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Management of Viral Hepatitis C: Therapeutic and Economic Study in Morocco

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Abstract
Viral hepatitis C is not only a major public health problem by its significant morbidity and mortality worldwide, but also a medical and economical burden. Over the last 5 years, numerous research laboratories have enabled the development of several direct acting anti-HCV molecules whose effectiveness is well established. Great progress has been made in particular in the field of therapy although the cost of these treatments is today the focus of discussions, dissemination of new antiviral treatments to direct action should be a priority for public powers to heal and reduce the complications of this disease, thus the line ministry has given permission to market a generic of sofosbuvir drugs at an affordable price, acceptable and 80 times cheaper than the princeps. The first part of this paper elucidates the news of new drugs available to treat HCV, in the second part economical study aspects of the different therapeutical strategies currently available in Morocco. Thus we will study impacts of economical consequences of the therapy used against chronic hepatitis C.
Keywords: Sofosbuvir; hepatitis C; direct-acting antiviral; guideline and management of viral hepatitis C; therapeutic and economic study in morocco; sustained virological response

1. Introduction

Viral hepatitis C remains a public health problem with its high prevalence worldwide and risk of progression to cirrhosis and hepatocellular carcinoma. This disease is usually silent and asymptomatic for a long time (De Ledinghen 2002). Much of HCV carriers do not know their HIV status (Zou, et al. 2001). In Morocco, the prevalence of viral hepatitis C in the general population is 1.58% (Baha, et al. 2013). 20-30% of patients with chronic hepatitis C can evolve to liver cirrhosis after 20 years (Seeff 2002, Myers, et al. 2012).

The treatment of chronic viral hepatitis C is changing every day, allowing a gradual improvement in the eradication rates of hepatitis C virus (HCV). Great therapeutic progress has been made. Historically, the duration of HCV treatment was 24 to 48 weeks with uncertain effectiveness and cure rates ranged from 40% to 50% of cases, with treatment intolerance and a lot of side effects. From 2011, new antiviral drugs on the market permit many advantages:

- cure rate of viral hepatitis C which exceeds 90%
- ease of administration,
- the treatment duration was reduced to 24 see 12 weeks using new protocols,
- Tolerance of antiviral drugs with fewer side effects.

Scientific research advances have enabled the arrival of new drugs and new drug combinations, to improve the effectiveness and even manage to eradicate HCV in 90% of patients (Liver 2014, Pawlotsky 2014) .The main drawback of these new drugs is the high cost that far exceeds the cost of research and development. At present, the use of most of these new treatments should be based on the severity of liver disease evaluated either by liver biopsy (LB) or by non-invasive methods such as fibrotest (Sogni). Although the therapeutic strategies used as a therapeutic arsenal to eradicate the infection by the hepatitis virus is proved by several studies, the economic consequences of the choice of treatment remains to be studied.

2. Objectives of treatments

The primary goal is to quickly and sustainably eradicate virus without possibility of relapse (Marcellin, et al. 2007).

The secondary objectives are to:

- protect the liver,
- decrease of fibrosis progresses (Duchatelle, et al. 1998, Poynard, et al. 2002)
- allow regression and even decompensate histological lesions of fibrosis including cirrhosis and HCC (Cardoso, et al. 2010)

- Improve patient's quality of life.

3. Therapeutic target

Each stage of the HCV life cycle including the involvement of an enzyme (receptor binding, endocytosis, translation, cleavage of the polyprotein, viral replication...) is a potential target for developing new antiviral product. Currently there are several websites inhibitions (Schaefer and Chung 2012):

- Protease inhibitors,
- Inhibitors nucleoside or nucleotide polymerase,
- Inhibitors non nuclesosidic polymerase,
- Other anti-NS5A inhibitors

4. Classification of viral drugs

There are three main antiviral HCV classes:

- Antivirals targeting the viral host,
- Direct acting antivirals (DAA),
- Active substances targeting host proteins are also under consideration (if are cyclophilin inhibitors).

