Hepatitis C Virus Direct Acting Antivirals and Disruptive Innovation

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In 2011, a new wave of direct acting antiviral treatments to combat the hepatitis C virus entered the market. In this paper we discuss how the entrance of these pharmaceutical products fit the definition of a disruptive innovation along with how they affected patients, providers and insurers.

INTRODUCTION: CONTEXT OF HEPATITIS C VIRUS TREATMENTS

The hepatitis C virus targets the liver, increasing risk of future liver related disease and cancer (Mantravadi, 2017a, 2017b). The 25th anniversary of the discovery of the virus showed promise for new treatments and cure rates increased even higher. In 2011, a new wave of treatments, known as direct acting antivirals (DAAs) for hepatitis C virus (HCV) entered the market. The direct-acting antivirals are protease or polymerase inhibitors. Current DAA treatments on the market include simeprevir, sofosbuvir, ledipasvir, ombitasvir/paritaprevir/ritonavir with dasabuvir, daclatasvir-sofosbuvir, and elbasvir-grazoprevir, and the newest most effective medication, sofobuvir-velpatasvir, as approved in mid-2016 (Merck Sharp & Dohme Corp., 2016). Older medications, boceprevir and telaprevir, have been discontinued.

Almost immediately after approval of boceprevir and telaprevir in 2011, which was the first introduction of DAAs into the market, each succeeding year showed another innovation in treatment and a new Food and Drug Administration approval of a DAA, resulting in immediate changes in treatment availability, health care costs, and treatment recommendation. Boceprevir (Victrelis) (Merck Sharp & Dohme Corp, 2015) and telaprevir (Incevik) medications were both FDA approved in 2011. Boceprevir was approved for use in patients with compensated cirrhosis (U.S. Food and Drug Administration, 2016). Finally, in 2014, the manufacturer of telaprevir discontinued the product, due to reduced market demand and availability of more efficacious treatments on the market. In addition, boceprevir was discontinued by Merck by the end of 2015 (Mantravadi, 2016; Merck Sharp & Dohme Corp, 2015).

In contrast to the prevailing treatments (pegylated interferons and ribavirins), direct-acting antivirals are administered in the form of an oral tablet, are more efficacious, and have significantly less side effects (Jazwinski & Muir, 2011; Welsch, Jesudian, Zeuzem, & Jacobson, 2012). Currently, these are the available treatment options for patients, in addition to the standard PEGylated/ribavirin regimens. For the average patient, however, the high costs of these newer medications on the market seems to preclude usage. The advent of DAAs are creating a trend in a slow shift away from classical, older therapies

towards successive rounds of newer treatments, with each medication posing fewer side effects and higher cure rates (Alter & Liang, 2012).

Starting direct acting antiviral treatment for patients with cirrhosis may additionally reduce the likelihood of future negative outcomes and/or current effects of the virus, and thus associated costs, as patients begin to reach sustained virologic response (Ward & Mermin, 2015). The high costs of these drugs very well may be offset by long-term savings. The use of direct acting antiviral treatments results in the avoidance of loss of productivity, liver transplant and treatments, liver cancer, negative liver related health outcomes, especially for the extremely ill patients (PriceWaterhouseCoopers Health Research Institute, 2014). In patients with severe forms of liver disease (cirrhosis), the use of DAAs would save $14,473 in medical expenses related Toliver cancer (Mantravadi, 2017a, 2017b).

The use of DAAs in HCV infected patients are a prime example of disruptive innovation in the pharmaceutical industry, as newer and more efficacious DAA medications are entering the market after FDA approval. This is already evident in the discontinuation of boceprevir and telaprevir, as well as the swiftly changing treatment recommendations for HCV by nationally recognized organizations, as with the approval of daclatasvir and elbasvir-grazoprevir, and recently, sofosbuvir-velpatasvir. In addition, patient pent up demand from delayed treatments due to ineffective medications (watch and wait strategies) contribute to uptake and implications in the market (Mantravadi, 2016). In this paper, the recent rapid research and development of new DAAs, along with swift Food and Drug administration approval for market entry, is analyzed in the context of disruptive innovation in the pharmaceutical industry, and implications of the rapid, emerging changes in treatment.

