A Thesis

titled

The Cost-Effectiveness of Treatments in Non-Cirrhotic Saudi Arabian Patients with Genotype 1 and Genotype 4 Chronic Hepatitis C

by

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Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Master in science Degree in pharmaceutical science

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April 2017
An Abstract of
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Objectives:
Chronic Hepatitis C (CHC) is a costly disease to treat considering the development of the Direct Acting Antivirals (DAAs). In Saudi Arabia, economic changes require pharmacoconomic evaluations to allocate resources properly. The research aimed to (1) estimate the total costs of hepatitis C treatment choices recommended by the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) based on data from the Saudi Food and Drug Authority (SFDA), (2) develop and operationalize the decision tree model and calculate the base-case incremental cost-effectiveness ratio (ICER), (3) perform deterministic and probabilistic sensitivity analyses testing the underlying assumptions in the decision tree model.
**Method:**

A cost-effectiveness analysis was performed on a hypothetical cohort comparing different chronic hepatitis C treatment strategies from the Saudi Food and Drug Authority’s (SFDA) perspective over a three-month period using a decision tree model. Data for this study were obtained retrospectively from the (SFDA) and published literature. Costs were measured in United States Dollars (USD). Life-years gained (Ly) were the outcomes measured in this study. Since the SASLT guidelines differ between genotype 1 and genotype 4, there were two separate decision tree models and analyses for each genotype cohort at a willingness to pay (WTP) of $65,000.

**Result / Discussion:**

In genotype 1 base-case analysis, the incremental cost-effectiveness comparison between the interventions showed that both Elbasvir/Grazoprevir and Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir with Ribavirin dominated Sofosbuvir with Simeprevir and Ledipasvir/Sofosbuvir. Against Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir with Ribavirin, the ICER was $33,796/Ly for each additional cure. In genotype 4 base-case analysis, Paritaprevir/Ritonavir/Ombitasvir with Ribavirin dominated Sofosbuvir/Ledipasvir and Sofosbuvir with Simeprevir. Except for Sofosbuvir with Simeprevir, the interventions compared in genotype 1 are competitive and cost effective while in genotype 4 Paritaprevir/Ritonavir/Ombitasvir with Ribavirin is highly recommended. Interventions in both genotypes will be dominated by Sofosbuvir low-priced generics with Simeprevir.
I dedicate this work to my family and friends who supported me throughout my life
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List of Abbreviations

CEA..........................Cost-Effectiveness Analysis
CER..........................Cost-Effectiveness Ratio
CHC .........................Chronic Hepatitis C
DAAs ......................Direct Acting Antivirals
DSA..........................Deterministic Sensitivity Analysis
G1-7 .......................Genotype 1 to 7
GDP .......................Gross Domestic Product
HCV .......................Hepatitis C Virus
ICER .....................Incremental Cost-Effectiveness Ratio
IL28B ......................Interleukin 28B
INF-α ......................Interferon Alfa
KACST .....................King Abdulaziz City for Science and Technology
Ly .........................Life-Years Gained
MOH .......................Ministry of Health
NS3/4A ....................Nonstructural Protein S3 and 4A
NS5A .......................Nonstructural Protein 5A
NS5B .......................Nonstructural Protein 5B
PHC .......................Primary Healthcare Center
PSA .......................Probabilistic Sensitivity Analysis
QALY .....................Quality-Adjusted Life-Year
RNA..........................Ribonucleotide Acid

SASLT ....................Saudi Association for the Study of Liver Diseases and Transplantation

SCOT ......................Saudi Center for Organ Transplantation

SFDA ......................Saudi Food and Drug Authority

SVR .........................Sustained Virologic Response

USD .........................United States Dollars

WHO .........................World Health Organization

WTP .........................Willingness to Pay
List of Symbols

There are no symbols to be indicated
Chapter 1

Introduction

1.1 Background

Hepatitis C is a viral infection carried by the bloodstream which infects liver cells. After the replication of the virus, Ribonucleic Acid (RNA) within the infected liver cells continues to spread to other liver cells, causing hepatitis C. The virus upon prolonged incubation beyond 24 weeks is considered a chronic infection. The implications of this disease may lead to liver fibrosis, liver cirrhosis, liver cancer, or death. Hepatitis C virus (HCV) is a blood-borne virus that is transmitted via unsterile syringes or similar equipment which injects drugs into the bloodstream or by blood donation. With no vaccination developed for hepatitis C virus, the best way to prevent this infection is by avoiding these behaviors, using sterilization, or blood screening. Hepatitis C virus infection through occupational, perinatal, and sexual contact happens less frequently than percutaneous exposures. There are 7 genotypes of hepatitis C virus and more than 100 subtypes, each has their characteristics and prevalence worldwide and respond differently to treatment. Furthermore, there are possibilities that one individual can be infected with more than one genotype. The virus genotype and degree of liver damage are used to guide disease management and treatment decisions.
Chronic Hepatitis C (CHC) is one of the world’s major causes of liver disease and a potential cause of mortality and morbidity with 500,000 deaths each year.\textsuperscript{7,8} 130-175 million individuals worldwide are infected with HCV.\textsuperscript{8} Chronic hepatitis C genotype prevalence differs depending on the region and geographical distribution of the population. Genotype 1 and genotype 4 are the most prevalent genotypes worldwide with approximately one-third of the cases occurring in East Asia and Africa.\textsuperscript{7} Only one genotype 7 infection has been reported, and it was linked to a Central African immigrant in Canada.\textsuperscript{5,6,9,10}

In Saudi Arabia, between 100,000 and 110,000 individuals are infected with CHC.\textsuperscript{11} Genotype 4 followed by genotype 1 are considered more prevalent than other genotypes in Saudi Arabia while genotype 3 and genotype 6 are found in extremely rare cases.\textsuperscript{12} The Ministry of Health (MOH) in Saudi Arabia stated that 1,327 new cases of Hepatitis C were identified in 2015 with an incidence rate of 4.21 per 100,000 population.\textsuperscript{13} Although it is hard to measure hepatitis C virus prevalence in Saudi Arabia, blood testing and screening suggest a prevalence rate of 0.4\%-1.1\% of the total population.\textsuperscript{14,15} Linkage to care and treatment is critical in improving health for individuals found to be infected with hepatitis C virus. Such linkage is important considering major developments in hepatitis C virus treatments. With these developments, the epidemiology of the disease could differ within the upcoming years.

Over the last 25 years, hepatitis C virus treatments developed from the first approved treatment alfa interferon (INF-\(\alpha\)) in 1991, which had a poor sustained virologic response (SVR) to the scientific breakthrough of the Direct Acting Antivirals (DAAs).\textsuperscript{14} Pegylated-interferon was developed and approved in 2001 for HCV
treatment in combination with ribavirin. Boceprevir and Telaprevir were the first-generation DAAs approved for HCV treatment in 2011, but they were discontinued within two years consequently of second-generation DAAs approval. These second-generation DAAs shows a promising future in eradicating this virus infection. Thus, they are now the standard-of-care for hepatitis C virus treatment in Saudi Arabia recommended by the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT).

These drugs in Saudi Arabia cost between $58,000 – $67,000 for 12 weeks of treatment in retail pharmacies based on Saudi Food and Drug Authority’s (SFDA) price regulations.

