

## INTRODUCTION AND RATIONALE

**H**epatitis C virus infection (HCV) is a global health problem, with nearly 2 million new infections occurring every year, up to 85% of those patients become chronic having serious long term health risks (*Aunins et al., 2018*).

The prevalence of HCV infection in Middle Eastern countries varies geographically. Where the average overall HCV prevalence rate in most countries of the Middle East ranges from 1% - 4%, with the exception of Egypt. It has the highest known prevalence rate of HCV globally (*Ghaderi-Zefrehi et al., 2016*). That was attributed to the mass antischistosomiasis treatment campaigns that were conducted in the 1960s and 1970s using insufficiently sterilized intravenous injection equipment (*Mostafa et al., 2010*).

Given the heavy burden of HCV in Egypt, the Egyptian government and EMOH launched huge nationwide campaigns to treat patients with chronic HCV with the latest and most effective therapies (*Kamal and Abdelhakam, 2018*).

The goal of HCV treatment is to obtain a sustained virologic response (SVR), classically defined as undetectable HCV RNA 12 weeks or more following treatment completion (*Hessel et al., 2016*).

Different categories of conventional interferon were known as a “key drug” to treat hepatitis C patient (*Davis et al., 1989*).

Although, the addition of RBV and improvement of conventional interferon with pegylation had enhanced the rate of sustained virological response, yet most of the cases remained non-responders or relapsed after the termination of the treatment because of prolonged treatment, adverse side effects and low SVR rates of interferon plus RBV based therapies, there was a need to improve the long-term viral clearance rate with more effective drugs, having less side effects (*Fried et al., 2002*).

Major advances in the development of drugs to treat people with chronic HCV have occurred in the last 3 years with the advent of direct-acting antiviral (DAA) agents. Several new, all oral, interferon-free regimens are available and more are in development. Phase III drug trials of DAA regimens report cure rates consistently over 90% and significantly fewer adverse events compared with previous regimens (*Evon et al., 2017*). However, DAAs should not be administered as monotherapy because this may lead to drug-resistance (*Khullar and Firpi, 2015*).

Sofosbuvir (Sovaldi<sup>®</sup>) is a nucleotide analogue of HCV nonstructural protein NS5B inhibiting the virus RNA polymerase, in combination with other DAAs, is approved for the treatment of HCV infection of all genotypes (*Wyles et al., 2017*).

Daclatasvir (Daklinza<sup>®</sup>) inhibits the NS5A protein as a result appears to act on viral replication, assembly and secretion stages of the viral life cycle, thereby causing a rapid decline in both intra- and extracellular levels of HCV RNA (*McCormack, 2015*).

Hepatitis C virus NS5A replication inhibitor daclatasvir (Daklinza) is indicated for use in combination with sofosbuvir (sovaldi) with or without ribavirin, in a pangenotypic all-oral regimen. A 12-week regimen of daclatasvir plus sofosbuvir achieved high sustained virological response regardless of prior treatment experience (*Keating, 2016*).

Audiovestibular toxicity has been reported as a consequence of treatment of both pegylated and non-pegylated interferons, that were used previously for treatment of HCV (*Johnson et al., 2008; Salkic et al., 2009; Sharifian et al., 2013; Asal et al., 2015*).

The prevalence of audiovestibular toxicity with the use of ototoxic medications is variable (*Handelsman et al., 2017*). Some studies were done to evaluate the effect of Sovaldi on hearing (*Abd-Elmo'men et al., 2017; Ismail et al., 2018*).

However, to the best of the authors' knowledge no studies have been conducted to evaluate the effect of Sovaldi/Daklinza regimen on balance and vestibular function, accordingly this work was designed to study the effect of sofosbuvir (Sovaldi<sup>®</sup>) in combination with Daclatasvir (Daklinza<sup>®</sup>) on vestibular and balance function in patients with chronic hepatitis C.

