REVIEW ARTICLE

ROLE OF GENERICS IN TREATMENT OF HEPATITIS C INFECTION

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With the discovery of newer and newer DAAs, the cure of Hepatitis C seems to be a reality. But their high price and availability is a big hindrance. Sofosbuvir launched by Gilead costs about $ 84000 per 12-week course. Since its launch there is a huge debate regarding the complex pricing mechanism of DAAs. The pricing involves negotiation of patent holder with health insurance companies through their Pharmacy Benefit Managers (PBMs). Several rebates are also involved in this pricing mechanism amongst which only few are declared ones. Different countries are adapting different strategies to overcome this pricing issue. The branded companies have also issued licenses to companies to form generic version of the drugs and to market them to selected middle and low income countries. Few countries that are not in the list have rejected the patent and started producing their own generics. It is due to these generics that the price of DAAs had undergone a significant reduction but their manufacturing and efficacy needs regular scrutiny.

Keywords: Generics, Pricing; Direct Acting Antivirals (DAAs); Hepatitis C Virus

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INTRODUCTION

The cure of hepatitis is a reality now with discovery of newer and newer DAAs and dream of "No" to hepatitis C seems to be true. This is evidence based expectation that DAA will provide effective and safe treatment for HCV. But the pricing and availability of the new DAAs and the diversity across the globe in this regard has raised a lot of questions that need a deep insight to the situation.

Sofosbuvir being the leading DAA got FDA approval in December 2013. Gilead sciences being the patent holder for the drug launched it at a price of $ 84000 for a 12-week course (approximately $ 1000 per pill).

This high price is practically impossible for most of the patients across the globe as 74% of hepatitis C patients are living in middle income countries.[1]

In this review, we have tried to learn the drug pricing mechanisms adapted by pharmaceutical industry, possible strategies to overcome the pricing issues and the role and efficacy of generics in this whole situation.

Pricing of DAAs:

The pricing in pharmaceutical industry is not only a complex issue but also a confidential business and major money trading is never disclosed to the public. When a manufacturing company launches its product, and sets a wholesale acquisition cost (WAC) that is publically available, even that cost is not a true representative of expenditures served on the product. The mechanism involves a lot of negotiation between the manufacturing company and the health insurance companies mostly through Pharmacy benefit managers (PBMs), who try to convince them for several discounts or rebates which are ultimately subtracted from the WAC. Finally, the drug becomes available at whole sale distribution which provides it to pharmacies, from where the drugs are accessible to the end users. Discounts, rebates and shares are involved on each step making the pricing more complex.[2,3]

Hill *et al* analysed the actual cost of the new DAAs. According to him the predicted cost for 34 grams Sofosbuvir (400 mg/day for 12 weeks) is about $ 68–136. Similarly 5 gm daclatasvir (60 mg /day for 12 weeks) costs about $ 10–30.[4] Gilead since the launch of Sofosbuvir in 2013 have generated a revenue of about $ 31 billion worldwide in 2 years and in USA alone it is expected to reach up to $ 172.5 billion.[5]

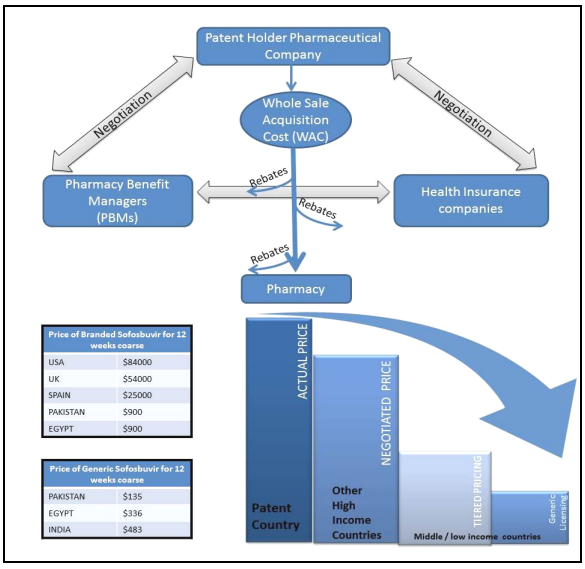

Figure-1: The complex chain of pricing of DAAs and the marked difference in prices of Sofosbuvir in relationship to generics.