4.1. Antivirals targeting host and virus

4.1.1. Pegylated Interferon alpha (Pegasys and Viraferonpeg)

The interferon was identified in 1957 by Isaacs and Lindenmann for its antiviral properties. Interferons are proteins belonging to the cytokines family which are secreted by endogenous cells of the immune system (Pawlotsky 2002). Pegylated interferon is a long-acting form of interferon which is administered by subcutaneous injection at a rate of one per week, initially used only in the treatment of HCV and later in association with ribavirin. The administration of interferon is associated with several side effects (flue-like symptoms: muscle pain, tiredness, headache, convulsions, dizziness, thinning hair, depression) (Liu 2005, Bhatti and Berenson 2007)

4.1.2. Ribavirin (Copegus®, Rebetol® Ribavir®)

Ribavirin nucleoside of guanine shows antiviral properties *in vitro* toward many viruses. Its mode of action remains partly unsolved but several mechanisms seem to be involved with a dual action both directly on the virus (AAD) and indirectly on the host. Apparently ribavirin inhibits the replication of the viral RNA by inhibiting RNA polymerase (NS5B). Ribavirin is administered orally twice daily at 12 hours apart. It is marketed in three dosage forms (capsules, tablets 200 mg and oral solution dosed at 40mg/ml). Ribavirin dosage depends on viral genotype and the patient's weight; it is between 800 mg and 1200 mg/day (Bhatti and Berenson 2007, Husson 2008).

4.2. Direct antiviral agents hepatitis C

4.2.1. Protease inhibitors

NS3 protease has an RNA helicase activity. It is made functional by the Association to the NS4A cofactor. It cleaves other non-structural proteins (NS4B, NS5A and NS5B). Inhibitors of HCV protease have better antiviral potency in preventing the release of functional non-structural proteins, they have a pan-genotypic activity except for genotype 3 (Loustaud-Ratti, et al. 2009).

- NS3-4A protease inhibitors: first generation of the first wave, Telaprevir (Janssen) and Boceprevir (Merck) These protease inhibitors can be used in combination with or without Pegylated interferon and even in combinations without ribavirin(Bacon, et al. 2011, Jacobson, et al. 2011, Poordad, et al. 2011, Zeuzem, et al. 2011).
- NS3-4A first generation protease Inhibitors are the second wave of new drugs approved in 2014/2015 in the US by the FDA or by HAS in France. This is the case of Simeprevir (Janssen), and Faldaprevir (Boehringer Ingelheim, Germany). These molecules acting on genotypes 1, 2 and 4 but not on the genotype 3 (Lahser, et al. 2012).
- Other protease inhibitors are in development, these molecules are called (2nd generation protease inhibitors), they have similar activity to Telaprevir and boceprevir for example: Danoprevir, Soveprevir, Vedroprevir...

4.2.2. NS5B Polymerase inhibitors of HCV

The NS5B RNA-dependent RNA polymerase ensures viral replication, polymerase inhibitors that interfere with HCV replication. These products are two different mechanisms:

- Nucleos(t)ide inhibitors,
- Non-nucleos(t)ide inhibitors

The activity of these products is equivalent to all genotypes; they have a high genetic barrier to resistance.

The nucleos(t)ides act by competitive inhibition at the active site of the enzyme; they mimic the natural substrate of the polymerase, making it ineffective. As the active site of the enzyme is well preserved, these molecules may have similar efficacy on all genotypes. These nucleoside or nucleotide NS5B polymerase inhibitors are currently represented by two molecules:

- a nucleotide inhibitor, Sofosbuvir, which has a strong pan-genotypic antiviral activity and a high genetic barrier resistance (Huang, et al. 2010, Lawitz, et al. 2014, Lawitz, et al. 2013, Osinusi, et al. 2013).
- a nucleosidic inhibitor, the Mericitabine, which has antiviral activity.

Non-nucleoside inhibitors that act by direct interaction with the active site or by binding to the allosteric site thus preventing the initiation process: non-nucleotide NS5B polymerase inhibitor: Dasabuvir and Lomibuvir ...

5. Combination and therapeutic schemes

For decades, the standard treatment for chronic hepatitis C is based on pegylated interferon and ribavirin taken which enabled eradication of 20% to 50% of HCV virus (Asselah 2014).

In 2011, the placing on the market of first generation protease inhibitors (Telaprevir and Boceprevir) are used as a combination therapy with pegylated interferon and ribavirin. This protocol improved the cure rate over 70% (Jacobson, et al. 2011).

From 2014, a new generation of direct acting antivirals is providing doctors and patients that act on all genotypes, and are used with single regimens administered orally, short, without adverse effects

5.1. Before 2011 dual therapy:

Combination therapy based on pegylated interferon and ribavirin is the standard treatment in the management of HCV.

