Public Health Impact of Antiviral Therapy for Hepatitis C in the United States

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Despite dramatic improvements in antiviral therapy for hepatitis C, there is reason to believe that the uptake of antiviral therapy remains limited. The aims of this study were to determine the number of patients being treated with antiviral therapy in the U.S., to estimate the public health impact of these treatment patterns, and to identify barriers to treatment for patients with hepatitis C. Data on the number of new patient pegylated interferon prescriptions each year, from 2002-2007, was obtained from Wolters Kluwer Inc., which maintains an electronic audit of pharmacies nationwide. A Markov model was created of the population with chronic hepatitis C in the U.S. from 2002 to 2030, and was used to estimate the number of liver-related deaths caused by hepatitis C that will be prevented by current treatment patterns. The National Health and Nutrition Evaluation Survey (NHANES) Hepatitis C Follow-Up Questionnaire was used to investigate reasons for lack of treatment and to identify strategies for improving access. Approximately 663,000 patients received antiviral therapy between 2002 and 2007, and treatment rates appear to be declining. If this trend continues, only 14.5% of liver-related deaths caused by hepatitis C from 2002-2030 will be prevented by antiviral therapy. Results from the NHANES questionnaire suggest that the primary barrier to treatment is lack of diagnosis, with 69/133 (adjusted proportion 49%) of respondents previously unaware that they had hepatitis C. *Conclusion:* Efforts to improve rates of diagnosis and treatment will be required if the future public health burden of hepatitis C is to be ameliorated. (HEPATOLOGY **2009;50:1750-1755.**)

Hepatitis C is a major public health burden in the United States. It causes nearly 8,000 deaths per year,[1] is the leading cause for liver transplantation,[2] and has contributed to a rise in the incidence of hepatocellular carcinoma.[3] Quality of life is impaired for patients infected with the virus, even among those without cirrhosis.[4] As of 2001, there were an estimated 3.2 million people in the U.S. with chronic hepatitis C. Although the incidence of new infections has declined, the number of deaths may continue to increase 2- to 4-fold over the next 20 years due to prevalent cases with long-standing infection.[5,6]

The future public health burden of hepatitis C could potentially be mitigated by antiviral therapy.[5] In the last two decades there have been dramatic improvements in treatment for hepatitis C. The benefit of adding ribavirin to interferon was demonstrated in a series of studies in the late 1990s,[7] and then pegylated interferon was approved at the end of 2001. Combination therapy with pegylated interferon and ribavirin can now achieve sustained virological response (SVR) in 50% of patients,[8] compared to rates of 17% with standard interferon alone.[7] Patients who achieve SVR enjoy long-term remission of disease, with liver-related mortality rates comparable to the general population.[9-11]

Despite these improvements, there are reasons to believe that the uptake of antiviral therapy may be limited. Patients with hepatitis C are more likely to lack health insurance and a usual source of care.[12,13] Studies have demonstrated that primary care physicians lack knowledge about risk factors and testing for hepatitis C.[14,15] Access to a specialist willing to prescribe antiviral therapy may be another limiting factor.[16] Finally, many patients

Abbreviations: NHANES, National Health and Nutrition Evaluation Survey; SVR, sustained virological response.

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have contraindications to treatment, or do not wish to suffer the myriad side effects.[17] For these reasons, we hypothesized that the public health impact of antiviral therapy may be limited, as much by low utilization as by the inherent limitations in the available medications. Several studies from the Veterans Affairs Healthcare System and Health Maintenance Organizations have reported low treatment rates among patients identified to have hepatitis C.[18,19] However, no national data exist on the number of patients currently receiving antiviral therapy in the U.S., or the impact of current practice patterns on the burden of hepatitis C. The aims of this study were to determine the public health impact of current antiviral therapy and to identify barriers to treatment of hepatitis C.

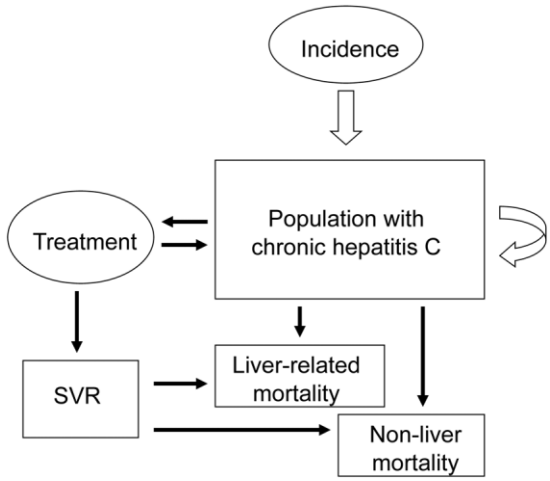

Fig. 1. Structure of the Markov model representing the population infected with hepatitis C in the United States.