With the advent of generics, the whole scenario is rapidly changing. The price of active pharmaceutical ingredient (API) used in the formation of Sofosbuvir is also declining. In 2015 the price has fallen by a mean of $ 702/kg/month and the lowest observed price by the end of 2015 was $ 2501/kg API. At this rate, approximately $ 84 are required to produce a 12 weeks API for a single person. Adding the cost of formulation and packing and also considering a reasonable profit margin of 50% the net cost should be around $ 178.[6]

Cost-effectiveness and affordability:

Cost effectiveness needs to be scientifically analysed before the start of any new project. The analysis not only needs consideration of cost involved for research and invention but also the benefits the society will have along with their willingness to pay for it. Several studies were performed to analyse the cost effectiveness of DAAs. Linas *et al*. evaluated SOF/RBV for genotype 2 and 3 and found SOF based regimens cost effective for treatment experienced and cirrhotics.[7] Similarly Linder *et al.* proved cost effectiveness of DAAs for relatively advanced fibrosis but at the same time showed that DAA treatment for patients with minimal fibrosis can be delayed till availability of cheaper alternatives.[8]

It is not necessary that a cost-effective drug is affordable as well. With the advent of DAAs more and more patients have become eligible for therapy so the overall cost burden has increased a lot. Currently this affordability is the major hindrance in initiating the DAA therapy for most of the patients globally. Different strategies can be adapted to overcome this burning issue.

Strategies to overcome high price issues:

1. Negotiate the price with patent holder:

Most of the high-income countries are negotiating the price with the patent holders e.g. in case of Sofosbuvir, Spain have negotiated with Gilead, to set a price of $ 28,000 for 12-week therapy for their nationals and France have negotiated the same therapy for $ 61,000.[1]

2. Tiered pricing:

According to this mechanism Gilead is providing its branded drug at less price of about $900/12 week in about 101 low and middle income countries categorized on the basis of per capita gross national income of the countries. E.g. In Pakistan, Egypt and India the branded drug is available at above mentioned price.[9]

But even this price is not affordable for most of the patients in these countries. Furthermore, several other low/middle income countries with high hepatitis C burden like Brazil, Thailand and Morocco are not included in the list of 101 countries selected by Gilead.

3. Voluntary licensing agreement:

The patent holder can sign a licensing pact with companies to manufacture and market its products according to pre-decided terms and conditions. Gilead signed a similar agreement with 11 Indian companies who can formulate the generic Sofosbuvir but they can only market their generic in those 101 countries Gilead selected on tiered basis. According to the agreement the companies are supposed to pay 7% loyalty to the Gilead.[10]

4. Rejection of Patent:

In some countries patent opponents, have filed cases against Gilead stating that the formulation of Sofosbuvir is not inventible enough and several similar molecules are already available in pharmaceutical industry. On these grounds, China rejected the patent of Gilead and several Chinese companies are manufacturing their own generics and also marketing them.[11]

5. Special exception under TRIPS:

Trade related aspects of intellectual property rights (TRIPS) agreement provides an opportunity to the least developed countries that they are exempted from several provisions of international laws and agreements. This flexibility is opted by Bangladesh and is producing their own generic at a price less than being offered by Gilead to countries like Pakistan and India. They can also market their products to the countries where TRIPS flexibility applies.[12]

6. Compulsory Licensing by local governments:

A country can declare Hepatitis C virus infection as health care emergency and can issue a compulsory license in vast public interest negating the patent rights. The government has to pay some compensation to the patent company for this compulsory licensing.[1]

Different countries are using different strategies for the provision of DAAs to their people. The brand leaders are also adapting certain strategies to supply their patent to middle/low income countries at relatively affordable rates to justify their high prices in high income countries. Gilead has also adapted the 1st three strategies in this regard. Other companies like Bristol-Myers Squibb which is the patent holder of Daclatasvir, is also making its way globally.

The company has showed commitment for the royalty free licensing as well as tiered pricing in 112 low and middle income countries. The company has also launched a free drug donation program for 10,000 HCV/HIV co-infected patients across Africa and South East Asia.[13]

Response of different countries towards the changing scenario of hepatitis c virus infection:

Keeping in mind the changing global scenario in the treatment revolution of HCV different countries are moving forward according to their local demands, regulatory bodies and political will.