5.1.1. Pegylated alpha Interferon (PEG-IFNa)

Administration of the pegylated interferon alpha is administrated by one injection once a week subcutaneously for a period of 6 months with genotype 2, 3 and 5 and 12 months if genotype 1, 4, 6. The pegylated interferon alpha has a side effect: flu-like illness, tiredness, weight loss, psychiatric disorders (depression, anxiety ...), neutropenia, thyroid dysfunction and skin reaction at the injection site (Duclos-Vallée and Samuel 2000).

5.1.2. Ribavirin

Ribavirin is taken orally 2-3 tablets 2 times/day with meals for a period of 6 months for genotypes 2, 3, 5 and 12 months for genotypes 1, 4 and 6. Ribavirin has many side effects: anaemia, heart disorders (Duclos-Vallée and Samuel 2000).

5.1.3. Drawback combination of this therapy

Combination therapy is associated with many drawbacks (Pariente, et al. 2003):

- tolerance and adherence, resulting discontinuation of treatment in 10 to 30% of cases during the first 6 months;
- the duration of treatment,
- Decrease of efficacy: a sustained virological response (SVR) barely equal 55% depending on the genotypes (Manns, et al. 2001).

5.2. From 2011: Triple therapy

With the appearance of two protease inhibitors first generation: Boceprevir/Telaprevir inhibitors of the serine protease NS3 of HCV. These two molecules are used in combination with pegylated interferon and ribavirin; allow us a therapeutic advantage of 25 to 30% compared to the combination therapy. In addition to the possibility of reducing the 24-week treatment period in almost half of patients. The protease inhibitors have drawbacks as: dermatologic complications, anaemia, these side effects are amplified by the concomitant use of ribavirin, and they have many drug interactions (McHutchison, et al. 2009).

5.3. From 2014: the revolution of the management of HCV

The new DAAs drugs are used in combination with pegylated interferon and ribavirin. Treatment with interferon is characterized by the risk of side effects, prompting experts AFEF recommend abandoning the use of interferon. Several regimens are proposed in the treatment of HCV by international consensus conferences and the learned society; these guidelines are shown in Table 1.

Table 1: Recommended treatment regimens (May 2014) for the different genotypes by the ANRS (National Agency of INSERM) and AFEF (French Association for the Study of the Liver).

Molecules	genotypes	References
SOFOSBUVIR+PEGYLATED INTERFERON+RIBAVIRINE	**Pangenotype**	(Lawitz, et al. 2013, Chazouillères , Lawitz, et al. 2013)
SOFOSBUVIR+RIBAVIRINE	**Pangenotype**	(Gane, et al. 2013, Jacobson, et al. 2013, Osinusi, et al. 2013)
SOFOSBUVIR+DACLATASVIR	**Genotypes 1 et 3**	(Lawitz, et al. 2014, Pol, et al. 2015, Dhaliwal and Nampoothiri 2014)
SOFOSBUVIR+SIMÉPRÉVIR	**Genotype 1b**	(Chazouillères , Dieterich, et al. 2014, Kwo, et al. 2015)

The guidelines of AFEF (French association of the liver study) for HCV treatment recommends the us combination with direct-acting antiviral (DAA) drugs, this protocol without pegylated interferon has a consequences (Chazouillères):

- SVR surrounding 100%
- increase the antiviral efficacy without increasing toxicity,
- lack of cross-resistance,
- Lack of drug interactions and toxicities direct cross.

6. Economic study of algorithms in Morocco

Pharmaco-economic evaluation of drugs used in the treatment of chronic HCV is hampered by lack of information on the extent of health criteria and cost data. Our study aimed to evaluate the economic cost of the treatment of chronic HCV and proceeded to a comparison of therapeutic strategies in effect. So we made the main purpose of this study is to make a pharmaco-economic comparison of four strategies recommended in Morocco:

- Dual therapy: pegylated interferon alpha and ribavirin,
- Triple therapy with protease inhibitor: Boceprevir), pegylated interferon alpha and ribavirin.
- Triple therapy with sofosbuvir: sofosbuvir) coupled with pegylated interferon and ribavirine
- Sofosbuvir combined with Daclatasvir

Initially, the cost of medical taken direct expenses and current treatment costs were determined. Indeed we compare the costs of different protocols in Morocco. Finally we evaluated the economic impact on the treatment of HCV.

