Cost Effectiveness of Novel Treatment of Hepatitis C Virus in Lebanese Patients

Introduction:

The epidemiology of the hepatitis C virus (HCV) differs across countries. In 2012, prior to the introduction of direct acting antivirals (DAAs), an estimated 130–170 million persons (2%-3% of the world's population) were living with HCV infection.[1] According to the World Health Organization (WHO), the most affected regions are Africa and Central and East Asia, with Egypt having the highest rates in the world.[1] Moreover, in the United States, 3.2 million people are infected with HCV with a 1% prevalence.[2] Similarly, in Spain with 1% prevalence of HCV, 482,000 people are infected.[3] Nevertheless, these numbers have been decreasing not only with successful treatment but also with the increase in the number of treated patients.[2]

In a systematic review and meta-analysis describing the epidemiology of HCV in the Fertile Crescent region, HCV prevalence among the general population was at 0.2% in Iraq and Lebanon, at 0.3% in Jordan and at 0.4% in Syria.[4] More recent data has confirmed that in Lebanon, HCV-infected patients are limited in number with 0.199% viremic prevalence; 15% of infected patients acquired HCV from blood transfusions in 2007 and 9% acquired HCV from IV drug use in 2015.[5,6] A recently published study showed that the majority of lebanese patients diagnosed with HCV were mainly infected with genotype 1 (47%), followed by genotype 4 (33.9%).[7] In another study, Lebanon was considered an area of low HCV prevalence ranging from 0.16 to 1.22%, reaching higher prevalence of 27% among hemodialysis patients.[8]

In terms of disease staging, the Metavir liver fibrosis scale ranges from F0 (no liver damage) to F4 (compensated cirrhosis), whereearly stages of liver disease (fibrosis levels of F0, F1, or F2) are commonly confirmed in the majority of patient biopsy samples. [2] Consideration of treatment at early stages of liver disease is relevant to many HCV-infected individuals; However, effective and expensive treatment regimens remain a challenge to payers and other stakeholders who must consider the costs and health benefits of HCV treatment strategies[9]. Unfortunately, a high proportion of Lebanese patients with HCV-infected patients were diagnosed at an advanced liver fibrosis stage and at an age above 40 years, which indicates that the disease may still be undetected and untreated at early stages despite the availability of novel direct acting antiviral on the Lebanese

market[7]. The pressure on third party payers to provide full access to all HCV patients regardless of stage of disease warrants the need for a cost effectiveness study for better understanding of the impact of HCV on the budget and policies of the Lebanese health care system. Such pressure was due to recent evidence published in Europe, Canada and United States determining the cost of illness of HCV as well as the cost effectiveness of early treatment instead of delayed treatment with the highly effective novel therapy (DAAs). [9] The study by Leidner et al. is one example, determining the cost effectiveness of these new treatment regimens, focusing on initiation in early stages of the disease versus advanced stage, calculating cost and quality adjusted life years (QALY) gained after receiving HCV treatment.[10]

In the MENA region, Obach et al. have explored the cost-effectiveness of different treatment initiation strategies in Egypt, a country with economic issues and limited resources.[11] This study evaluated standard drug treatment regimens in addition to DAAs, and concluded that immediate HCV treatment of patients at early fibrosis stages was less expensive and more effective.[11]

Aim of the Study

The aim of the study is to assess whether initiation of novel DAAs at early stage of hepatitis C is cost effective in Lebanese patients starting at a given level of fibrosis. Such assessment could assist decision makers in choosing the timing to start DAAs in treating HCV-infected patients.

Ethics Approval:

The study has been approved by the Lebanese American University Institutional Review Board.

Method:

Analytic Overview: This study was conducted from the payer's perspective to evaluate cost effectiveness of two treatment strategies: delayed treatment (fibrosis stages F3 and F4) versus early treatment (fibrosis stages F0, F1, or F2). For a standard patient reaching late stages F3-F4, complications associated with the disease were assumed to occur and then incurred the cost of such complications to the cost of therapy for F3-F4 stages. The model followed a standard patient's QALY at different disease stage and throughout the disease progression.

Direct medical costs were identified and measured for each treatment strategy. Incremental cost effectiveness analysis was then conducted measuring the incremental cost per QALYs gained and per life year extended.