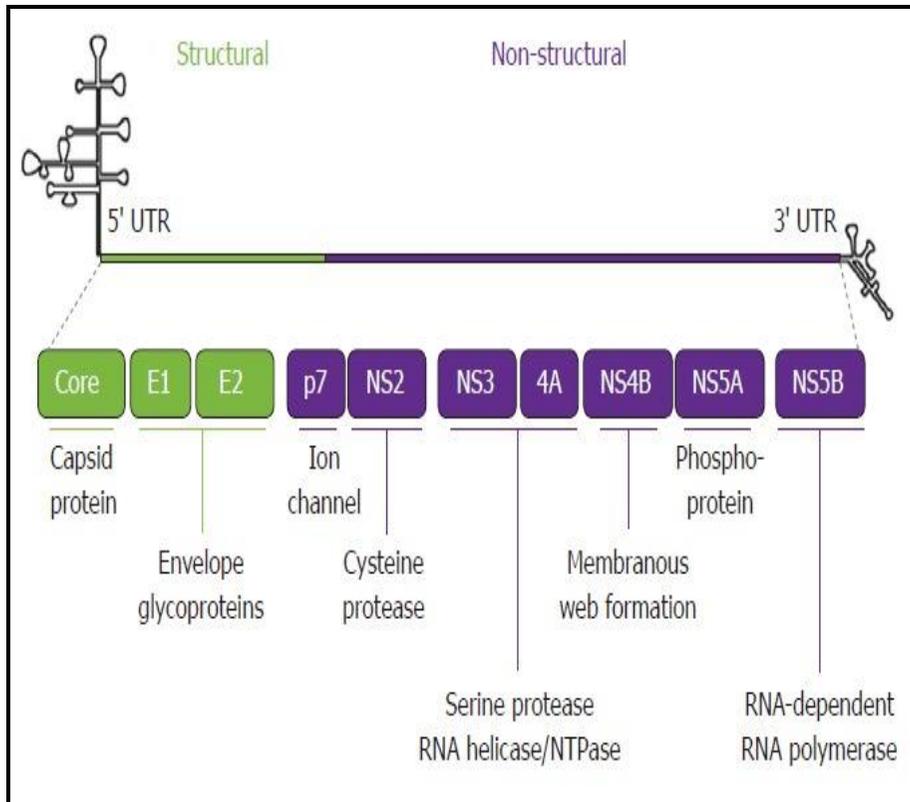
## AIM OF THE WORK

To investigate if there is vestibular and/or balance affection after Sovaldi/Daklinza regimen administration

**Chapter I****HEPATITIS C VIRUS**

**H**CV is a positive-sense, single-stranded enveloped RNA virus approximately 9600 nucleotides in length. Approximately 10<sup>12</sup> viral particles are generated daily in a chronically HCV-infected patient (*Neumann et al., 1998*). Due to the highly error-prone RNA polymerase, HCV displays remarkable genetic diversity and propensity for selection of immune evasion or drug resistance mutations (*De Francesco and Migliaccio, 2005*).

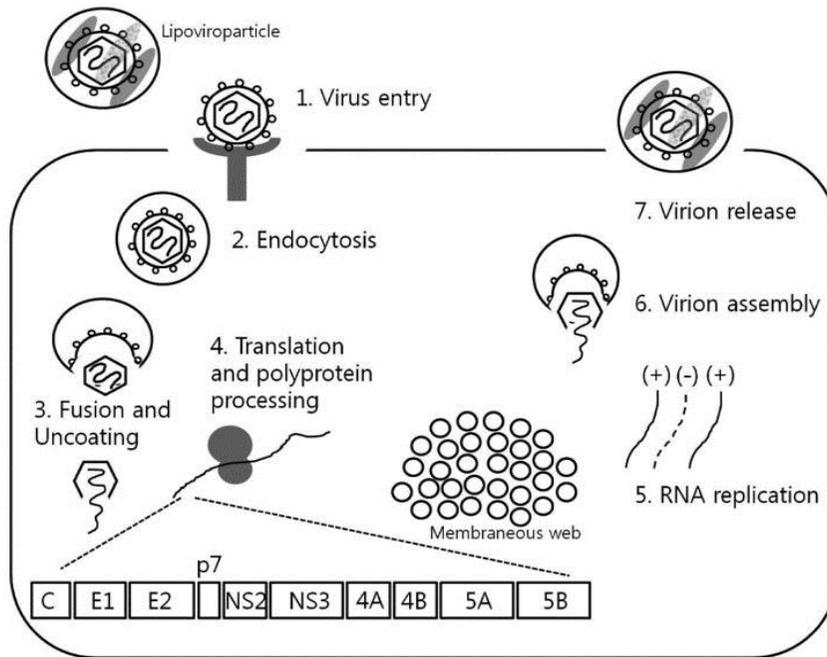
Hepatitis C virus (HCV) contains structural proteins (Core or C protein, E1 and E2 or envelope proteins), and nonstructural proteins (P7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) (*Pawlotsky, 2013*). HCV contains error prone RNA polymerase and mutation is present during each viral replication (*Ogata et al., 1991*). As a result, HCV exists as a quasispecies characterized by the presence of various genetically distinct variants which protect the HCV from host defenses as well as anti-HCV agents (*Pawlotsky, 2006*).