1. Pakistani Perspective

In Pakistan, the latest reported prevalence of HCV infection is 6.7%[14] with an estimated 10 million people infected with Hepatitis C virus. Liver biopsy data of 1000 patients from Centre for Liver and Digestive Diseases Holy Family Hospital Rawalpindi showed that 90% of patients had mild to moderate disease (Metavir F0/F2). A total of 90% had genotype 3a or 2a.[14] Seventy percent patients had IL28B CC, CT a favourable genotype.

Most common age group is between 35–55 years which is the most productive period of life. If this group is not cured this ends up with decompensated cirrhosis and HCC whereas HCC is the 3rd commonest preventable malignancy in Pakistan. On a rough estimate, there are more than 15000 patients who need Liver Transplant in Pakistan with no national Liver Transplant centre in the country.

This pool of 10 million is the constant source of spread Hepatitis C along with new infected cases. Only way forward to eradicate HCV infection in Pakistan is through preventive program and a centralized modal of treatment of hepatitis C that may be close to Egyptian model. The key to success for cure of hepatitis C is availability and licensing of cheap new DAA with quality assurance.

Till 2013 conventional interferon and peginterferon plus ribavirin was standard of care treatment in Pakistan. In 2014 Pakistan started "Physician demand" program for Sofosbuvir (Sovaldi) in collaboration with Pakistan MOH and GILEAD Global access program at subsidize price of 1800 US$ (1.80.000/- PKR) for complete treatment of 6 month with RBV free of cost by Ferozsons Laboratories Limited. This price was still high for common hepatitis C Pakistani patients. SOVALDI got formally registered in Pakistan in March 2015 and up till now about 25,000 patients have been on Sovaldi treatment which is the trade mark of GILEAD. After this about 8–10 different generic Sofosbuvir companies got registered in Pakistan of different pharmaceuticals companies. The cost of these generic varies from 250–300 US$ (25000–30000) with RBV. Till date thousands of patients are on treatment using these generics.

Initial data from different centres and different authors from all over Pakistan had shown encouraging RVR and SVR in large group of patients. Up till now the published data of these drugs is limited. One study from our own Centre for Liver and Digestive Diseases Holy Family Hospital Rawalpindi showed a RVR of 94.4% using branded drug.[15] Another study in which generic brands from different companies were also included showed a ETR of 94% and SVR 82% respectively showing comparable results.[16] A multicentre RESiP study including 1147 patients from 8 different centres in Pakistan including generic users as well showed a SVR12 of 93% using Sofosbuvir and RBV for 24 weeks. Treatment naïve non-cirrhotics showed a SVR of 97%, treatment experienced non-cirrhotics 94%, treatment naïve cirrhotics 89% and treatment experienced cirrhotics 86% respectively.[17]

In conclusion in Pakistan the generics are freely available at lower cost. Physicians are using the DAAs as first line therapy including SOF+DAC or in combination with RBV for treatment naïve and experienced patients of chronic hepatitis C. Data is encouraging in this regard in both naïve and treatment experienced genotype 3a patients with a response of up to 80–90%. The SVR in cirrhotic patients is round about 70–80%. Regarding this local data, the number off course is small and follow up is of short duration. In coming few months multi-centre data regarding SOF and DAC will be available to draw concrete results of efficacy and safety for generic DAAs in chronic hepatitis C patients.

2. Global Perspective

2.1. Egypt:

Egypt has a high prevalence of HCV infection of about 14.7%.[14] IFN+RBV was standard of care till April 2015 when two DAAs SOF + Simeprevir got registered and are available for treatment since then. Gilead in collaboration with MOH Egypt reduced the cost of SOF to $ 300 for 28 capsules a pack. Similarly Janssen is supplying its branded Simeprevir at price of $ 250 per pack. Ledipasvir+Sofosbuvir as part of national treatment program for Hepatitis C are next to be available soon.