THEORY OF DISRUPTIVE INNOVATION

The theory of disruptive innovation was popularized in 1995 by Christensen. This theory illustrates the uptake and growth of new innovations in the market. The key tenet of the theory is the origination and movement of entrants and how they are able to target overlooked needs of consumers. Disruptive innovators are usually smaller organizations, with fewer resources, introducing the products at lower prices. Such a combination – unique market (either low end or new markets), and lower priced innovations that target consumer needs – results in high volume uptake, creating disruption in the market (Christensen, Raynor, & McDonald, 2015). A key example of disruptive innovation healthcare, is the uptake of cholesterol lowering medications and disruption of angioplasty (surgery of blood vessel, for heart attacks) (Glabman, 2009); more modern examples of disruption include IBM Watson's healthcare data analytics (Hoyt, Snider, Thompson, & Mantravadi, 2016) and telemedicine.

ARE DIRECT ACTING ANTIVIRALS A DISRUPTIVE INNOVATION IN PHARMACEUTICAL MARKETS?

In several facets, DAAs are acting similar to disruptive innovations. The entry of HCV DAAs has created a new market foothold; translating patients without options for treatment (non-users of HCV treatments) into consumers. The market for efficacious treatments for HCV with low side effects did not exist, until 2011 and the ongoing wave of DAAs. It becomes evident that disruption of prevailing HCV treatments with DAAs is a process; now, each approval of a more effective DAA is beginning to disrupt peginterferon-ribavirin prevalent treatments as well as the DAA market itself. For example, the approval of a pan-genotype (all strains) HCV medication (sofosbuvir-velpatasvir) disrupted other DAA medications, who were only approved for treatment of certain strains of HCV. Further, DAA treatment regimens that no longer had to be used alongside the hard to tolerate ribavirin medication disrupted the use DAAs that did. Similarly, DAA medications with effectiveness close to 100% disrupted other DAAs (boceprevir and telaprevir) that ranged in the low 90% for HCV "cures".

It becomes evident that DAA treatments have disrupted other less effective medications, through a glance of the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America clinical practice treatment recommendations. (American Association for the Study of Liver

Diseases and the Infectious Diseases Society of America, 2016). With the market entry of DAAs, clinical practice recommendations were immediately updated, and each FDA approval of a new DAA resulted in a continuous update in treatment recommendations. Ineffective regimens, such as peginterferon-ribavirin, or DAA combination regimens with ribavirin were disrupted by newer regimen combinations. The first set of clinical practices was published as an article in 2015. However, published recommendations soon grew outdated, and in order to accommodate continuous changes in improved effectiveness, clinical practice recommendations were soon posted on the AASLD-IDSA HCV recommendations website. During 2016, it was harder to keep track of clinical practice recommendations for HCV treatments, as there were multiple updates in clinical practice, with each of the new DAAs.

THROUGH THE LENS OF DISRUPTIVE INNOVATION: ANOMALIES IN THE THEORY

In the context of better, and more affordable innovations, DAAs do not fit the clear-cut theory of disruptive innovation. Disruptive innovations and technologies provide complex healthcare solutions that vastly improve the current set of healthcare services, yet are usually affordable and cheaper. Manufacturers of DAAs have chosen to maintain a high-end pricing strategy for these medications. Competition for such medications has yet to create a full on price war to reduce prices even further and make medication affordable for all patients. Disruptive innovations in pharmaceuticals are usually introduced by new entrants rather than dominant players in the pharmaceutical industry (Glabman, 2009), although this is not the case for HCV DAAs. The manufacturers of DAA products can be considered as a value adding process based business model, where "people, equipment, raw materials, energy, and capital," (Hwang & Christensen, 2008) as well as research and development, are combined in value in the form of pharmaceutical products. This is one argument that DAA manufactures use for high pricing models – DAA prices are based on research and development costs. However, manufacturing costs have been estimated in the literature to be lower than pricing (Andrieux-Meyer, Cohn, de Araújo, & Hamid, 2015).