**Fig. (1):** Hepatitis C virus RNA (genome) (*Monjur, 2018*).

## Life cycle

HCV life cycle includes viral attachment, entry, fusion, viral RNA translation, posttranslational processing, HCV replication, viral assembly and release (*Ploss and Dubuisson, 2012*).

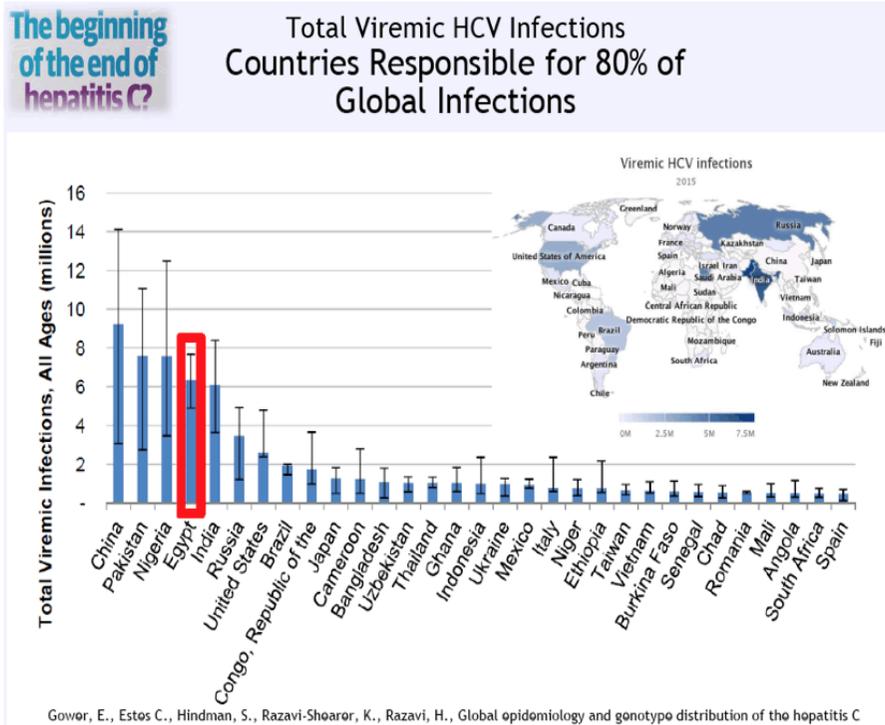


**Fig. (2):** The steps of the viral life cycle are depicted schematically (*Ploss and Dubuisson, 2012*).

**Epidemiology of HCV:**

Viral hepatitis was estimated to be the 7<sup>th</sup> leading cause of mortality globally (*Stanaway et al., 2016*).

Each year, 1.75 million people newly acquire hepatitis C virus infection. These people are at risk of a slow progression to severe liver disease such as cirrhosis, hepatic decompensation, hepatocellular carcinoma and death, unless they receive timely testing and treatment (*WHO, 2017*).



**Fig. (3):** Egypt has a very high burden of infection and disease: Egypt ranked 4<sup>th</sup> amongst all countries for the burden of viral hepatitis C infection (*Gower et al., 2014*).

HCV has six main genotypes (1–6) with multiple subtypes (*Islam et al., 2015*). Several recent studies discussed the epidemiology of HCV infection worldwide. HCV genotype 4 infection is common in the Middle East, Northern Africa, and SubSaharan Africa. Although genotype 4 constitutes about 20% of HCV infections worldwide, the prevalence in Egypt is more than 90% (*Waked et al., 2016*).