Model Details: The model was conducted based on the natural history of HCV infection during a one-year period, where patients in the early treatment strategy were treated with DAAs upon early diagnosis at F0-F1-F2 with 90% cure rate, while patients in the delayed treatment strategy were treated at F3-F4 stage of the disease following the course of disease progression presented in Figure 1. An efficacy rate, defined as achieving a sustained virology rate (SVR) 12 weeks after last treatment dose, was assumed equal to 90% in both treatment strategies. Such efficacy rate prevents overestimation of findings, since the efficacy of these novel drugs was reported to range from 85% to 99%, depending on the agent used, HCV genotype, and liver disease stages (efficacy of 95-99% for patients at early stage, and of 85-90% in patients with more advanced stages).[9,12] Also, these novel drugs were devoid of adverse events associated with the injection of pegylated interferon and other standard therapies.[9,12] Disease progression was simulated according to time of diagnosis and patient characteristics, known to be influential factors in the progression of liver fibrosis. An assumption was made that in each treatment strategy a standard patient was treated, with DAAs being used once per current practice in the region. We then calculated the average cost associated with treatment at F1-F2 versus cost of treatment at F3-F4 along with its associated disease complications. Annual transition probability of a standard patient from one disease stage to the next was adopted from the literature as listed in Table 2.[13-20] The time horizon of the analysis was the lifetime of a middle-aged patient with life expectancy at every stage based on the literature (12 years for patients in late stages vs. 20 years for patients in early stages).[13-20] Direct medical costs, QALYs and cost effectiveness analysis were computed to determine incremental direct medical cost per additional outcomes gained when disease is detected and treated at early stage versus at later stage.

Outcome Measures:[13-20] Outcome measures used in this model included life year expectancy and QALYs, while the model inputs were the duration of transit states or disease progression (probability of transitions). An extensive literature review was conducted gathering disease outcome variables from relevant studies that pertaining to our study analysis. Value based used in our analysis and other reported values are summarized in

table 2.[13-20] Variables retrieved for this model were probability, utilities, disease progression, complications and extended life years with treatment, and were either calculated as an average of available data, or adopted from one study that is very similar in design and population to our study. Disease progression from one stage to the next, life expectancy and QALYs were retrieved from different studies.[2,10,14] This study was complemented by a brief survey to verify assumptions of estimated data derived from the literature to country specific practice. The survey was completed by fouteen experts in the field(gastroenterologist and infectious diseases physicians) who practice in different institutions, and inquired about the most commom HCV genotype seen in their patients, the stages at which their patients were diagnosed, patients' clinical presentation upon diagnosis, prescribed medications, frequency of follow-up and the cost of disease including drug treatment and complications management.

Cost: Direct medical costs were identified from HCV diagnosis and management guidelines and then measured and valued using cost database from Lebanese third party payers. Costs included: cost of novel DAAs medications used in Lebanon (dual therapy (ledipasvir/ sofosbuvir) or triple therapy (paritaprevir/ ritonavir/ ombitasvir) +/- dasabuvir) for a 12-week-treatment cycle), laboratory testing (i.e. CBC, INR, HCV viral load), medical procedures for diagnosis (i.e. biopsy, Ultrasound), and complications cost (i.e. ascites, esophageal varices, hepatorenal syndrome, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma, and spontaneous bacterial peritonitis).

Identified costs were measured based on data from third party payers and from a private hospital. Novel therapies were used in our practice for certain patients and this analysis could clarify if significantly higher therapy cost is worth the higher therapy effectiveness. Furthermore, frequency of resources use and occurrence of events (i.e. frequency of hospitalization and physician visits, required diagnostic testing, and necessary complication drug and medical management) were estimated from the literature.[9,11]

Model Analysis and Assumptions:

Measured costs were valued based on the natural history of the disease. Thus, direct medical costs of early treatment for a patient diagnosed and treated at F0-F1-F2 were calculated as total expected costs at first year of receiving drug treatment along with medical follow-up and diagnostic tests, multiplied by the expected response

rate of 90% plus the failure rate of 10% of those who may progress to advanced stage requiring additional direct medical treatment (assumed the same as the one calculated for delayed treatment). Direct medical cost of delayed treatment when the patient was delayed treatment until F3-F4, was calculated based on transition probabilities of disease progression along with related complications, and probability of remaining stable at F4. Therefore, the expected annual cost of each advanced stage (Decompensated Cirrhosis (DC), Hepato-Cellular Carcinoma (HCC), and death) were multiplied by probabilities of occurrence during that one-year duration when receiving treatment, and values were used as reported in the literature.