1.2 Pharmacoeconomics

In recent years, pharmacoeconomic evaluation has been introduced to healthcare technology assessment organizations expanding the spectrum of economic evaluations and outcomes research. Pharmacoeconomics is defined as the branch of economic evaluations that deals with pharmaceutical products and different disease management strategies. The aim of pharmacoeconomic evaluation is to allocate health resources to obtain optimum value for patients and healthcare organizations. Pharmacoeconomic evaluation key components are:
• The perspective of the evaluation: it determines the viewpoint of the study and indicates which costs and outcomes to be included in the evaluation. There are several perspectives for a pharmacoeconomic evaluation such as payer, provider, government, patient, or society. Few evaluations have been studied from societal perspective while provider and payer perspective were the common viewpoint in most economic evaluations.

• Time horizon of the study: it indicates the length of consequences following the studied population on the evaluated strategies outcomes and costs to be included in the evaluation model. Annual discounting for outcomes and costs is determined by the time horizon of the evaluation as well.

• Costs: the monetary value calculated for each strategy in comparison based on the perspective of the evaluation. Costs included in the evaluation could be: direct medical costs (such as drug cost), direct nonmedical costs (e.g. transportation costs to the hospital), indirect nonmedical costs (e.g. cost of missing work), intangible costs (i.e. unquantified costs that are difficult to measure such as cost of pain or grief), and opportunity costs (i.e. cost lost due to chosen one strategy instead of the alternative).

• Outcomes: it is the consequence of each treatment or strategy in comparison. Can be divided into three different categories: economic outcomes, clinical outcomes, and humanistic outcomes. Economic outcomes are the direct, indirect, and intangible costs for each treatment strategy. Humanistic outcomes are the consequences on the patient’s quality of life or functional activities after treatment. Clinical outcomes are the medical effects on the patient resulted from
managing a disease or from treatment. The outcomes could also be categorized as final outcomes (e.g. years of life gained) or intermediate outcomes (e.g. reduction in blood pressure).

There are two types of pharmacoeconomic evaluation depending on the evaluation components measured:

- Partial pharmaco-economic evaluation: which are cost analysis, cost of illness analysis, and cost-minimization. Cost analysis and cost of illness analysis are used to estimate the costs related to certain diseases or health states in a defined population with no comparison with other alternatives. In cost-minimization analysis, the outcomes are equal for each strategy which favor the decision for the least expensive comparator.

- Full pharmaco-economic evaluation: which are cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. Cost-benefit analysis measures in monetary units both costs and outcomes of each strategy compared which is useful to compare different medical services or programs. Cost-utility analysis captures the patient preferences by integrating quality and quantity of patient-years expressed as Quality-Adjusted Life-Years (QALY) in the outcomes of each strategy. Cost-effectiveness analysis compares different outcomes (intermediate or final) of each strategy in natural units (nonmonetary units). The main difference between these analyses is based on the unit of outcomes measured (i.e. dollar, QALY, life expectancy) and whether the outcomes are final or intermediate.
Due to the complications in converting outcomes into monetary values and difficulties measuring the intangible and indirect costs, societal perspective and cost-benefit analysis are barely used.

The scarce healthcare resources and budget cutoffs in different healthcare management organizations have increased the importance of pharmacoeconomic evaluation. These pharmacoeconomic evaluation techniques are used by healthcare practitioners in decision making and budget control among different aspects of applied pharmacoeconomics.

1.3 Cost-effectiveness Analysis

Cost-effectiveness analysis (CEA) is a full pharmacoeconomic evaluation that compares outcomes and costs of different treatment strategies to determine the best value to return for the strategy’s expenditure. Cost-effectiveness analysis is interchangeably mistaken with cost-utility analysis. The main difference from cost-utility analysis is the ability to use intermediate or final outcomes in the analysis while cost-utility analysis uses QALY’s as an outcome. Costs in cost-effectiveness analysis are measured in monetary values. The result of the cost-effectiveness analysis is expressed as a ratio called the Incremental Cost-Effectiveness Ratio (ICER) which is the additional cost and effectiveness gained in comparison to alternative strategies. The ICER is calculated by dividing the difference between two interventions’ cost on the difference between their outcomes. The results can also be interpreted using the cost-effectiveness plane which is a four-quadrant diagram (quadrant I upper right, quadrant II upper left, quadrant III lower left, and quadrant IV lower right) explained in (Figure
1.1). Dominance in CEA results represents an intervention’s low cost and high effectiveness to other comparators. Cost-effectiveness analysis allows comparison of different health outcomes such as life-years gained, reduction in blood pressure, weight loss, and smoke prevention. Each healthcare provider or payer set a ceiling price for any intervention or medical service called the willingness to pay (WTP) threshold. By the World Health Organization (WHO) approach, the WTP threshold can be set arbitrarily by estimating it to be less than three-folds the country’s Gross Domestic Product (GDP) per capita. ICER’s below the WTP threshold are considered in the decision-making.

![Image of Cost-effectiveness plane](modified)

**Figure 1.1: Cost-effectiveness plane (modified)**

C1-6: component 1 to 6, WTP: willingness to pay, Q I-IV: quadrant I to IV, C1: comparator is more effective, less expensive, and below the WTP, C2: comparator is more effective, more expensive, and below the WTP, C3: comparator is less effective, less expensive, and below the WTP, C4: comparator is more effective, more expensive, and above the WTP, C5: comparator is less effective, less expensive, and above the WTP, C6: comparator is less effective, more expensive, and above the WTP.
This kind of analysis is commonly used in pharmacoeconomic evaluations due to the wide outcomes that could be used. Several countries (e.g. UK, Australia, Germany) use cost-effectiveness analysis as part of their national formulary decisions and public policy making.\textsuperscript{23,24}

### 1.4 Need for Study

The total health care expenditure associated with chronic hepatitis C in Saudi Arabia is difficult to determine due to lack of literature. In 2015, the Saudi Arabian government spent 7.25\% ($16.5 billion) of total expenditures on health.\textsuperscript{14} With the new recommendations to prioritize the new DAAs as first-line therapy in the treatment of chronic hepatitis C, it became a huge burden on every country, considering the high cost of treatments. Furthermore, adding the cost of preventing and monitoring chronic hepatitis C and its complications (such as liver cirrhosis, fibrosis, or cancer), extending the treatment in experience-patients, or co-infection with other disease states, the economic burden on governments and health organizations is continuing to grow. In 2014, there were 198 liver transplants in Saudi Arabia reported by the Saudi Center for Organ Transplantation (SCOT) with a total cost of $18,386,000, the expert panel estimated that 45\% of total liver transplantation in Saudi Arabia is attributed to HCV.\textsuperscript{26,27} Thus, chronic hepatitis C is an expensive disease to manage for all managed care organizations which require economic allocation of resources toward medication selection and purchases to avoid huge budget impacts.\textsuperscript{28} Although healthcare system in
Saudi Arabia is provided and monitored by the Ministry of Health (MOH), drug registration is regulated and monitored by the drug sector in the Saudi Food and Drug Authority (SFDA) while branded drugs’ patency is obtained from King Abdulaziz city for science and technology (KACST).\textsuperscript{29-31} Patients in Saudi Arabia prefer branded drugs over generics and can purchase these expensive drugs from retail pharmacies without a prescription.\textsuperscript{24} With the treatments’ high prices and new DAAs developed, more pharmacoeconomic studies should be considered prior to giving recommendations by government agencies and hospital’s formulary committees in Saudi Arabia. The determinant of treatment guidelines in Saudi Arabia is based on clinical experience and expert judgment. Although pharmacoeconomic studies are helpful, decisions should not be based solely on them. The use of pharmacoeconomic analyses takes into consideration the clinical and economical perspectives. Therefore, it will be helpful and more efficient for improved judgment and budget control rather than relying on educated guesses or one-sided perception. Saudi Arabia is currently experiencing a new economic phase where pharmacoeconomic studies will be considered greatly.\textsuperscript{32-35} Additionally, due to the lack of pharmacoeconomic studies in Saudi Arabia, this study attempts to fill this gap and add a pharmacoeconomic perspective for decision makers in the government or hospitals regarding budget control and disease guidelines. Considering the benefits of these studies could lead to conducting further studies on different diseases in Saudi Arabia. Also, filling the gap in current literature will encourage future studies in the pharmacoeconomic field.
1.5 Goal of the Study

The goal of this study is to determine the cost-effective choice between chronic hepatitis C genotype 1 and genotype 4 treatments recommended by the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) from the perspective of the Saudi Food and Drug Authority (SFDA).