In Egypt, chronic HCV infection occurs in around 10% of the population which is about 8 million individuals (*Waked*

*et al., 2016*). In 2017, 15% of an estimated population of 80 million is HCV positive, of which 93% are infected with genotype 4 (*Ahmed et al., 2018*).

### **Clinical presentation**

The incubation period for hepatitis C is 2 weeks to 6 months (*WHO, 2016*). It can present as acute or chronic hepatitis. Most of the cases of acute hepatitis C are asymptomatic. In Egypt, up to 85% of HCV infections persist for life, leading to chronic hepatitis cases. A long-term study showed that complications occurred at a much faster rate in those with (Hepatitis B virus (HBV) or Schistosomiasis) coinfection (*Struthers, 2007*).

The severe liver disease develops in approximately 10%–20% of chronically infected people, but progression to end-stage liver disease is slow and typically does not occur until  $\geq 20$  years after infection. This progression is often clinically silent, most people are unaware of their infection in the absence of HCV testing. Nonetheless, HCV is a major cause of cirrhosis and hepatocellular cancer and is the leading cause for liver transplantation (*Holtzman, 2015*).

Factors affecting disease progression include duration of infection, age at the time of infection ( $\geq 40$  years of age), male gender, alcohol intake, coinfection with other viruses (HBV or HIV), insulin resistance, obesity, immune-depressed patients,

organ transplants, elevation of alanine aminotransferase (ALT) and genetic factors such as IL28B gene (*Maasoumy and Wedemeyer, 2012*).

The major cause of death is primarily due to liver cirrhosis and its complications including liver failure, hematemesis from oesophageal varices, hepatic encephalopathy and hepatocellular carcinoma (*Ruane et al., 2015*).

### **Transmission (WHO, 2016).**

The hepatitis C virus is a blood borne virus. It is most commonly transmitted through:

- Injecting drug use through the sharing of injection equipment.
- Reuse or inadequate sterilization of medical equipment, especially syringes and needles in healthcare settings.
- Transfusion of unscreened blood and blood products.

Hepatitis C cannot spread through breast milk, food, water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.

In Egypt, hepatitis C is just a problem in every family (*Bayomy Helal et al., 2018*). Intrafamilial transmission has been accused for this high incidence. (there are two patterns of intrafamilial transmission: horizontal transmission between patients infected with HCV and their household contacts

sharing the same residential space due to shared behaviours and living conditions, and vertical transmission through the perinatal route that was found to have a minimal role)

### ***Screening for HCV infection***

Screening for anti-HCV antibodies with a serological test identifies people who have been infected with the virus. If the test is positive for anti-HCV antibodies, a nucleic acid amplification test for HCV ribonucleic acid (RNA) is needed to confirm chronic infection (PCR) (*WHO, 2016*).

By detecting HCV infection early, antiviral treatment can be offered earlier in the course of the disease which is more effective than starting at a later stage (*Hayashi and Takehara, 2006*). As a result, The Egyptian government and Ministry of Health (EMOH) conducted several large national surveys investigating the prevalence of HCV among the general population in Egypt (*Miller and Abu-Raddad, 2010*).

In order to provide a framework for control of HCV infection, and markedly reducing the prevalence and burden of HCV in Egypt, so the National Committee for Control of Viral Hepatitis (NCCVH) set its goal to target disease elimination and announce Egypt free from the blood born disease by 2030, that is by enhancing access to diagnosis, treatment, and prevention of transmission in order to reduce the health and economic impact on the individual and the community (*El Akel et al., 2017*).

***Prevention (WHO, 2016).*****Primary prevention:**

There is no vaccine for hepatitis C, therefore prevention of HCV infection depends upon reducing the risk of exposure to the virus in health-care settings and in higher risk populations, for example, people who inject drugs, and through sexual contact.

The following list provides a limited example of primary prevention interventions recommended by WHO:

- Hand hygiene: including surgical hand preparation, hand washing and use of gloves.
- Safe handling and disposal of sharps and waste.
- Provision of comprehensive harm-reduction services to people who inject drugs including sterile injecting equipment.
- Testing of donated blood for hepatitis B and C (as well as HIV and syphilis).
- Training of health personnel.
- Promotion of the correct and consistent use of condoms.