Materials and Methods

Number of Patients Treated for Hepatitis C

To determine the number of patients receiving antiviral therapy in the U.S., data were obtained from Wolters Kluwer on the number of new patient prescriptions for pegylated interferon products (peg-interferon α-2a and peg-interferon α-2b) each year from 2002-2007. Wolters Kluwer maintains a longitudinal nationwide sample of patients filling prescriptions at retail, mail-order, and specialty pharmacies.[20] This sample captures ≈31% of paid prescriptions nationwide. Every patient is given an encrypted unique identifier in order to differentiate between new prescriptions and refills. Prescription data from this sample are then linked to a second database that measures total monthly prescription volume in the U.S. from a random sample of pharmacies with computer management systems. This database represents 80% of U.S. retail prescriptions. In this fashion, the number of prescriptions from the longitudinal patient sample is projected to determine the total number of prescriptions per year for a given product. Demographics of subjects in the Wolters Kluwer longitudinal sample (Source Lx) compare similarly to those from the U.S. census, as shown in Appendix A.

Impact of Antiviral Therapy on Burden of Disease

Markov Model Structure. In order to estimate the impact of current practice patterns on the future burden of hepatitis C, we created a dynamic population Markov model of patients with chronic hepatitis C in the U.S. from 2002-2030. During this time the population could change in size due to new infections, or due to patients being removed from the cohort because of death from liver disease or other causes, as shown in Fig. 1. The primary endpoint of the model was the number of liver-related deaths projected to be prevented by antiviral therapy during this period.

Input Data and Model Assumptions. All variables included in the model are shown in Table 1. Baseline prevalence was obtained from the National Health and Nutrition Evaluation Survey (NHANES),[21] and annual incidence of new infections was obtained from the Centers for Disease Control.[22] The proportion of acute cases progressing to chronic hepatitis C was estimated from the proportion of cases in NHANES with positive antibody but negative RNA.[21] The number of patients receiving antiviral therapy between 2002 and 2007 was obtained from national pharmacy data (Wolters Kluwer database, as described above). The number of patients receiving antiviral therapy each year after 2007 was projected by fitting a three-parameter inverse linear equation to the 2002-2007 data, with optimization performed according to the least-squares criterion.[23] Liver-related mortality rate without treatment was based on current mortality attributable to hepatitis C,[1] and was assumed to increase by 10% of the baseline rate each year[5,6] to account for the increasing average duration of infection. Nonliver mortality rate was based on life tables from the National Center for Health Statistics,[24] and was assumed to increase by 10% of the baseline rate each year to account for aging of the hepatitis C population. The SVR rate was set at 50% in the base-case analysis,[8] with a 10-fold reduction in liver-related mortality risk among those achieving SVR.[9-11] Calculations were performed using Excel (Microsoft, Redmond, WA). The model cycle length was 1 year, and no discounting was performed.

Sensitivity Analysis. Sensitivity analysis was performed on all variables. This was done both to determine susceptibility of the base-case estimate to uncertainty sur-

Table 1. Variables Used in the Markov Model

Variable	Base-Case Value	Sensitivity Analysis	Reference
Prevalence of hepatitis C, 2001	3.2 million	2.7–3.9 million	21
Annual incidence of new infections	19,000/year	10,000–20,000/year	22
Progression to chronic hepatitis C	78%	60%–90%	21
Number of patients treated	See Fig. 2	1.5 times the estimates in Fig. 2	Wolters Kluwer data
SVR	50%	40%–75%	8
Liver-related mortality (LRM) w/o treatment	8,000/year	6,000–12,000/year	1, 5, 6
Non-liver related mortality among hepatitis C cohort	13,000/year	10,000–18,000/year	24
Odds of LRM in SVR vs no SVR	0.1	0.05–0.2	9–11
Odds of LRM in treated vs. untreated	1	1–2	25

SVR, sustained virological response; LRM, liver-related mortality.

rounding the variables, as well as to estimate how many extra lives could be saved by improvements in various aspects of medical care. For example, future advances in antiviral therapy may improve rates of SVR, or public education campaigns could increase the number of cases detected. Finally, because current guidelines recommend selecting patients for treatment in part based on their risk of future complications,[25] in sensitivity analysis the treated patients were assumed to have a 100% higher risk of liver-related death than those untreated.

