately one-third of the patients evaluated were disqualified for treatment. This represented a significant amount of wasted resource, as all initial visits were billed, regardless of whether the patient could receive treatment or not. Likewise, patients with incomplete basic work-up consumed at least two clinic visits prior to liver biopsy scheduling, further increasing costs.

This difficulty can be resolved if the DHPR designates an adequate staff for the evaluation of candidates prior to clinic referral. The staff may be trained to detect contraindications for treatment; for example, thrombocytopenia, anemia, evidence of decompensated chronic liver disease such as hyperbilirubinemia or coagulopathy, and history of suicidal attempts. Specific guidelines for each of these criteria can be given in print form for easy and objective reference. Historical data are more subjective than laboratory results, and may require referral to a health professional for clinical decision making. In our experience, the most common reason for denial of treatment was advanced chronic liver disease and this could be a specific target for patient screening at a pre-entry level.

Drug availability is another area of concern that needs to be addressed. Only one dispensing facility in the metropolitan area was available to supply the needs of the entire clinic population, and only one morning per week was assigned for dispensing the antiviral medications. Although this facilitated education by a registered nurse on medication administration, it constituted a big problem for patients living outside the metro area. They had to come to the clinic one day and pick up their medication another day, even though both sites were relatively close. Most patients were highly motivated to start and continue treatment and were willing to go through the inconveniences of getting the medication. Occasionally, however, the medication was not available on the day of drug dispensing. Two factors may account for this. One, since the dose of peginterferon was based on weight, many concentrations need to be available to provide for all patients. Even though an estimate of need was performed a priori, sometimes patients were sent home empty-handed. Two, the distribution center was grossly understaffed and no provisions were made for drug dispensing during the holiday break or other absences. As a result, many patients ended up with a 4-8 week hiatus in their treatment, during which viral loads can increase and thus lower treatment efficacy. Setting up multiple distribution centers throughout the island with adequate

staffing to insure uninterrupted service, and using our present population to re-estimate peginterferon needs may avoid drug availability concerns. Finally, using a peginterferon with a unitary dose formulation may facilitate drug dispensing.

Management of side effects is an important aspect of CHC treatment. As in the case of drug dispensing, ensuring an adequate control of side effects of antiviral therapy can have a direct impact on treatment response. A significant amount of patients exhibit hematologic side effects with interferon and ribavirin, namely neutropenia, anemia and thrombocytopenia. The first two can be reversed by the use of the bone marrow stimulation factors filgrastim and erythropoietin, thus allowing the full recommended dose of interferon and ribavirin and increasing chances for cure.

These factors, however, are very expensive. Erythropoietin 40,000 IU weekly (usual dose in this setting) costs approximately \$ 450/week, while filgrastim 300 mcg twice a week costs approximately \$350/week. Our treatment model places the responsibility of paying for these on the Health Reform. They frequently denied these medications, thus forcing dose reduction. The treatment of depression can also be affected, although this is a less serious problem due to the availability of generic fluoxetine. Treatment of side effects need to be taken into account when calculating total medication costs, as these can be significant. Our experience demonstrated that, under appropriate supervision, non-gastroenterologists can adequately evaluate and treat these patients. This has important implications, especially if satellite clinics are established in an effort to extend services to other parts of the island.

It should be noted that the experiences obtained while conducting the clinic need to be tabulated and gathered in an orderly fashion for statistical interpretation. The need of a statistician working together with the clinician is of paramount importance to detect trends and identify needs which can be addressed in future designs, such as those suggested above.

## Resumen

La hepatitis C crónica (CHC; por sus siglas en inglés) es un problema de salud significativo en Puerto Rico. Más del 50 % de la población tiene seguro médico que provee el gobierno (Reforma), y éste no cubre tratamiento para CHC. La falta de acceso a tratamiento puede resultar en un aumento de enfermedad terminal del hígado, lo que representa un gran impacto a la socio-economía en el futuro. En la búsqueda de estrategias al tratamiento de CHC en la población cubierta por Reforma, el Departamento de Salud de Puerto Rico y la División de Gastroenterología

de la Universidad de Puerto Rico han desarrollado una clínica piloto para la evaluación y tratamiento de CHC. La UPR y el Departamento de Salud negociaron una tarifa por paciente, para incluir el cuidado médico y laboratorios de seguimiento. Los estudios virales fueron sufragados por una aportación de una compañía farmacéutica al Departamento de Salud. Los medicamentos fueron comprados al por mayor y con descuento y servidos en una farmacia pública. El Departamento de Salud presupuestó fondos para 200 pacientes con Reforma. Se estableció una clínica para el tratamiento de estos pacientes bajo la dirección de un médico internista supervisado por la facultad de Gastroenterología. Aquellos pacientes con anticuerpo HCV positivo fueron referidos a esta clínica. La Reforma costó los laboratorios iniciales: CBC, panel hepático, panel metabólico, TSH, HbsAg, HIV, ultrasonido y biopsia de hígado. Estas pruebas fueron requeridas previo a la evaluación para posible tratamiento. La visita inicial consistió en una evaluación médica para determinar posibilidad de tratamiento y consejería. Los candidatos a tratamientos fueron referidos al Servicio de Gastroenterología para biopsia de hígado. El genotipo y carga viral se ordenaban cuando el paciente regresaba a la clínica con el resultado de la biopsia. Los medicamentos utilizados fueron interferon pegilado y ribavirina, los cuales se distribuían por una farmacia pública. El paciente se educaba en el método de administración. Las visitas de seguimiento fueron programadas a los meses 1, 3, 6 y 12, pero se permitían visitas no programadas. Durante las mismas se revisaban los laboratorios ordenados para vigilar posibles toxicidades. Los costos de otros problemas médicos y el tratamiento de las complicaciones a interferon / ribavirina fueron cubiertas por Reforma a través de referidos al médico primario. La carga viral fue repetida a las 12 semanas para discontinuar terapia en aquellos que no demostraron respuesta. El presupuesto establecido por visitas médicas y costos de laboratorio fue de \$1,500.00 por paciente. El costo aproximado del genotipo de HCV fue de \$123.00 y la carga viral de \$200.00. 405 pacientes fueron referidos desde febrero 2002 hasta abril 2003 (el número total de pacientes se aumentó debido a la gran cantidad de ausencias y de pacientes que no eran candidatos a tratamiento). 30% de los pacientes fueron mujeres y el mayor factor de riesgo fue abuso de sustancias intravenosas. Aproximadamente 80% de los pacientes estaban desempleados. Al momento 101 pacientes habían comenzado tratamiento y 48 esperaban biopsia de hígado.

El tratamiento de CHC en la práctica es costoso y consume muchos recursos. La mayoría de los gastroenterólogos de la comunidad refieren los pacientes para tratamiento. El establecimiento de una clínica dedicada

al tratamiento de CHC dirigida por un médico primario bajo la supervisión de especialistas reduce costos y facilita el cuidado de una mayor cantidad de pacientes. El volumen de servicios permite la negociación de los precios de medicamento, laboratorios y seguimiento médico. El Departamento de Salud de PR reconoció la importancia en tratar y prevenir la transmisión de CHC para reducir la carga futura que esta enfermedad y la cirrosis hepática puede representar a la comunidad. A pesar que no se ha visto todavía los resultados de esta clínica, creemos que este modelo se puede aplicar en otras clínicas dedicadas al tratamiento de CHC, a un menor costo y con la misma eficacia.

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