**Secondary and tertiary prevention:**

For people infected with the hepatitis C virus, WHO recommends:

- Education and counselling on options for care and treatment.
- Immunization with the hepatitis A and B vaccines to prevent coinfection from these hepatitis viruses and to protect their liver.
- Early and appropriate medical management including antiviral therapy if appropriate.
- Regular monitoring for early diagnosis of chronic liver disease.

## Chapter IV

# HEPATITIS AND AUDIOVESTIBULAR EFFECTS

### *Effect of Hepatitis on hearing:*

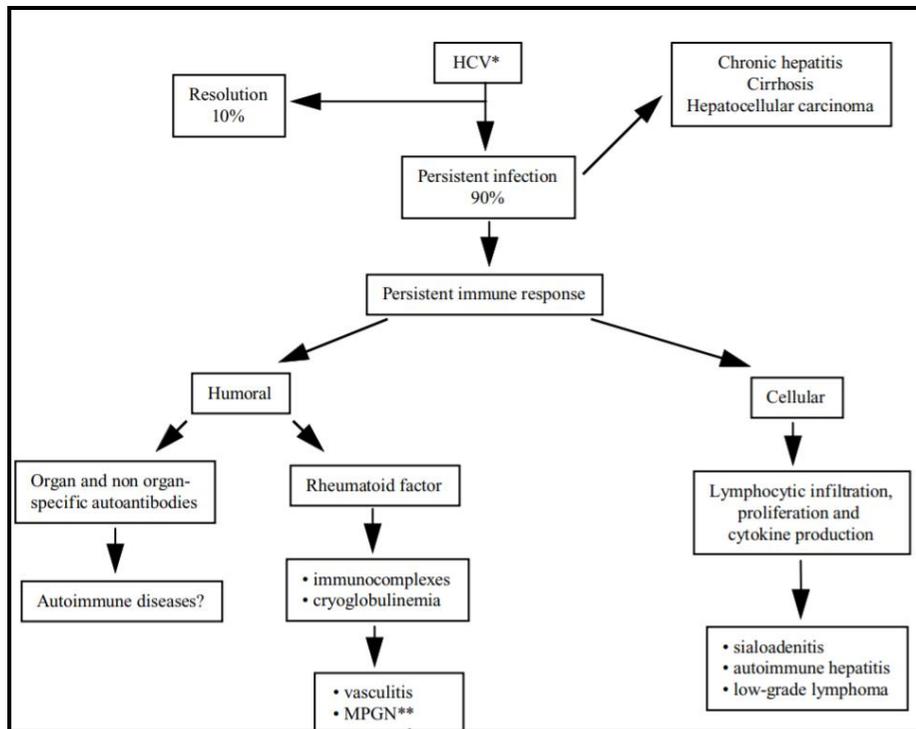
Hearing loss is a known complication of viral infections such as coxsackievirus, cytomegalovirus, herpes, influenza, measles, and mumps. These etiologies most commonly produce sensory neural hearing loss. Pathogenically, their hearing loss is related to acoustic neuritis with fibrosis for measles and direct viruses -induced cytolysis by atrophy of the organ of corti for mumps viruses (*Greco et al., 2011*).

Hearing loss due to viral infection can be unilateral or bilateral, ranging from mild to severe hearing loss that is mostly permanent. Viral hepatitis has been shown to be associated with various extra hepatic manifestations. Its otologic manifestations are similar as well (*Joglekar et al., 2010*).

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have emerged as a global health problem (*Wu et al., 2014*) where 185 million individuals have been infected with HCV worldwide (*Tang et al., 2016*).

Hepatitis C virus has been strongly suspected for many clinical manifestations that are different from those induced at the primary site of action. Where it exhibits a wide range of

extrahepatic complications, affecting various organs in the human body (*Mathew et al., 2016*). These complications have been described, in up to 74% of HCV patients, leading to significant impairment in the quality of life even in patients with only mild liver disease (*Cacoub et al., 2014*).



(\* Membranoproliferative Glomerulonephritis)

**Fig. (4):** Pathophysiology of various extrahepatic HCV complications (*Dore et al., 2007*).

HBV also colonized in extrahepatic tissues leading to wide pathological damage including cardiovascular, digestive system, circulatory, nervous system, hearing and endocrine system disorders (*Kang et al., 2015*).