1.6 Specific Aims

1.6.1 To estimate the total costs of hepatitis C treatment choices in Saudi Arabia based on data from the Saudi Food and Drug Authority (SFDA).

1.6.2 To develop and operationalize the decision tree model and calculate the base case incremental cost-effectiveness ratio (ICER).

1.6.3 To perform deterministic and probabilistic sensitivity analyses testing the underlying assumptions in the decision tree model.
Chapter 2

Literature Review

In this chapter, there will be an overview of topics related to this study which are: chronic hepatitis C, hepatitis C epidemiology and treatments, the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) guidelines, hepatitis C economic burden and Saudi Arabian economy, and Saudi Arabian health system and the role of the Saudi Food and Drug Authority (SFDA).

2.1 Chronic Hepatitis C

Hepatitis C is a blood-borne viral infection carried via HCV through the bloodstream to infect liver cells.\textsuperscript{36} Depending on the incubation period, the disease could be acute or chronic. The implications of this disease may lead to liver fibrosis, liver cirrhosis or liver cancer and death. Injectable drugs users are the most susceptible population to HCV.\textsuperscript{1,3} With no vaccination developed for HCV the best way in preventing this infection is by avoiding these behaviors or using sterilization or blood screening. HCV infection through occupational, perinatal, and sexual exposures occurs with much less efficiency compared with percutaneous exposures. Thus, they are
unlikely to be a major source of new HCV infections.\textsuperscript{3} HCV (positive single-stranded virus) attack the liver’s RNA strand to begin the replication process.\textsuperscript{2} To be able to replicate, the virus creates nonstructural proteins (e.g. NS3, NS4A, NS5B).\textsuperscript{2} The replication process requires NS5B polymerase and NS3/4A protease.\textsuperscript{2} Drugs targeting the viral replication showed positive results in curing the patients.\textsuperscript{2,5} Innate clearance of the viral load in response to an acute infection had been related to Interferon alfa treatment and the presence of interleukin 28B (IL28B) gene.\textsuperscript{2,20,21} Acute hepatitis C infection is usually undiagnosed by the host (asymptomatic).\textsuperscript{2,3,5} The presence of viral RNA in the bloodstream for 12-24 weeks is diagnosed as chronic hepatitis C.\textsuperscript{2} There are seven genotypes of CHC, of which most studies were conducted on the first six genotypes.\textsuperscript{2,5} Hepatic decomposition and portal hypertension from CHC progression are symptomatic; hence the host gets diagnosed.\textsuperscript{2,5} Undetected or incurable CHC burden the patient’s vital systems, by complications such as cirrhosis or hepatocellular carcinoma, and could lead to death.\textsuperscript{1,2,5}

2.2 Epidemiology of Chronic Hepatitis C

Hepatitis C virus is one of the major causes of liver disease worldwide and a potential cause of mortality and morbidity infecting at least 150 million individuals and responsible for 500,000 deaths.\textsuperscript{1,2,7,8} Considering the way HCV is transmitted, drug addictive people would be the most susceptible population to be infected.\textsuperscript{1} CHC genotypes prevalence differ depending on the region and geographical distribution. Messina et al. reviewed 1,217 studies representing 117 countries and 90\% of the global
population, and they reported that G1 is the most prevalent worldwide (46.2% of all CHC cases), one-third in East Asia. Genotype 1 and genotype 2 endemic strains are found in West Africa, genotype 3 in South Asia, genotype 4 in the Middle East and Central Africa, genotype 5 in Southern Africa, genotype 6 in South East Asia, and only one genotype 7 infection in Canada (Figure 2.1).1,9,10 In the United States between 2.7 and 4.1 million people, including 35% of patients on the wait list for liver transplant, are suffering from CHC.7

In Saudi Arabia, between 100,000 and 110,000 individuals are infected with CHC.11 Genotype 4, followed by genotype 1, is considered more prevalent than other genotypes in Saudi Arabia, while genotype 3 and genotype 6 are found in extremely rare cases.12 The Ministry of Health (MOH) in Saudi Arabia stated that 1,327 new cases of Hepatitis C were identified in 2015 with an incidence rate of 4.21 per 100,000 population.14 Although it is hard to measure HCV prevalence in Saudi Arabia, studies done on blood donation centers suggested a prevalence rate of 0.4%-1.1% and an average age of 40 years (Figure 2.2).15,27 A study estimated that 200,000 hepatitis C Saudi patients would develop cirrhosis within the next 20 years, of them 1,500 new cases of hepatocellular carcinoma each year.37 Considering the major advancements that have been made in HCV treatments, the epidemiology of the disease would differ within the upcoming years.
Figure 2.1: Chronic hepatitis C prevalence worldwide

Figure 2.2: Age distribution of HCV infections in Saudi Arabia
2.3 Treatments for Chronic Hepatitis C

HCV treatments over the last 5 years showed promising development. From the first approved treatment Interferon Alfa (INF-α) in 1991, which had a poor sustained virologic response (SVR), to the scientific breakthrough of the Direct Acting Antivirals (DAAs). Pegylated-Interferon was developed and approved in 2001 for HCV treatment in combination with Ribavirin. Patients carrying the Interleukin 28B (IL28B) genotype CC has high response rate to Ribavirin and pegylated-Interferon treatment than other genotypes. Boceprevir and Telaprevir were the first-generation DAAs approved for HCV treatment in 2011. These treatments were discontinued in practice upon the approval of Sofosbuvir and Simeprevir in 2013 for HCV treatment. In 2014, Ledipasvir, Ombitasvir, and Paritaprevir were also approved, followed by Ritonavir, Dasabuvir, and Daclatasvir in 2015. Grazoprevir and Elbasvir were approved for HCV treatment in 2016. Sofosbuvir was among the first DAAs to reach a cure rate above 90% with an SVR after 12 weeks of treatment. Despite similarities in the mechanism of action of these new drugs, Sofosbuvir and Dasabuvir are the only approved drugs inhibiting HCV nonstructural protein 5B (NS5B) polymerase, the key enzyme mediating viral replication. Ledipasvir, Ombitasvir, Elbasvir, and Daclatasvir inhibit HCV nonstructural protein 5A (NS5A) that serves a role in viral replication, assembly, and secretion. Other drugs inhibit HCV nonstructural protein S3 and 4A (NS3/4A). These second-generation DAAs are now the standard-of-care for HCV treatment in Saudi Arabia as recommended by the SASLT (Table 1).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name in Saudi Arabia</th>
<th>FDA Approve date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Copegus®</td>
<td>1988</td>
</tr>
<tr>
<td>Pegylated Interferon</td>
<td>Pegasys®</td>
<td>2001</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Olysio®</td>
<td>November 2013</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi®</td>
<td>December 2013</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>Harvoni® (Ledipasvir/Sofosbuvir)</td>
<td>October 2014</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir</td>
<td>Viekirax®</td>
<td>December 2014</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td>July 2015</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>Exviera®</td>
<td>July 2015</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza®</td>
<td>July 2015</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Zepatier®</td>
<td>January 2016</td>
</tr>
</tbody>
</table>