When it comes to health care sectors most in need of disruptive innovation, pharmaceuticals are fourth behind hospitals/health systems, health care information technology and primary care services. In other words, innovation within the pharmaceutical market is high, and the willingness to pay for such innovation is high, as well (Dafny & Mohta, 2017). Nonetheless, this indicates that patients are more accepting of high and rising costs in the pharmaceutical industry. However, the high prices of DAA medications make scale up and high volume use in practice difficult (Rosenthal & Graham, 2016).

Manufacturers of DAAs have built a different business model compared to other mediations in the pharmaceutical industry. The entry of DAAs created a new market of treatments, akin to the Apple iPod (Christensen, Raynor, & McDonald, 2015; Dafny & Mohta, 2017; Hwang & Christensen, 2008; Plsek, 2014). Sovaldi was first introduced, and then followed by Harvoni at an even higher price of $94,700. These two medications have the highest market share, and are the most popular DAAs (Feuerstein, 2016a, 2016b). The savings from direct acting antivirals very well might improve due to volume and the price competition brought on by the influx of new Food and Drug Administration approved medications (Graham, 2016). This price competition is already evident with the cost of Merck's elbasvir-grazoprevir, while volume based discounts will likely be seen in sofosbuvir-based treatment regimens. The introduction of elbasvir-grazoprevir at a wholesale acquisition cost of at $54,600, aimed to kick start competition and increase manufacturer sales compared to other high cost DAAs (Feuerstein, 2016a,b).. A first pan-genotype strain DAA was introduced in summer 2016, by the manufacturer of Sovaldi and Harvoni. With a strategic pricing of $74,760 for sofosbuvir-velpatasvir, Gilead's price reduction of a new medication in a same medication class was an unusual move by a pharmaceutical company (Feuerstein, 2016a, 2016b). This is almost a model of cannibalization, where Gilead is competing with its own DAA products. Although Sovaldi and Harvoni may remain with the major market share of DAAs, revenue for these products has decreased due to the pressure of competing drug prices (Hough, 2017). Although there is a price reduction, this may not be a feasible or affordable pricing strategy for increased volume or

access to DAAs. In this context, DAAs become an innovation that is high in quality, but not affordable, while typically disruptive innovations are lower priced (Glabman, 2009)..

Further due to the high cost of the medications, the volume of DAAs used in practice becomes an issue. Issues with coverage of DAAs, both at the public and employer sponsored insurance level prevent their utilization of the demand for effective medications. Payment systems determine usage – if insurers cover then volume and usage will soon follow (Glabman, 2009); in other words, if insurers/ health plans embrace and cover the use of DAAs, these innovations are more likely to be accepted at the consumer level. Surveys reveal that payers and clinical executives, such as the AASLD-IDSA, have the most influence on driving the adoption of disruptive innovations, such as HCV DAAs (Dafny & Mohta, 2017). According to disruptive innovation theory, innovations such as DAAs will not catch on to mainstream patient usage (peginterferon or delayed treatment), until quality, or in this case price, is met. DAAs will become a disrupter when the volume of use becomes higher than the number of patients on peginterferon or watch/wait strategies. The upfront costs becomes barriers to access and the use of these medications is currently limited, but slow change towards increased usage is set in the future. Further, the use of DAAs is hindered by the high number of individuals in the public insurance system, primarily in Medicaid, with currently high costs preventing high volume usage.