6.1. Inventory of anti HCV medications marketed in Morocco

Since the discovery of HCV in 1989, treatment algorithms have followed the scientific research progress and allowed a better management of this disease; Table 2 gives the state of play for anti-HCV treatment.

Table 2: list of drugs treatment of chronic hepatitis C marked in Morocco.

NAME OF DRUG	DCI	FORM	DOSAGE	PRESENTATION	PRICE MAD	LABORATORY
COPEGUS	**Ribavirine**	Oral	1000 mg/day if <75 kg Weigh 1200 mg/j if weigh ≥75 kg	168 Cp 200 mg	**5510**	ROCHE
REBETOL	**Ribavirine**	Oral		140 capsule 200 mg		MSD
RIBAVIR	**Ribavirine**	Oral		84 capsule 200 mg	**900**	Pharma5
PEGASYS	**Peg-Interferon α 2a**	Injection	180µg/week	Syringe 135 µg Syringe180 µg	**2231** **2577**	ROCHE
VIRAFERON	**Peg-Interferon α 2b**	Injection	1,5µg/kg/week	Syringe 100 µg Syringe 120 µg	**2028** **2497**	MSD
VICTRELIS 200 mg	**Boceprevir**	Oral	800mg 3x/day	Box of 336 pills	**25590**	MSD
SSB400	**Sofosbuvir**	Oral	400mg/day	30 pills 400 mg	**3000**	Pharma5
Dakasvir	**Daclatasvir**	Oral	60mg/day	28 pills 60 mg	**1549**	Pharma5

6.2. Cost of current treatment algorithms in Morocco

The current state highlighted the following therapeutic strategies:

- Protocol 1: combination therapy is recommended standard treatment before 2011: Pegylated interferon

alpha and ribavirin.

- Protocol 2: This is a recommended triple therapy since 2011 which is the subject of a combination of anti-protease (boceprevir), the pegylated interferon alpha and ribavirin.
- Protocol 3: A triple therapy is used in Morocco from December 2105 that alternatively the anti-polymerase (sofosbuvir) coupled with pegylated interferon and ribavirin.
- Protocol 4: combination therapy is recommended from February 2016 that uses the association: sofosbuvir and Daclatasvir.

Table 3: Average Cost therapeutic strategies recommended in Morocco

Release date	Protocol	Duration of treatment	Average cost (MAD)	Efficiency: (RVS)	Major side effects
Before 2011	**protocol 1 : Peginterferon alpha-2a/b + ribavirine**	12weeks	**35883,00**	20 à 50% (Fried, et al. 2002, Davis, et al. 2003, McHutchison, et al. 1998)	Asthenia, flu-like symptoms.... (GOURNAY and RICHOU 2008, Sparsa, et al. 2000)
		24 weeks	**71766,00**		
		48 weeks	**94860,00**		
After 2011	**protocol 2 : Peginterferon alpha-2a/b + Ribavirine+Boceprevir**	28 weeks	**262479,00**	50 à 70 % (Bacon, et al. 2011, McHutchison, et al. 2009)	Drug eruption, anemia.... (McHutchison, et al. 2009)
		48 weeks	**449956,00**		
December 2015	**Protocol 3 : Peginterferon Alpha-2a/b + Ribavirine + sofosbuvir**	12 weeks	**44883,00**	About 90% (Lawitz, et al. 2015)	Are those of interferon and ribavirine (Negro)
February 2016	**Protocol 4 : sofosbuvir + daclatasvir**	12 weeks	**13500,00**	More than 95% (Negro , Hezode, et al. 2015)	

Average cost of care for chronic viral hepatitis C due to HCV genotype 1-6 by:

- Protocol 1 is considered a standard treatment using interferon Pegylated and ribavirin, this algorithm recommended for adult's naive treatment with compensated liver disease not previously treated. the cost for treatment ranges between 24,336.00 to 189,720.00 MAD ((1US$=9 MAD) This variation in treatment costs is mainly due to the different doses, depending on the weight of patient, depending on genotype, depending on variety of the price marketed drugs.
- Protocol 2, this therapeutic strategy (combination pegylated interferon, ribavirin and boceprevir) is considered a second-line treatment since it comes after failure of first treatment with ribavirin and pegylated interferon. According to Table 3, the cost is between 235,536.00 and 496,152.00 MAD. This cost difference is mainly due to the variation of doses used according to the weight of the patients and the duration of treatment.
- Protocol 3, this protocol use the combination of pegylated interferon, ribavirin and sofosbuvir, in that case the average cost is 44883,00 MAD for 12 week treatment.
- Finally the average cost of Protocol 4 (using sofosbuvir and Daclatasvir) is 13500,00 MAD for a 12 week treatment.