Table 2.1: Currently approved chronic hepatitis C medications in Saudi Arabia.\textsuperscript{14,18} NS3/4A protease inhibitors end with suffix ‘previr”, NS5A inhibitors end with the suffix “asvir”, and NS5B inhibitors end with the suffix “buvir”.\textsuperscript{14} These treatments in Saudi Arabia cost between $58,400 – $66,400 for 12 weeks of treatment in retail pharmacies based on Saudi Food and Drug Authority’s (SFDA) price regulations.\textsuperscript{20} Hospitals might have different prices for these medications depending on the source of supply.\textsuperscript{21}
2.4 The SASLT Guidelines

The Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) treatment recommendations for CHC genotype 1 are an Interferon-free regimen with a preference for Ledipasvir/Sofosbuvir and Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir as the first line of therapy. In genotype 1b non-cirrhotic treatment-naïve patients these two treatments have the same regimen of a single dose daily for 12 weeks of treatments while for genotype 1a patients with the same conditions, the only difference is the addition of Ribavirin to the Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir regimen. Sofosbuvir is given for 12 weeks for genotype 1a, genotype 1b, and genotype 4 treatment-naïve patients without cirrhosis in separate combination with Pegylated-Interferon, Simeprevir, or Daclatasvir. For genotype 4 treatment-naïve patients without cirrhosis, a single dose of either Ledipasvir/Sofosbuvir, Paritaprevir/Ritonavir/Ombitasvir with Ribavirin, or Sofosbuvir in combination with pegylated-Interferon, Simeprevir, or Daclatasvir is recommended for 12 weeks of treatment. The preferences between these treatments are guided by the SASLT grading from A to D which is based on evidence quality. Grade A recommendations have one randomized control trial done on the treatment at least while grade B is based on high-quality systematic reviews and cohort studies. Grade C and D recommendations are based on experts’ opinions or nonanalytic studies. Moreover, there are two strength levels: level 1 recommendations are strong and based on high-quality evidence of patients outcome and cost, level two recommendations are weak in evidence quality and certainty. SASLT treatment recommendations and grades for CHC are shown in (Table 2.2).
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Genotype 1a (Grade)</th>
<th>Genotype 1b (Grade)</th>
<th>Genotype 4 (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir/Ledipasvir</td>
<td>12 weeks (A1)</td>
<td>12 weeks (A1)</td>
<td>12 weeks (B1)</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>12 weeks (A1)</td>
<td>12 weeks (A1)</td>
<td>12 weeks (B1)</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir</td>
<td>12 weeks (A1)</td>
<td>12 weeks (A1)</td>
<td>12 weeks (A1)</td>
</tr>
<tr>
<td></td>
<td>with Dasabuvir and</td>
<td>with Dasabuvir</td>
<td>(with Ribavirin)</td>
</tr>
<tr>
<td></td>
<td>Ribavirin</td>
<td>(with Ribavirin)</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir with Pegylated-Interferon</td>
<td>12 weeks (B1)</td>
<td>12 weeks (B1)</td>
<td>12 weeks (B2)</td>
</tr>
<tr>
<td></td>
<td>with Ribavirin</td>
<td>with Ribavirin</td>
<td>(with Ribavirin)</td>
</tr>
<tr>
<td>Sofosbuvir with Simeprevir</td>
<td>12 weeks (A1)</td>
<td>12 weeks (A1)</td>
<td>12 weeks (B1)</td>
</tr>
<tr>
<td>Sofosbuvir with Daclatasvir</td>
<td>12 weeks (B1)</td>
<td>12 weeks (B1)</td>
<td>12 weeks (B2)</td>
</tr>
</tbody>
</table>

Table 2.2: SASLT treatment recommendations for non-cirrhotic treatment-naïve patients with genotype 1a, 1b, and 4 chronic hepatitis C

2.5 The Economy of Saudi Arabia and Hepatitis C Burden

Saudi Arabia is one of the largest consuming markets of pharmaceuticals in the middle east and southeast of Asia. In the 2016 census, the country’s population was 31 million people. Oil and hydrocarbons account for 90% of Saudi Arabia’s economy and revenue. Current low prices of oil are reflected in the government’s budget through a deficit of $96.5 billion in 2015. These changes in oil prices guided the
government approval to a comprehensive reform of the country’s economy plan, called the national transformation plan (Vision 2030), to vary revenues away from oil sectors within 15 years.33

With the new recommendations for guidelines stewardships globally to prioritize the new DAA’s as first-line therapy for CHC, it became a huge economic burden on every country (especially in developed countries with high prevalence). Furthermore, considering preventing and monitoring the disease the burden is continuing to grow. Also, adding the costs for the medications will create an even bigger burden. Medications cost for 12 weeks of treatments in Saudi Arabia is around $58,400-$66,400 per patient. Furthermore, the burden will continue to grow when treatment extension to 24 weeks, CHC manifestations, or co-infections (which is common in CHC patients) exist. In a 2014 study on Saudi population, HCV burden was projected to increase incidence in hepatocellular carcinoma (190%) and liver-related mortality (225%) by 2030 in the absence of DAAs.27 The cure rate, shorter duration, and fewer side effects of the DAAs bring perspective to their high cost in comparison to previous treatments. With proper economic evaluation analysis, healthcare organizations can predict their budget impact on these treatments and make an informed decision. In Saudi Arabia, there are several challenges for establishing such evaluations.24 Such challenges include; lack of expertise, establishing a WTP, government overbears treatments, and hospitals fixed budgets.24 Furthermore, the lake of a pharmacoeconomic advisory commission, like the National Institute for Health and Clinical Excellence (NICE) in the UK, may hinder the application of
pharmacoeconomic evaluations. Such advisory can be established jointly by the SFDA, the MOH, and Saudi experts in the field.

2.6 Health System in Saudi Arabia and the Role of the SFDA

In Saudi Arabia, the healthcare system is a structure of integrated health services provided and monitored by the Ministry of health (MOH) which is the major governmental provider in Saudi Arabia. Currently, The MOH represents 60% of the health system with a total of 244 hospitals and 2,037 primary healthcare centers (PHC). Other governmental providers include referral hospitals (including military and specialty hospitals), university hospitals, and red crescent emergency services (Figure 1). Those government bodies jointly operate 39 hospitals. Referral hospitals mostly provide health care to a defined population, usually their employees and dependents. The private sector provides healthcare services in large cities with a total of 125 hospitals. All government facilities of healthcare provide their services for free, while private establishments are based on a fee-for-services. Some patients seeking the private sector may pay out of pocket directly for the services or have their insurance coverage which could pay partially or in full based on the arrangement between the insurance company and the patient. Usually, non-Saudis and Saudis in private sector are provided with insurance from their employers.