In some states, Medicaid is beginning to be open to increasing coverage of these new medications, as evident in recent approval by Massachusetts (Graham, 2016). Medicaid and private insurers are lifting coverage restrictions following the announcement by the U.S. Department of Veterans Affairs health system to provide treatment to all veterans infected with Hepatitis C (U.S. Department of Veterans Affairs, 2016). Increased funding from the government for Veterans Affairs in 2016 and Medicare in 2014, along with drug manufacturer discounts, spurred this decision (Graham, 2016). In 2014, Medicaid had also requested funding from Congress to address the crisis while a matching grant from the federal government is another viable option for discussion (Carroll, 2014). Minor discounts from manufacturers have been offered to health plans, such as Kaiser, and certain Medicaid plans. However, it has been pointed out that small percent discounts on expensive medications for treatment of hepatitis C virus infection are not helping the crisis much (Barlas, 2015). Access to these medications remains low, and even with insurer negotiations for better pricing and increased competition, coverage criteria and high prices still remain as a barrier (Hiltzik, 2015; U.S. Senate Committee on Finance, 2015). However, patients cannot reap the benefits of DAA medications if they are not affordable – preventing disruption of current treatments. In other words, the effect of DAA medications at the population level, in terms of uptake as a disruptive innovator, is determined by accessibility (Ward & Mermin, 2017).

FUTURE AVENUES AND EFFECTS OF DISRUPTION: HCV DAAS

Future issues in DAA disruption will also center on pent up demand from patient facing delayed treatment due to peginterferon-ribavirin ineffectiveness. The new, emerging markets of “warehoused” patients with pent up demand for new DAAs is an avenue for further disruption (Smith, 2014). Prior to the newly approved oral agents, most newly detected cases of hepatitis C infection did not prompt antiviral medication due to side effects and limited efficacy of peginterferon-ribavirin regimens. Thus, only 11.8% of veterans newly diagnosed with hepatitis C virus infection were prescribed the available peginterferon-ribavirin regimens antiviral therapy from 1999-2003 (Butt, et al., 2007). The market entry of DAAs have been over a decade in the making. Initially, patients on ineffective peginterferon-ribavirin medications were placed on a watch/wait strategy, until newer medications were approved creating a hidden cohort of pent up demand for DAAs and potential for high volume disruption (Appleby, 2014).

Usually, there are three general options that have been used to deal with disruption innovation in the healthcare industry. First is to label the disruptive innovation as “untested and unsafe” (Plsek, 2014, p. 1). The second is to allow another organization to test the innovation, and then quickly accept the innovation upon the completion of a successful test. The third is to attain “a reputation as an innovator by identifying, pioneering, and publicizing disruptive innovations as business opportunities” (Plsek, 2014, p. 1). All three of these options are legitimate strategies for dealing with the challenge of disruptive innovation in health

care. In the case of HCV treatment with DAAs, all three options have been used by various health care organizations. In populations where HCV is highly prevalent, such as in the Medicare, Medicaid, and veteran populations, the first strategy is employed, where coverage of DAAs has been limited, in this case, only for patients with severe HCV (Plsek, 2014). However, the Veterans Affairs system has committed to universal coverage of DAAs for all veterans with HCV (U.S. Department of Veterans Affairs, 2016), employing the second type of strategy of adapting quickly to disruptive innovations. Finally, the pharmaceutical industry, is continuing a reputation of being an innovation – creating the new market of DAAs, and generating many disruption innovations within the new markets (Plsek, 2014). Manufacturers of DAAs are creating disruptive innovations, in the environment of price competition and Corporate Social Responsibility (CSR) (Bellow, 2012); the reduction in DAA pricings is in response to encouraging access to DAAs (Feuerstein, 2016a, 2016b) – a form of CSR created due to the disruptive innovation itself (Bellow, 2012). Overall, the disruption of DAA innovations is affecting the healthcare field in a multitude of ways, from the treatment practices of healthcare professionals and professional practices of HCV treatment/prescription, patients and access to effective medications, changing service delivery (prescription of DAAs) and coverage, as well as pricing and changes in competition (Plsek, 2014). DAAs can be considered in the context of disruptive innovations in its truest sense – as an innovations that represents a combination of value, quality, savings, convenience (Glabman, 2009).

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