Liver transplant was assumed not to be an option in Lebanon due to limited resources and expertise in this area, and therefore the probability of patient progressing to liver transplant was assumed equivalent to death. To facilitate computing costs of different variables, rounded numbers were used. To project usual course of the disease manifestations and treatment, a case scenario was simulated on a middle-aged patient with HCV who would undergo early treatment strategy versus delayed treatment strategy, and when in advanced stage, patient was expected to have transit probabilities with stage related utilities throughout disease progression. Data for the natural history of the disease and disease progression were adopted from HCV related guidelines and literature, as stated in Table 2.

Sensitivity Analyses were done on variables which are expected to alter the findings of the analysis such as drug cost of dual versus triple drug therapy, QALY at year one of receiving treatment at early stage, cost of major disease complications and use of medical facilities. As such, one-way sensitivity analyses were conducted as follow: a 25% decrease in dual drug cost to match cost of triple drug therapy, varying utility values between 0.8 and 0.9 for early disease stage, and a 10% increase in direct medical cost of disease complications among those receiving delayed treatment.

We expect this study to determine if early treatment could be a cost effective use of resources and if so, to identify the corresponding scenarios and threshold of direct medical costs. In the current era of evolving antiviral therapy for HCV infection, these results can support policy makers in their decisions to improve HCV screening at early stage and to guide disease management.

Results:

Cost data presented in table 1 highlighted that the burden of disease treatment was directly related to the novel drug therapy cost followed by the cost of managing complications related to advanced stage. Dual drug therapy and triple drug therapy costed 54,565 and 41,000 euro, respectively. Diagnostic tests, frequency of disease routine follow-up and complications were observed as expected in published guidelines, and related costs were estimated at around 10,000 euro per annual event occurrence (initial diagnosis 1,760 euro, symptoms management and follow up 7,400 euro, DC 11,656 euro, HCC 12,600 euro, liver related death 14,900 euro). Utilities and disease transition probabilities presented in table 2 showed that value-based used in model analysis were similar to those reported in several studies from different countries.

Initiation of treatment in a middle-aged HCV patient, as a case scenario, right after diagnosis atearly disease stage (F0-F2) was associated with a direct medical cost during the first year of 56,950 euro for projected 16 QALYs and life expectancy of 79 years throughout the disease. While direct medical cost during the first year when treatment was initiated at a later disease stage (F3-F4) would be 52,369 euro for projected 8.2 QALYs and a life expectancy of 76 years. Therefore, initiating DAAs treatment soon after diagnosis at early stage has led to an incremental cost effectiveness analysis (ICER) of 587 euro per QALY gained throughout the disease lifetime from time of diagnosis and treatment. On the other hand, when outcomes of such treatment were measured over only a one-year when the patient would receive drug treatment upon diagnosis at early stage instead of delaying treatment until an advanced stage, the ICER was 27,268 euro per QALY gained at year of receiving treatment. In addition, when extended life-year was used as an outcome measure, the analysis showed that early treatment is associated with 1,527 euro per additional life year extended.

Sensitivity analysis showed that with a 25% decrease in the cost of dual drug option, the incremental cost was decreased to 16,982 euro per QALY gained at year of receiving treatment. On the other hand, changing utility measures to the lower (0.8) and upper (0.9) values, led to varying incremental cost to 38,822 and 24,177 euro per QALY gained at year of receiving treatment. In addition, a 10% increase in medical cost of complications at advanced stage made early treatment strategy dominant with a saving of 656 euro.

The response rate to all survey questions was 36%. This survey was run to test the estimated values retrieved from the literature and used in this analysis. The survey results revealed that the most common genotypes were genotype 1a and 1b. Initial diagnosis is done at F2-F3 stage of the disease for the majority of patients, who commonly present with jaundice, nausea and right upper quadrant pain, while some patients present with extrahepatic manifestation and end stage liver disease. Questions related to treatment revealed that dual therapy with ledipasvir/sofosbuvir is the antiviral therapy of choice, with follow-up visits every 3 to 6 months depending on the stage of HCV. More than 80% of hospitalized patients are with stages F3-F4 of the disease, with more frequent hospitalization when in F4. While respondents were hesitant to provide cost estimation, 80% of them estimated annual cost of hospital admissions due to complications was around 25,000 euro. It is worth noting that this cost estimation was higher than the estimated cost computed from in-house data in our study, and for which sensitivity analysis was conducted to test results sensitivity to complications related costs.