The MOH delivers healthcare services at three levels: Primary, Secondary, and Tertiary. PHC provides preventative and curative services, referring patients who need advanced care to public hospitals (secondary healthcare services). Patients with a complex level of care are further referred to specialty hospitals (tertiary healthcare
services). The private sector provides healthcare services at all levels depending on their facilities and capability.\textsuperscript{29}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{health_system_structure_in_Saudi_Arabia_before_integrating_the_SFDA.png}
\caption{Overview of the health system structure in Saudi Arabia before integrating the SFDA\textsuperscript{29}}
\end{figure}

In 2003, The Saudi Food and Drug Authority (SFDA) was established under the Ministers Council resolution as an Independent government body that reports to the Council of Ministers President.\textsuperscript{30} The SFDA was found to help the MOH in their responsibilities and take over food, drug, and medical devices regulations.\textsuperscript{30} The purpose of the SFDA is to regulate, oversee, and control food, drug, medical devices, and set mandatory standard specifications by developing and enforcing an appropriate regulatory system.\textsuperscript{30} Also, ensure the safety of food; the safety, quality and efficacy of drugs; and the safety and effectiveness of medical devices, whether they are imported...
or locally manufactured.\textsuperscript{30} The SFDA is a leading regional regulatory authority with professional experts that contributes to the protection and advancement of healthcare in Saudi Arabia. Conducting researches and applied studies to pinpoint health problems and their causes is one of the SFDA’s objectives.\textsuperscript{30} Additionally, building a scientific database to be availed of informative, educational, advisory services and executive programs in food and drug arena. These objectives will be achieved through collaboration between the SFDA and specialists engaged in food and drug affairs and scientific centers. Drug registration is regulated and monitored by the drug sector within the SFDA. Within a series of steps, to assure the drug’s safety and efficacy as well as inspecting the manufacturing site, the registration process will be complete, and the drug is priced and available to the public.\textsuperscript{30} The drug can’t be marketed in community pharmacies without completing the registration process, while specialty hospital through previous permission from the SFDA can acquire the drugs without registration if deemed necessary. The patency for the drug is obtained from King Abdulaziz City for Science and Technology (KACST) in Saudi Arabia. Other countries patencies will not be considered within Saudi Arabia.\textsuperscript{31}
Chapter 3

Methodology

In this chapter, there will be an overview of the methods used to achieve the goal of this study. A full description of the study’s population, interventions, model development and building, data sources, and data analyses will be included.

3.1 Study Design

A cost-effectiveness analysis was performed on a hypothetical cohort comparing different chronic hepatitis C treatment strategies from the (SFDA)’s perspective over a three-month period using a decision tree model. The decision tree model was developed using TreeAge Pro software.\(^{38}\) Data for this study were obtained retrospectively from the (SFDA) and published literature. Costs were measured in United States Dollars (USD). Life-years gained (Ly) were the outcomes measured in this study. The data was implemented in the decision tree model following a hypothetical cohort to obtain the ICERs. Since the SASLT guidelines differ between genotype 1 and genotype 4, there were two separate decision tree models and analyses for each genotype cohort.
3.2 Study Population and Interventions

The study population in this study was 40 years old Saudi Arabian patients diagnosed with chronic hepatitis C genotype 1 or genotype 4 who were treatment-naïve (didn’t receive treatment for chronic hepatitis C before), non-cirrhotic, not diagnosed with liver cancer, and didn’t have a liver transplant or co-infections.

Treatment interventions included in this study were based on the SASLT recommendation’s (grade A1 and B1) and data availability in published literature.

- For genotype 1, four treatments were included:
  1. Ledipasvir/Sofosbuvir (grade A1).
  2. Sofosbuvir plus Simeprevir (grade A1).
  4. Ritonavir/Paritaprevir/Ombitasvir and Dasabuvir with or without Ribavirin (grade A1).

- For genotype 4, three treatments were included:
  1. Ritonavir/Paritaprevir/Ombitasvir with Ribavirin (grade A1).
  2. Sofosbuvir plus Simeprevir (grade B1).
  3. Ledipasvir/Sofosbuvir (grade B1).
3.3 Decision Tree Model

Decision tree model is an illustrative representation or mapping of all possible outcomes of a certain health state or intervention strategy in chronological order. The decision tree model is composed of decision node (depicted as a square), chance node (depicted as a circle), terminal or end node (depicted as a triangle), and pathways. The decision node is a point in the decision tree where a decision must be made to choose between several alternative strategies. The chance node is a point in the decision tree where chance (probability) play a role in which event can occur. Each branching from the decision node or chance node will create a pathway. The terminal node is where every pathway in the decision tree model ends. The sum of probabilities of all branches emerging from one decision node or chance node should be equal to 1. Each pathway is allotted with a specific outcome and cost values. The effectiveness value of each pathway is calculated by multiplying the probability of the pathway with their respective outcome value. The cost for each pathway is cumulatively aggregated at the terminal node where the incremental cost-effectiveness ratio (ICER) is calculated with the alternative intervention strategies. An example of a decision tree model built in TreeAge Pro software is shown in (Figure 3.1).
3.4 Model Development and Building in TreeAge Pro Software

The model was developed using TreeAge Pro software 2015, R1.0, Williamstown, MA. The model simulated the progression of non-cirrhotic chronic hepatitis C cohort who were under different treatment alternatives. The model followed the hypothetical cohort for three months. In genotype 1 model, the cohort was initiated on one of the four treatments then. In genotype 4, the cohort was initiated on one of the three treatments. Side effects of each treatment were integrated into the model. Cost, Outcomes, and side effects of the treatments were assigned for each pathway in the model. Probabilities for the treatments cure rate and side effects were assigned for each pathway. After creating the models, they were examined and validated by clinical and pharmacoeconomic expertise. The data was implemented for each cohort model to run the analysis and generate the base-case scenario obtaining the incremental cost-

Figure 3.1: Example of a decision tree model built in TreeAge Pro Software
effectiveness ratio (ICER). The decision tree model for each genotype cohort is shown in (Figure 3.1) and (Figure 3.2).

![Decision tree model for chronic hepatitis C genotype 1 build in TreeAge Pro software](image)

**Figure 3.2: Decision tree model for chronic hepatitis C genotype 1 build in TreeAge Pro software**
3.5 Data Source

3.5.1 Costs

All relative costs included in a cost-effectiveness analysis is based on the study’s perspective. For this study, only direct medical costs were included from the perspective of the Saudi Food and Drug Authority (SFDA). The costs included were drug costs and side effects treatment costs (anemia, rash, depression). Any costs
assumed to be applied to every patient in the cohort were disregarded from the analysis (e.g. laboratory tests cost). The cost of Ribavirin and Sofosbuvir were tested in the sensitivity analyses since they had generic drugs registered. The costs for side effects treatments were calculated based on the average common prescription drug costs used to treat it. All costs were obtained from the SFDA. All costs were converted to 2017 United States Dollars. All costs included in the decision tree models base-case analysis are shown in (Table 3.1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>66,446.48</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>49,647.06</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>37,680.16</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir</td>
<td>65,171.00</td>
</tr>
<tr>
<td>Dasabuvir</td>
<td>5,151.84</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>0.00</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>58,054.60</td>
</tr>
<tr>
<td>Depression treatment</td>
<td>160.96</td>
</tr>
<tr>
<td>Rash treatment</td>
<td>94.34</td>
</tr>
<tr>
<td>Anemia treatment</td>
<td>1,176.56</td>
</tr>
</tbody>
</table>

Table 3.1: Cost inputs into the decision tree models from the SFDA
3.5.2 Outcomes