Reasons for Lack of Treatment

Treatment decisions were investigated using data from the NHANES Hepatitis C Follow-Up Questionnaire. Every 2 years, NHANES selects a random sample of the U.S. population to participate in a health examination and laboratory testing. Beginning with the 2001/2002 version, participants testing positive for hepatitis C were sent a letter informing them of their test results. Four months later, they received a follow-up telephone questionnaire. In all, 277 subjects were contacted during the three iterations of this survey, the response rate was 136 (49%), and there were three partial completions, yielding a sample size of 133 completed questionnaires.

The NHANES questionnaire, which can be seen at http://www.cdc.gov/nchs/data/nhanes/pf_hcq_03_08.pdf, contains a series of questions about testing, follow-up, doctor's recommendations, and subject decision-making about treatment for hepatitis C. Responses to these questions were used to place subjects into the following categories with regard to treatment: (1) unaware of the diagnosis, (2) aware of the diagnosis, but did not seek further medical attention, (3) doctor did not recommend treatment, (4) subject refused treatment, and (5) treated. This classification was performed independently by two authors (M.V., R.T.), and agreement was 100%. Subjects who were previously unaware of their diagnosis and sought medical attention during the 4 months between notification of their diagnosis and receipt of the questionnaire were classified as "unaware." Sample weights were used to adjust for oversampling of African-Americans, Hispanics, and subjects age >65 in the NHANES study.[26] Chi-square analysis was then used to determine bivariate associations between these categories and variables such as age, gender, race/ethnicity, and insurance status. Calculations were performed using Stata 10.0 (StataCorp, College Station, TX).

Results

Number of Patients Treated for Hepatitis C. Results from the Wolters Kluwer prescription audit are shown in Table 2. There were ≈126,000 new retail prescriptions for pegylated interferon products in the year 2002, and this number had decreased to ≈83,000 prescriptions per year by 2007. The fitted line projecting future treatment rates is shown in Fig. 2. If this trend were to continue, fewer than 1.4 million patients would be treated cumulatively by 2030.

Impact of Antiviral Therapy on Burden of Disease. In the base-case analysis, without treatment the population with chronic hepatitis C would be expected to decrease slowly to ≈2.95 million by 2030, as shown in Fig. 3. With treatment, assuming current practice patterns continue, the population with chronic hepatitis C is expected to decrease to 2.37 million by 2030. There would be 259,000 liver-related deaths caused by hepatitis C between 2002 and 2030 without treatment, and current antiviral therapy would prevent 37,500 of these. Thus, the current state of antiviral therapy is projected to pre-

Table 2. Estimated Number of Patients Treated per Year with Antiviral Therapy for Hepatitis C in the U.S.

Year	Number Treated	95% Confidence Interval
2002	126,040	125,449–126,649
2003	107,131	106,653–107,614
2004	144,276	143,616–144,943
2005	114,197	113,580–114,823
2006	88,083	87,685–88,486
2007	83,270	82,897–83,647

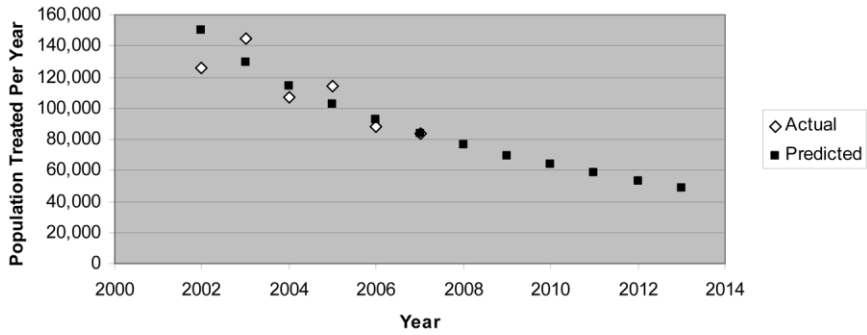

Fig. 2. Actual number of patients treated with antiviral therapy for hepatitis C per year between 2002 and 2007, and fitted line projecting future treatment rates.

vent only 14.5% of liver-related deaths caused by hepatitis C between 2002 and 2030.

These estimates were most sensitive to the number of patients treated and the selection of patients for treatment who are at higher risk for disease progression. The most influential variables are shown in Table 3; none of the other variables affected the results by more than 1%. If the discovery of new medications in the future increases rates of SVR to 75%, at current rates of treatment this would still only prevent 21.7% of liver-related deaths caused by hepatitis C. Only by increasing treatment rates by 75% and increasing SVR rates to 75% could more than half of the liver-related deaths be prevented.