Discussion:

In Lebanon, access to HCV treatment at early stage of the disease is challenging and limited depending on reimbursement policies of different public and private third party payers. DAAs are proven to be at least 90% effective and may prevent disease progression into more advanced cirrhotic stages. However, because of their high cost, they are limited to advanced stages of disease by several payers. Willingness to scale-up treatment coverage requires evidence based-cost effectiveness analysis to justify the high cost for the expected outcomes. Based on this study analysis using country specific cost data and based on current practice and guidelines of HCV patient management in Lebanon, the findings reveal that initiating DAAs at early stage of the disease could be considered a cost effective option. This option was associated with 1,527 euro per additional life year extended, 587 euro per QALYs gained when projecting the benefits throughout the disease lifetime, and 27,268 euro per QALYs gained at first year of receiving DAAs.

Sensitivity analysis indicates that the results are sensitive to the utility values), suggesting maintaining utility at a minimum of 0.85. While lower values of cost related to disease complications were used in the original analysis in order to avoid overestimating the findings, a 10% increase in these costs favored early treatment

strategy with a saving of 656 euro. On the other hand, a 25% in the cost of dual therapy led to significant improvement in the ICER value, with a decrease from 27,268 euro to 16,982 euro, which could encourage decision-making to adopt early treatment option and negotiate DAAs cost coverage agreement.

Furthermore, these findings support results reported by previous studies. Chahal et al. showed that treating all patients regardless of stage status (F0-F4) had an ICER of $39,475 per QALY gained compared to restricting treatment to advanced stages (F3/F4).[21] Chidi et al. showed that giving full access to all patients proved cost effective, costing $21,410 for 6.31 QALYs.[22] Leidner et al. showed that initiating treatment at F2 was a cost effective strategy with an incremental cost of $37,300 per QALY gained compared to diagnosis at F2 and treatment at F3, and being sensitive to the high cost of novel therapy.[10] When comparing Lebanon to other countries in the MENA region, it was shown that the majority of Lebanese HCV patients were 40-59 year-old and were at advanced fibrosis stage at diagnosis. Also, 47% of patients had HCV genotype 1 and 33.9% genotype 4, which differs from genotypes in other countries in the region where genotypes 4 and 2 were the most prevalent in Egypt, Algeria, Morocco, and Tunisia.[7] Along with the brief survey results, findings of these studies support that F4 is the most commonly diagnosed stage and resulting in delayed treatment, as per patient case scenario used. On the other hand, similar to our country, other MENA region and developing countries have been faced with concern related to cost effectiveness of HCV novel therapies. For instance, decision makers in Egypt are required to prioritize HCV treatment due to economic constraints and despite high prevalence of HCV.[11]

Similar to other studies, our findings would encourage policy makers to pay for early disease detection and treatment despite the high drug cost, as this cost could be worth the clinical effectiveness, the quality of life and the prevention of disease progression and complications.[10,13,22] The more DAAs treatment option is used instead of IFN/RBV, the lower the HCV prevalence would be in a decade.[23,24] Other alternatives, like boceprevir- and telaprevir-based therapies, were also cost effective but mainly for F3-F4 stages, suggesting that novel therapies may be preferred in HCV to optimize resource utilization.[25]

Because of its strengths, this study is a particularly appealing in the field of pharmacoeconomics. The authors selected the outcome measures based on an extensive literature review identifying several studies with high level of evidence-based medicine.[12,20] Also, they gathered information from field experts in the region using local survey to minimize the likelihood of overestimating the analysis. In addition, there was no discrepancies between the values of medical costs retrieved from private and public reimbursement bodies. Finally, in order to avoid overestimation of the results, the analysis was performed using the higher cost of the two available drug treatment options in our country, the lower cost range of medical follow-up and diagnostic testing, and the lower levels of utilities to account for the socio-economic situation of the Lebanese population. On the other hand, a major study limitation is the lack or limited access to complete in-house data measuring real life effectiveness data in HCV patients in Lebanon to reflect current application of clinical guidelines, outcomes measures and disease progression.

Conclusion:

In the current era of evolving antiviral therapy for HCV infection, this study showed that early treatment with DAAs could be cost effective compared to delayed treatment and thus reinforces the need to screen for HCV at early age so that novel therapy is initiated as soon as diagnosis is confirmed. Reimbursement bodies and decision makers could also refer to this study when reviewing policies related to Hepatitis C management.

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