Outcomes or interventions’ effectiveness is another important component in the cost-effectiveness analysis. The Outcome measured in this study is life-years gained (Ly) derived by the cure rate of each treatment intervention. The cure rate for each treatment is expressed as sustained virologic response (SVR) which represents the eradication of hepatitis C virus from the patient’s system. After completing the treatment course of three months, patients with SVR were considered cured. From published literature on Saudi Arabian population, the average patient’s age of chronic hepatitis C diagnosis was 40 years old.\textsuperscript{27,40} Based on the World Health Organization (WHO), the life expectancy of Saudi Arabian population is 75 years.\textsuperscript{41} By subtracting the average age of patient’s diagnosis from the population’s life expectancy, we find that the life-years gained for each successful treatment (complete cure) is 35 years. In the model, we assigned each successful treatment with 35 years (represented in the model as cured) and every treatment failure with 0 years (represented in the model as not cured). Not gaining any life-years did not mean death, but it represented that the treatment failed to cure the patient; therefore, the patient did not gain any life-years consequent to the treatment (i.e. the treatment was not effective).
3.5.3 Probabilities

In the decision tree model, probabilities assigned to each branch drive the cohort to separate pathways. For each genotype cohort in this study, the probability of each intervention’s successful cure and side effects were calculated based on pooled data from clinical trials (LONESTAR, C-WORTHY, COSMOS, ION-I, ION-II, ION-III, PLUTO, PEARL-III, PEARL-IV) and published literature.12,33,34,42-54 Treatments’ cure rates (probabilities) were measured by the ability of the patient to reach a sustained virologic response (SVR) within three months of treatment administration. Due to clinical trials combining results for genotype 1a and 1b, we assumed treatment outcomes and side effects were similar. The probabilities for each genotype decision tree model in this study are shown in (Table 3.2) and (Table 3.3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir SVR</td>
<td>0.973</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir SE</td>
<td>0.0267</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir SVR</td>
<td>0.9645</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir SE</td>
<td>0.0179</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir + Dasabuvir with Ribavirin SVR</td>
<td>0.9766</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir + Dasabuvir with Ribavirin SE</td>
<td>0.0456</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir SVR</td>
<td>0.969</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir SE</td>
<td>0.0368</td>
</tr>
</tbody>
</table>

*Table 3.2: Probabilities input of chronic hepatitis C genotype 1 into the decision tree model*
<table>
<thead>
<tr>
<th>Variable</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/Sofosbuvir SVR</td>
<td>0.955</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir SE</td>
<td>0.00</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir SVR</td>
<td>0.998</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir SE</td>
<td>0.05</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir + Ribavirin SVR</td>
<td>0.998</td>
</tr>
<tr>
<td>Ritonavir/Paritaprevir/Ombitasvir + Ribavirin SE</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Table 3.3: Probabilities input of chronic hepatitis C genotype 4 into the decision tree model*

### 3.6 Data Analysis

#### 3.6.1 Cost-effectiveness analysis

The cost-effectiveness analysis in this study was carried through TreeAge Pro software on a hypothetical cohort of chronic hepatitis C patients. There were two separate analyses using the costs, outcomes, and probabilities described in this study. In genotype 1 base-case analysis, Ribavirin cost were $0 to allow combining genotype 1a and 1b interventions into one analysis, assuming they had similar outcomes, and examine Ribavirin’s cost in sensitivity analysis. The effectiveness measured was life-
years gained (Ly). The cost was estimated in 2017 United States Dollars (USD). Probabilities were calculated based on pooled data from clinical trials and published literature. The time horizon for both analyses was three months; therefore, no annual discounting was performed. The perspective in this study was from a governmental body (the SFDA). The willingness to pay (WTP) were set to $65,000 based on Saudi Arabia’s GDP per capita ($21,000). After running the analyses, the base-case ICER’s were generated. Sensitivity analyses were then performed to test the robustness of each base-case scenario.

3.6.2 Sensitivity analyses

Sensitivity analyses were performed in this study under different ranges of cost and efficacy to test the underlying assumptions in the decision tree model. Uncertainties surrounding the base-case scenarios were explored through deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). Deterministic sensitivity analysis (one-way sensitivity analysis) assess uncertainties by setting low and high values for each input independently without changing the base-case value inputs. The deterministic sensitivity analysis performed in this study examined the cost of Sofosbuvir and Ribavirin because they had generic alternatives registered in the SFDA. Probabilistic sensitivity analysis utilizes statistical distributions of parameter inputs to run multiple simulations. Distributions for costs, outcomes, and probabilities inputs in this study were used in the probabilistic sensitivity analyses to generate 1,000 Monte Carlo simulations for both models.
Probabilities assumed to have beta distribution with standard deviation ranged between 0.01-0.05 as obtained from clinical trials for each intervention. The cost inputs of every intervention were varied by 30% on both ends. Acceptability curves for each genotype analysis were represented at a willingness to pay of $65,000.
Chapter 4

Results

This chapter contains the cost-effectiveness analyses results. The effectiveness and cost of each intervention will be covered as well as the base-case scenarios and sensitivity analyses done in this study.

4.1 Effectiveness

The study population was 40 years old Saudi Arabian patients diagnosed with genotype 1 or genotype 4 chronic hepatitis C. Life-years gained (Ly) was the effectiveness measure in this study. For genotype 1, Paritaprevir/Ritonavir/ombitasvir plus Dasabuvir with Ribavirin had the highest cumulative life-years gain of 34.18 years, followed by Ledipasvir/Sofosbuvir, Elbasvir/Grazoprevir, then Sofosbuvir plus Simeprevir with a cumulative life-years gain of 34.07, 33.91, and 33.76 years respectively. For genotype 4, both Paritaprevir/Ritonavir/ombitasvir with Ribavirin and Sofosbuvir plus Simeprevir had the highest cumulative life-years gain of 34.96 years followed by Ledipasvir/Sofosbuvir with a life-years gain of 33.42 years.
4.2 Cost

The perspective in this study was from the SFDA; therefore, only direct medical costs were included in the model. These costs included were the cost of medications and cost of treating the side effects (anemia, depression, and rash). For genotype 1, Elbasvir/Grazoprevir was associated with the lowest cumulative cost of $58,107. Ledipasvir/Sofosbuvir, Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir with Ribavirin, and Sofosbuvir plus Simeprevir had cumulative costs of $66,485, $70,388, and $87,350, respectively. For genotype 4, the lowest cumulative cost was for Paritaprevir/Ritonavir/ombitasvir with Ribavirin intervention of $65,223, followed by Ledipasvir/Sofosbuvir and Sofosbuvir plus Simeprevir with cumulative costs of $66,446 and $87,332, respectively.