By March 2015, 850,000 patients were registered to the program and 25000 had been treated with the new treatment protocol. In 1st phase only patients with F2, F3, F4 and compensated cirrhosis were included. Using new DAAs government aim is to achieve <2% prevalence by 2025 and >90% drop in prevalence by 2030.[18–20] Overall ETR was 98.3% at 12 weeks by using SOF+RBV.[21]

The program concludes that DAAs are effective in eradicating the infection and must be available at low price whatever the mode is used either by generic licensing or any other option of branded drug with low price.

2.2. Indonesia:

Indonesia is having adult anti HCV prevalence of 0.8% with estimated 2 million people infected with the disease. Genotype Ib is the commonest genotype with prevalence rate of 36.5%.[14] With the use of IFN based therapies in the past, the local data suggests a SVR of 73.5% in genotype I Indonesian patients.[22] Currently Boceprevir is the only available DAA in Indonesia therefore it is to be used in combination with PEG-IFN. Although Indonesia is included in the list of countries with whom Gilead had signed the voluntary licensing agreement but the end users are still waiting for the new DAAs due to some legal delay. Due to protests and increasing demand of Indonesian people the government has now decided to cover Sofosbuvir under national health plan.[23] We can expect that the upcoming new DAAs will replace the use of PEG-INF soon.

2.3. India:

India being number 5 while sharing the global HCV burden and about 12 million Indian population are thought to be infected with HCV.[14,24] As India is thought to be the "Pharmacy of developing world", Gilead signed a voluntary agreement with 11 Indian companies to market the generic version of Gilead's Sofosbuvir and Ledipasvir/Sofosbuvir not only across the India but also in several low and middle income countries across the globe.[25] Similarly seven Indian companies are marketing generic Daclatasvir in India since January 2016.

Freeman *et al* presented a data evaluating these generics at an International liver congress in Barcelona. The results are quite comparable with original drugs. A SVR4 of 94.4% have been reported in all genotypes.[26]

Despite good efficacy and a low cost from $ 177 to $ 300 for a three-month coarse treatment, India lacks a national strategy for Hepatitis C prevention and treatment. To eliminate the disease by 2030 they need to treat more than 5500 patients per day. Another issue is the high PCR cost, which is approximately equal to the one month treatment cost in India.[27]

2.4. Spain:

In Spain, there are about 50,000 adults with hepatitis C viremia and genotype Ib is the most prevalent genotype.[14] With the launching of Sofosbuvir by Gilead the Spanish health authorities allocated about 125 million for the purchase of drug and negotiated for the price to about $25000/12 weeks' therapy. This amount can only treat 5000 patients in a year.[1]

Due to social pressure by patients and doctors the government gave a national plan for hepatitis C treatment in February 2015 and decided to prioritize the new DAAs for patients with advance fibrosis (F3-F4) only.[28] Furthermore the Health Ministry took responsibility for treating these patients. Therefore by September 2015 about 30,000 were treated with Sofosbuvir but still leaving behind a significant number of HCV patients. People are demanding a compulsory licensing for the new DAAs which has led to a strong debate on ethical and legal grounds.

Efficacy of generics:

With such low price of generics, one question that bothers a curious mind is: are these generics equally effective as compared to the branded DAAs? To date very limited data is available. Freeman *et al*. presented data of about 448 patients including 51% treatment naïve and 31% cirrhotic patients who used generic DAAs for HCV. End of treatment response was 99.6% and SVR4 was 94.2% respectively. The SOF/LDV group achieved a SVR of 93.2% whereas SOF/DCV group had SVR of 97.4%. Genotype 3 patients showed a SVR of 90% whereas Genotype 2, 4, 5/6 showed 100% response rate although the number of patients was quite low for this group.[26]

Samir Shah from India also shared very encouraging data and found the generic drugs equally effective.[29] Preliminary data from our own centre using generic drugs in genotype 3 patients is showing a RVR of 90% so far. Although more extensive data is required and further studies are awaited but results so far are very encouraging.

CONCLUSION

The development of DAAs has no doubt revolutionized the HCV therapy but a high price by pharmaceuticals is a big hindrance. Generic drugs are providing a very effective and cheap alternative. Middle and low income countries are adapting mechanisms for the provision of these generics for their patients. More efforts are required to improve the availability of these drugs around the globe. Furthermore, actions should be taken to regulate the efficacy and cost of these generics at regular intervals.

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