Reasons for Lack of Treatment. Results from the NHANES questionnaire indicate that the primary reason for lack of treatment is lack of diagnosis, as shown in Fig. 4. Of the 133 respondents, 69 (proportion adjusting for sample weights 49%, 95% confidence interval [CI] 39%-60%) were previously unaware of their diagnosis, 12 (adjusted proportion 9%, 95% CI 3%-16%) did not follow up with a doctor about their hepatitis C, 33 (adjusted proportion 24%, 95% CI 15%-33%) were recommended by their doctor not to be treated, 8 (adjusted proportion 6%, 95% CI 1%-10%) refused treatment, and 11 (adjusted proportion 12%, 95% CI 4%-19%) were treated. This suggests that the largest barrier to treatment is failure to diagnose infection with hepatitis C. Physician recommendation appears to be the second most common reason why patients are not treated. Although the questionnaire does not provide sufficient medical detail to judge the appropriateness of these recommendations, it is concerning that 28% of the 100 subjects who had seen a doctor by the time of the survey had the understanding that no further follow-up for their hepatitis C was necessary.

Reasons for lack of treatment did not differ substantially by race or ethnicity. Males were slightly more likely to be unaware of their diagnosis (odds ratio [OR] 2.2, 95% CI 1.06-4.5), but less likely to have their doctor recommend treatment (OR 0.36, 95% CI 0.16-0.80). Despite this, the rates of treatment were identical between males and females. Not surprisingly, limited access to medical care appears to be a major barrier to diagnosis and treatment of hepatitis C. Respondents who lacked health insurance were more likely to be unaware of their diagnosis (OR 4.8, 95% CI 1.8-12.7) and less likely to be treated (OR 0.3, 95% CI 0.03-2.6). Additionally, respondents lacking a usual source of care were more likely to be unaware of their diagnosis (OR 19.0, 95% CI 2.4-148.1) and no respondents lacking a usual source of care had received treatment.

Discussion

In this study we estimated the number of patients currently receiving antiviral therapy for hepatitis C in the U.S., identified reasons for lack of treatment, and pro-

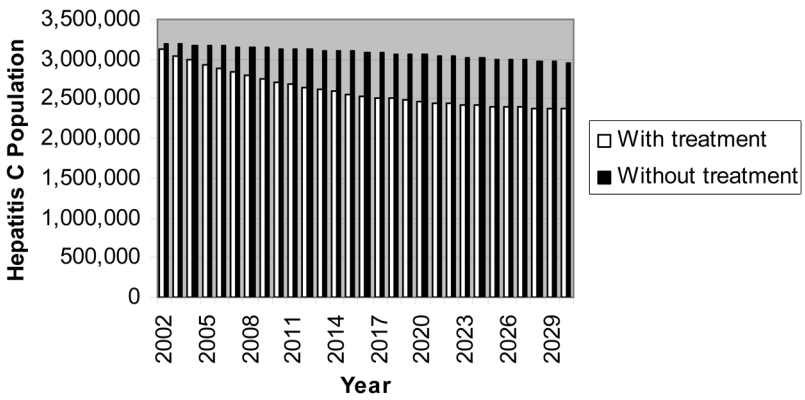

Fig. 3. Projected population size of people with chronic hepatitis C in the U.S., with and without antiviral therapy.

Table 3. Sensitivity Analysis of the Percentage of Liver-Related Deaths Between 2002 and 2030 Projected to be Prevented by Current Antiviral Therapy

Change from Base-Case Assumption	Liver-Related Deaths Prevented
50% more patients treated	30.2%
75% SVR	21.7%
Treated patients 100% more likely to die w/o treatment than untreated patients	29.0%
75% more patients treated, with 75% SVR	57.2%

SVR, sustained virological response. Variables not listed in this table had less than 1% impact on the results in sensitivity analysis.

jected the impact current therapy will have on preventing liver-related deaths over the next two decades. We found that relatively few patients have been treated with pegylated interferon, and treatment rates appear to be declining. These findings are similar to a recent report from Europe, in which treatment rates varied by country from <1% to 16% of hepatitis C patients ever treated.[27] If this trend continues, antiviral therapy may prevent fewer than 15% of liver-related deaths caused by hepatitis C in the U.S. between 2002 and 2030.