4.3 Base Case Analysis

4.3.1 Genotype 1

In genotype 1 base-case analysis, the cost-effectiveness ratio (cost per 1 Ly) of the interventions were $1,713 per Ly for Elbasvir/Grazoprevir, $1,952 per Ly for Ledipasvir/Sofosbuvir, $2,059 per Ly for Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir with Ribavirin, and $2,588 per Ly for Sofosbuvir plus Simeprevir. The incremental cost-effectiveness comparison between the interventions showed that both Elbasvir/Grazoprevir and Paritaprevir/Ritonavir/ombitasvir plus Dasabuvir with Ribavirin were cost-effective at WTP of $65,000. Elbasvir/Grazoprevir showed
dominance on Sofosbuvir with Simeprevir and extended dominance (occur between three interventions were the median intervention is sought not cost-effective in the presence of the other two interventions) on Ledipasvir/Sofosbuvir. Elbasvir/Grazoprevir against Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir with Ribavirin, the ICER was $33,796/Ly for each additional cure. Results of the genotype 1 cohort base-case scenario and cost-effectiveness analysis are shown in (Table 4.1) and (Figure 4.1).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Total Cost ($)</th>
<th>Ly (Years)</th>
<th>Cost/1 Ly ($/Ly)</th>
<th>ICER ($/Ly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>58,107</td>
<td>33.91</td>
<td>1,714</td>
<td>Reference</td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir + Ribavirin</td>
<td>70,388</td>
<td>34.18</td>
<td>2,059</td>
<td>33,796</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>66,485</td>
<td>34.07</td>
<td>1,952</td>
<td>53,190*</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>87,350</td>
<td>33.76</td>
<td>2,588</td>
<td>-40,052**</td>
</tr>
</tbody>
</table>

* The intervention was extendedly dominated, ** The intervention was dominated; negative sign due to the intervention being less effective and more expensive

Table 1.1: Results from genotype 1 cohort base-case scenario
Figure 4.1: Results of the cost-effectiveness analysis for Genotype 1 cohort.
### 4.3.2 Genotype 4

In genotype 4 base-case analysis, the cost-effectiveness ratio (cost per 1 Ly) of the interventions were $1,865 per Ly for Paritaprevir/Ritonavir/Ombitasvir with Ribavirin, $1,988 per Ly for Ledipasvir/Sofosbuvir, and $2,498 per Ly for Sofosbuvir plus Simeprevir. The incremental cost-effectiveness comparison between the interventions showed that Paritaprevir/Ritonavir/Ombitasvir with Ribavirin was cost-effective at WTP of $65,000. Paritaprevir/Ritonavir/Ombitasvir with Ribavirin showed absolute dominance on Ledipasvir/Sofosbuvir and Sofosbuvir plus Simeprevir. Results of the genotype 4 cohort base-case scenario and cost-effectiveness analysis are shown in (Table 4.2) and (Figure 4.2).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Total Cost ($)</th>
<th>Ly (Years)</th>
<th>Cost/1 Ly ($/Ly)</th>
<th>ICER ($/Ly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paritaprevir/Ritonavir/Ombitasvir + Ribavirin</td>
<td>65,223</td>
<td>34.96</td>
<td>1,865</td>
<td>Reference</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>66,446</td>
<td>33.42</td>
<td>1,988</td>
<td>-795*</td>
</tr>
<tr>
<td>Sofosbuvir + Simeprevir</td>
<td>87,332</td>
<td>34.96</td>
<td>2,498</td>
<td>0**</td>
</tr>
</tbody>
</table>

*Table 4.2: Results from genotype 4 cohort base-case scenario*

* The intervention was dominated; negative sign due to the intervention being less effective and more expensive, ** Null ICER due to the intervention’s equal effectiveness and increased cost*
Figure 4.2: Results of the cost-effectiveness analysis for Genotype 4 cohort
4.4 Sensitivity Analyses

4.4.1 Genotype 1

Deterministic (One-way) and probabilistic sensitivity analyses were performed on the uncertainties surrounding the base-case scenario of genotype 1 model inputs. The cost of Sofosbuvir and Ribavirin were altered individually while keeping all other parameters exactly as the base-case input values. Ribavirin and Sofosbuvir generics’ costs registered in the SFDA was $627.5 and $4,480, respectively. After running the one-way sensitivity analyses at a $65,000 WTP, the cost of Ribavirin showed no effect on the robustness of the base-case scenario (Figure 4.3). Varying Sofosbuvir’s cost resulted in Sofosbuvir plus Simeprevir and Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir with Ribavirin being cost-effective with an ICER of $33,796/Ly for each additional patient on Paritaprevir/Ritonavir/ombitasvir plus Dasabuvir with Ribavirin (Figure 4.4). In the probabilistic sensitivity analysis, 1,000 simulations using different parameter inputs in the base-case analysis simultaneously at different WTP thresholds are shown in the acceptability curve for genotype 1 analysis (Figure 4.5). At $65,000 WTP, Ledipasvir/Sofosbuvir was cost effective in 27% of all cases followed by Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir with Ribavirin (26% of all cases) and Elbasvir/Grazoprevir (24.5% of all cases). The frequency of being the optimal intervention (cost effective) at $65,000 WTP are shown in (Figure 4.6). A cost-effectiveness scatterplots showing all generated simulations between the three optimal interventions against each other individually are shown in (Figure 4.7), (Figure 4.8), and (Figure 4.9). In the scatterplots, allocation of dots tilting to the right means the
comparator is less effective while tilting upward represent an increase in the cost of intervention and vice versa.

Figure 4.3: One-way sensitivity analysis at Ribavirin’s high value for genotype 1
Figure 4.4: One-way sensitivity analysis at Sofosbuvir’s low value for genotype 1
Cost in US dollars, Effectiveness in life-years gained, ELB/GRZ: Elbasvir/Grazoprevir,
P/R/O+DSV+RBV: Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir + Ribavirin,
SOF+SIM: Sofosbuvir + Simeprevir, SOF/LDV: Ledipasvir/Sofosbuvir
Figure 4.5: Cost-effectiveness acceptability curve showing the cost-effectiveness probability at the willingness-to-pay in genotype 1 probabilistic sensitivity analysis.
Figure 4.6: Frequency distribution of optimal intervention at $65,000 willingness-to-pay in genotype 1 probabilistic sensitivity analysis

Figure 4.7: Cost-effectiveness scatterplot of Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir with Ribavirin (intervention) vs. Elbasvir/Grazoprevir (comparator) in genotype 1 sensitivity analysis
Incremental cost in US dollars, incremental effectiveness in life-years gained, WTP: willingness to pay in US dollars
Figure 4.8: Cost-effectiveness scatterplot of Ledipasvir/Sofosbuvir (intervention) vs. Elbasvir/Grazoprevir (comparator) in genotype 1 sensitivity analysis
Incremental cost in US dollars, incremental effectiveness in life-years gained, WTP: willingness to pay in US dollars
Figure 4.9: Cost-effectiveness scatterplot of Ledipasvir/Sofosbuvir (intervention) vs. Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir with Ribavirin (comparator) in genotype 1 sensitivity analysis
Incremental cost in US dollars, incremental effectiveness in life-years gained, WTP: willingness to pay in US dollars
4.4.2 Genotype 4