6.3. Discussion study pharmaco therapeutic economy

A reading of Table 3 we see that protocols 3 (combining pegylated interferon, ribavirin and sofosbuvir) and protocols 4 (associating sofosbuvir and Daclatasvir) are:

- In term of economic are less expensive than the other two combinations namely combination therapy (interferon and ribavirin) and triple therapy (boceprevir, interferon and ribavirin)
- In term of efficacy these combinations allow a sustained virologic response (SVR) excess of 90%. the cost efficiency (SVR) ratio varies from therapeutic strategy to another, if the SVR for combination therapy and triple therapy with anti protease inhibitors is from 20 to 50% and from 50 to 70% respectively, this SVR exceeds 90% for therapy with polymerase (protocols 3 and 4) (Osinusi, et al. 2013, Gane, et al. 2013).
- In term of duration, protocols 3 and 4 allowed the passage of a complex treatment for a long period which exceeds 48 weeks to a single treatment in only 12 weeks (Lawitz, et al. 2013, Zeuzem, et al. 2014).

- In term of tolerance, protocols 3 and 4 are therapies less side effects months and more tolerated (Hanslik and Ouzan , Naqvi, et al. 2015)

It can be concluded that treatments by sofosbuvir revolutionized the treatment of HCV, this treatment is: cheaper than other protocols, SVR increased until than 95%, better tolerated and more efficient and more economical .

In Morocco, access to care is very depending on medical coverage or not, owning a mutual or sickness insurance, economic management is evaluated on several points of views:

- CNOPS perspective
- CNSS perspective
- RAMED perspective
- Private insurance perspective
- Patient's perspective

Since 2012, management of hepatitis C This is a national priority by Ministry of Health, which launched the program of access to care for viral hepatitis C by mobilizing a budget of 65 million DH for the purchase of dual therapy: pegylated interferon and Ribavirine. In December 2015, the authorization for the market by the Ministry of SSB400 * (sofosbuvir) and dakasvir* (Daclatasvir) by a Moroccan laboratory at a price of 3000 MAD box of 28 tablets is 9000 MAD 3 months of treatment for sofosbuvir and at a price of 1549 DH box of 28 tablets is 4647 MAD 3 months of treatment, for comparison, the cost of that course of 12 weeks is more than 451,000 MAD in France and 800 000 MAD to the USA. This will allow a saving of several million DH payers (health insurance or local authority Patient Care Provider: hospital, clinic or doctors, and the Company), especially as the new recommendations of the AFEF suggest not more use interferon because of the side effects except in exceptional cases.

7. Conclusion

The first drugs used 25 years ago in order to treat hepatitis C were interferon administrated every day, few years after, ribavirin was used which is an oral antiviral to increase efficiency of interferon. This combination therapy: interferon, ribavirin was the standard of care in the treatment of hepatitis C with a sustained virologic response of 20 to 70% depending on the genotype and especially with many side effects (Laguno, et al. 2004, Siebert, et al. 2003, Fried, et al. 2002).

In 2011, two protease inhibitors have obtained marketing authorization: Telaprevir and boceprevir, the both molecules used in combination with pegylated interferon and ribavirin, this combination therapy have increased SVR up to 25%, but this effectiveness is confronted with the appearance of several side effects and a lot of drug interactions.

Since 2014, the development of new molecules by different research centers around the world causes the change of the paradigm of HVC, with the emergence of new direct-acting antivirals (DAA), a great advance in managing HCV has been crossed (Chazouillères).

We start with a complex treatment, heavy and lasting at least 48 weeks with significant side effects and a sustained virological response that hardly exceeds 50%, to a regimen single oral, short, well tolerated with no adverse events and especially with RVS now exceeding 90% in just 12 weeks (Chazouillères).

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