Fortunately, new treatments for hepatitis C are anticipated to become available in the next several years, which should increase rates of SVR among patients receiving treatment.[28] However, treatment first requires a diagnosis, and in this study we found that approximately half of all people with hepatitis C in the U.S. are unaware of their diagnosis. There are several possible reasons for this situation. First, lack of health insurance poses an obvious barrier to testing. In 2001, 30% of patients with hepatitis C were uninsured,[12] and this number has likely increased since that time. Second, because hepatitis C is usually asymptomatic, patients without any other medical problems may not seek medical attention. In the NHANES survey, we found that respondents lacking a usual source of medical care were 19 times more likely to be unaware of their diagnosis. This is unfortunate, because those patients without comorbidities may be the best candidates for antiviral therapy. Finally, identification of risk factors and testing for hepatitis C may be a low priority during a busy primary care appointment. It has been estimated that provision of all recommended preventative care would consume 7.4 hours of each primary doctor's day, leaving no time for other tasks.[29] Because the U.S. Preventative Services Task Force has concluded that insufficient evidence exists to recommend screening for hepatitis C, physicians may consider this a low priority.[30] Furthermore, physicians may not realize the value of diagnosing hepatitis C, because prior studies have identified limited knowledge about the disease among primary care physicians.[14] Thus, increasing the number of patients diagnosed will require education of the public and physicians alike, as well as attention to the worsening problem of the uninsured in the U.S.

Even if all patients with hepatitis C were aware of their diagnosis, a number of barriers to treatment would still remain. First, many patients will be ineligible for currently available antiviral therapy due to decompensated cirrhosis, comorbidities, or other reasons. Second, some patients may not follow up for further care, and others may not be referred to a specialist who prescribes antiviral therapy. In our study we could not differentiate between lack of referral by the primary physician versus lack of treatment by the specialist, but prior studies have suggested that lack of referral is a major barrier. In one survey of primary care physicians, 72% would not refer a patient with normal liver enzymes for treatment,[14] despite evidence that such patients can develop progressive disease.[31] Additionally, patients in some areas may have limited access to specialists who treat hepatitis C, because 20% of all gastroenterologists prescribe 80% of antiviral therapy in this country.[16] As mentioned above, it is possible that future improvements in antiviral therapy will increase enthusiasm for treatment among the medical community, and thus increase the number of patients treated. However, very little is known about health services delivery and quality of care for hepatitis C, and further research in this area is needed.

Although this study is the first to examine the public health impact of antiviral therapy for hepatitis C, it does have several important limitations. First, the Wolters Kluwer sample includes only commercial pharmacies, and does not include Veteran's Affairs pharmacies or patients treated in clinical trials. Therefore, it is possible that the true number of patients treated for hepatitis C each year in the U.S. is being underestimated. Conversely, NHANES estimates were used for the prevalence of hep-

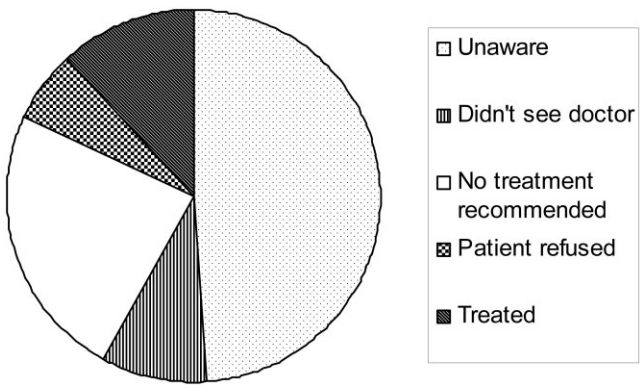

Fig. 4. Reasons for lack of treatment among respondents to the NHANES Hepatitis C Follow-Up Questionnaire (n = 133).

atitis C, which may themselves be an underestimate due to the exclusion of homeless and institutionalized individuals. Thus, because potential errors in the numerator and denominator lie in the same direction, estimates of the proportion treated may be reasonably correct. A second important limitation is that the NHANES questionnaire does not provide sufficient detail to thoroughly examine patient and physician decision-making about testing and treatment for hepatitis C. Finally, any attempt to predict the future is likely to be imprecise. Therefore, projections regarding future treatment rates and liver-related deaths are only intended to provide a rough overview of the public health impact of antiviral therapy. The strength of this study is that it provides the first look at nationwide practice patterns for treatment of hepatitis C.

In conclusion, despite tremendous advances in antiviral therapy, current antiviral therapy is projected to prevent fewer than 15% of liver-related deaths caused by hepatitis C between 2002 and 2030. One of the key findings of this study is that the future development of new and better medications will have a less than optimal impact on this problem unless more patients are diagnosed and referred for treatment. Increased public health efforts are needed to improve access to antiviral therapy for patients with hepatitis C.

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