In genotype 4 deterministic (One-way) and probabilistic sensitivity analyses, uncertainties surrounding the base-case scenario were conducted. Individually, the costs of Sofosbuvir and Ribavirin were altered while keeping all other parameters exactly as the base-case input values. Ribavirin and Sofosbuvir costs low values were $627.5 and $4,480, respectively, and high values were the same to that in the base-case analysis. After running the one-way sensitivity analyses at a $65,000 WTP, the cost of Ribavirin showed no effect on the robustness of the base-case scenario (Figure 4.10). Varying Sofosbuvir’s cost resulted in Sofosbuvir plus Simeprevir dominating other interventions at a total cost of $42,165 (Figure 4.11). In the probabilistic sensitivity analysis, 1,000 simulations using different parameter inputs in the base-case analysis simultaneously at different WTP thresholds are shown in the acceptability curve (Figure 4.12). At $65,000 WTP, Paritaprevir/Ritonavir/Ombitasvir with Ribavirin was cost effective in 37.8% of all cases followed by Sofosbuvir plus Simeprevir (36% of all cases). The frequency of being the optimal intervention (cost effective) at $65,000 WTP are shown in (Figure 4.13). A cost-effectiveness scatterplot showing all generated simulations between Paritaprevir/Ritonavir/Ombitasvir with Ribavirin versus Sofosbuvir plus Simeprevir are shown in (Figure 4.14). In the scatterplot, allocation of dots tilting to the right means the comparator is less effective while tilting upward represent an increase in the cost of intervention and vice versa.
Figure 4.10: One-way sensitivity analysis at Ribavirin’s high value for genotype 4 Cost in US dollars. Effectiveness in life-years gained, P/R/O+RBV: Paritaprevir/Ritonavir/Ombitasvir + Ribavirin, SOF+SIM: Sofosbuvir + Simeprevir, SOF/LDV: Ledipasvir/Sofosbuvir
Figure 4.11: One-way sensitivity analysis at Sofosbuvir’s low value for genotype 4
Cost in US dollars, Effectiveness in life-years gained, P/R/O+RBV:
Paritaprevir/Ritonavir/Ombitasvir + Ribavirin, SOF+SIM: Sofosbuvir + Simeprevir,
SOF/LDV: Ledipasvir/Sofosbuvir
**Figure 4.12**: Cost-effectiveness acceptability curve showing the cost-effectiveness probability at the willingness-to-pay in genotype 4 probabilistic sensitivity analysis. Willingness-to-pay in US dollars, P/R/O+RBV: Paritaprevir/Ritonavir/Ombitasvir + Ribavirin, SOF+SIM: Sofosbuvir + Simeprevir, SOF/LDV: Ledipasvir/Sofosbuvir.
Figure 4.13: Frequency distribution of optimal intervention at $65,000 willingness-to-pay in genotype 4 probabilistic sensitivity analysis

Figure 4.14: Cost-effectiveness scatterplot of Paritaprevir/Ritonavir/Ombitasvir with Ribavirin (intervention) vs. Sofosbuvir plus Simeprevir (Comparator) in genotype 4 sensitivity analysis
Incremental cost in US dollars, incremental effectiveness in life-years gained, WTP: willingness to pay in US dollars
Chapter 5

Discussion

The study addresses the economic evaluation of genotype 1 and genotype 4 treatment alternatives in non-cirrhotic Saudi Arabian patients utilizing data from the SFDA, clinical trials, and published literature. In the base-case analyses, Elbasvir/Grazoprevir in genotype 1 and Paritaprevir/Ritonavir/Ombitasvir based regimen in both genotypes were cost-effective at a willingness to pay (WTP) of $65,000/Ly. In genotype 1, Ledipasvir/Sofosbuvir showed slight increments in cost and efficacy than Elbasvir/Grazoprevir, but Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir with Ribavirin had higher cost-effectiveness profile than Ledipasvir/Sofosbuvir. Thus, Ledipasvir/Sofosbuvir were dominated by the presence of both interventions in the cohort treatment. In the absence of Elbasvir/Grazoprevir clinical data on genotype 4 patients’ treatment, Paritaprevir/Ritonavir/Ombitasvir with Ribavirin dominated other comparators. The study findings were similar to a recent study done in the United States that showed Paritaprevir/Ritonavir/Ombitasvir based regimens cost-effective.\textsuperscript{36,56} Saab et al. represented the treatment to be associated with lower cost-effectiveness ratios in both cohorts, which is not the case in this study. However, most of the published studies within the last years involved comparisons of DAAs with old regimens (INF-based); hence the interventions were presumed cost-
effective. In contrast, this study analyzed second-generation DAAs with high leveled quality evidence. Also, few clinical trials were done on genotype 4 second-generation DAAs which designated the assumptions in most studies to simulate genotype 4 to genotype 1 due to high relevance. Thus, numerous uncertainties found in pharmacoeconomic studies done on genotype 4.

5.1 Cost of Chronic Hepatitis C Treatment

CHC treatments are expensive as observed in the study analysis. The average cost for patient’s treatment on one of the interventions analyzed were $71,619. With CHC prevalence of 100,000 patients in Saudi Arabia, the treatment will cost $7.16 billion. This is a huge burden on the government represented in the MOH. In both cohorts, Elbasvir/Grazoprevir was the lowest intervention strategy observed with acceptable efficacy ($58,107). Based on the study’s analysis, switching G1 treatment guidelines to Elbasvir/Grazoprevir can save the MOH budget by $1.35 billion on average, assuming the treatments were not purchased outside the SFDA’s price jurisdictions. This is also an example of the benefits of applied pharmacoeconomics in the healthcare environment. Although in other countries CHC cost of treatment differs, they all agree on these medications having a high price.
5.2 Clinical Effectiveness

The second-generation DAAs has a high efficacy profile where the disease can be cured at a greater rate than the old regimens. With patients reaching an SVR after 12 weeks, these medications can justify the high price considering their lower disease complications, fewer side effects, and short administration. In this study’s analysis, all interventions were effective with an SVR of 95% in the lowest effective intervention.

5.3 Cost-Effectiveness of Chronic Hepatitis C in Saudi Arabia

Elbasvir/Grazoprevir and Ledipasvir/Sofosbuvir had lower cost-effectiveness ratio in genotype 1 analysis. Additionally, in sensitivity analyses, Sofosbuvir generic price (upon utilization with Simeprevir) showed the lowest cost-effectiveness ratio (CER) in both cohorts with 1,250$/Ly for genotype 1 and 1,206$/Ly for genotype 4. Paritaprevir/Ritonavir/Ombitasvir based regimens showed remarkable competitiveness in both cohorts’ treatments, but their prices should be revised since the medication is not taken alone. The cure rate of the interventions (>95%) and fewer side effects will create overall savings, in the long run, considering the complications of not treating CHC and the costs associated with that. However, there are huge similarities between the interventions’ effectiveness that don’t substantiate their vast variation in price. Also, lower side effects can minimize the patient’s expenditure on treatment and hospital visits. Therefore, these interventions are cost-effective for CHC patient treatment in Saudi Arabia.
In conclusion, the interventions compared in genotype 1 cohort are competitive, in exception of Sofosbuvir with Simeprevir, while Paritaprevir/Ritonavir/Ombitasvir with Ribavirin is highly recommended in genotype 4. Interventions in both genotypes can be dominated by Sofosbuvir’s low-priced generics with Simeprevir.

5.4 Limitations

Although the SFDA regulate drug prices, chronic hepatitis C in Saudi Arabia is predominantly treated within government or private hospitals where treatments costs are not publicly disclosed. An example of that was shown in sensitivity analyses where Sofosbuvir plus Simeprevir could be cost-effective in one hospital and not in another (dominated by other interventions). There are limitations to this study due to lack of literature and few clinical trials and pharmacoeconomic studies done (on genotype 4 especially) including the model didn’t confer adherence or patient medication preferences, the study population only included treatment-naive non-cirrhotic adults, and interventions actual side effects and their actual costs were not all included. Also, assumptions made in this study’s analysis, although they were assessed in sensitivity analyses, could restrict its generalizability. With access to real world data on Saudi Arabian patients and future collaboration with government hospitals, these limitations could be overcome.
5.5 Implications and Future Research

This study provides a pharmacoeconomic perspective for decision-makers in Saudi Arabia and hopefully serves as a platform triggering future economic evaluations. Continuing to conduct pharmacoeconomic research on different disease states in Saudi Arabia from the perspective of the SFDA will help toward establishing a socioeconomic advisory where different healthcare organizations can cooperate with to enhance the country’s health and prospers its economy.

Future studies should include real-world data on Saudi cirrhotic and treatment-experienced patients as well as other complication of CHC into the model to analyze the cost-effectiveness in the general population.
References


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