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Review Article

Oral Direct Acting Agent Clinical Trials for Hepatitis C Virus Infection: An Updated Meta-Analysis

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Abstract

Management of the patient with hepatitis C has evolved over the years: from the first interferons used in monotherapy, the pegylated interferons have been developed, used in association with ribavirin in dual therapy, then to the triple therapy of PEG-IFN and RBV with first-generation protease inhibitors up to today's phase of targeted therapies with second generation direct-acting antiviral agents.

Our work, using the MEDLINE, related to PubMed, and others database performs a meta-analysis of the treatments available today to facilitate the understanding of the different problems and provide an update on the proposed treatments and the different therapeutic indications. We focused on safety, efficacy and special populations treatments.

The addition of DAA to the traditional treatment regimen shows an increase in the rate of recovery in terms of SVR. The impact on the degree of sustained virological response is even very much deep if two of the second generation are added.

These positive data are to be associated with a reduction in serious adverse events

The future seems to open up new perspectives of efficacy and tolerability for all HCV genotypes and seeks to reduce the pill burden by improving the quality of life of patients and therapeutic adherence.

Keywords: *Oral Direct Acting Antiviral Agent; Hepatitis C Virus; Meta-Analysis; Safety; Efficacy*

Abbreviations

AASLD/IDSA Guidelines: American Association for the Study of the Liver Disease/Infectious Diseases Society of America; DAA: Direct-Acting Antiviral Agent; DDR: Drug Discontinuation Rate; EMA: European Medicines Agency; FDA: Food and Drug Administration; GRADE Method: Grading of Recommendation Assessment, Development and Evaluation; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; IDU: Injectable Drug Use; IFN: Interferon; NR: Non-responders; NS Proteins: Viral Non Structural Proteins required for RNA Replication; PEG-IFN: Pegylated Interferon; PRISMA Protocol: Preferred Reporting Items for Systematic Review and Meta-Analysis; RBV: Ribavirin; RCTs: Randomized Controlled Trials; SAE: Serious Adverse Events; SVR: Sustained Virological Response; WHO: World Health Organization

Introduction

Management of the patient with hepatitis C (HCV) has evolved over the years: from the first interferons (IFN) used in monotherapy, the pegylated interferons (PEG-IFN) have been developed, used in association with ribavirin (RBV) in dual therapy, then to the triple therapy of PEG-IFN and RBV with first-generation protease inhibitors (boceprevir and telaprevir) up to today's phase of targeted therapies with direct-acting antiviral agents (DAA Direct Antiviral Agents). In Italy, antiviral treatment is available through the National Health Service according to a series of criteria. These therapies, while ensuring a good efficacy and tolerability profile, are mainly active towards HCV genotypes 1 and 4, leaving part of the population uncovered. Today efficacy therapeutic combinations shorten the cure times.

The search for new treatments for hepatitis C does not stop. Although there is not yet a vaccine for HCV, the therapies have significantly improved the rates of healing of patients with a good tolerability profile. A particular problem still exists today in patients with HCV- Human Immunodeficiency virus (HIV) co-infection, which determines a clinical condition where the tendency towards the progression of liver disease is associated with the immune deficiency characteristic of HIV infection. If HIV infection can be controlled, but not eradicated, it is very important to get the healing of HCV infection now eradicable thanks to modern drugs available.

In Italy there are about 350,000 patients diagnosed, of which about 50,000 with cirrhosis of the liver. Currently, 125.000 patients have been included in the treatments made available by the Italian National Health Service, starting treatment since 2015. Patients with active drug addiction and illegal or migrants remain excluded from therapeutic indications, which however play a non-indifferent role.

Our work performs a meta-analysis of the treatments available today to facilitate the understanding of the different problems and provide an update on the proposed treatments and the different therapeutic indications.

The fundamental problem in the treatment of HCV is represented by the cost of the approved molecules which reduces the possibility of distributing the new therapies to all the subjects that would potentially need them. The renegotiations of prices, which will decrease due to the entry of new drugs or combinations on the market, will allow the realistic planning of the national eradication of the pathology if all the available tools will be used in the appropriate way.

Taking into consideration several studies at the same time, it will be possible to make a quantitative and qualitative evaluation of the more or less advantageous aspects that new treatments with direct antiviral drugs, addressed to patients suffering from hepatitis C, have if they were compared to the previous therapies identified by the Interferon – Ribavirin which have represented the "gold-standard" in the treatment of HCV infections.

The future seems to open up new perspectives of efficacy and tolerability for all HCV genotypes and seeks to reduce the pill burden by improving the quality of life of patients and therapeutic adherence.

Direct Acting Antiviral Agents (DAAs)

The World Health Organization (WHO) estimates that about 3% of the world's population is infected with the hepatitis C virus and that there are about 170 million people, chronic carriers of the disease, risk of developing cirrhosis and/or liver cancer [1].

Prior to the introduction of DAAs, the hepatitis C virus was treated with Peg-interferon alfa-2a which is an immunomodulatory agent normally administered by subcutaneous injection. Subsequently, a second antiviral were added to the treatment regimen, the Ribavirin, an oral nucleoside-analogue.

The DAAs are targeted to the various stages of the virus cell cycle. They are preferably bound to HCV proteins and, in particular, to viral non-structural proteins required for RNA replication (NS proteins). Telaprevir, boceprevir, simeprevir, faldaprevir, asunaprevir and danoprevir bind the NS3/NS4a complex; NS5a is the target of daclatasvir and ledipasvir while NS5b is targeted by sofosbuvir. The termi-

nal part of the drug name identifies the mechanism of action and therefore the class of membership. By convention, the protease inhibitors at the NS3/NS4a cleavage site have the suffix "*-previr*", the protease inhibitors encoded by NS5a terminate in "*-asvir*" and the RNA-polymerase inhibitors NS5b have the suffix "*-buvir*".

Direct antivirals can be classified into 1st generation DAAs (which include telaprevir and boceprevir) and 2nd generation to which they belong: sofosbuvir (Sovaldi®), simeprevir, ledipasvir and daclatasvir.

On November 18, 2014, the European Medicines Agency (EMA) approved the combination of sofosbuvir-ledipasvir (Harvoni®) and subsequently the combination ombitasvir-paritaprevir-ritonavir (Viekirax®) but also dasabuvir (Exviera®). In July 2016, the European Commission issued the marketing authorization for the combination sofosbuvir-velpatasvir (Epclusa®), the first fixed-dosage regimen designed to treat all six HCV genotypes.

Finally, on 18 July 2017 the US Food and Drug Administration (FDA) approved the combination sofosbuvir-velpatasvir-voxilaprevir (Vosevi®) for the treatment of cirrhotic patients affected by chronic HCV infection affecting any viral genotype.

Randomized Controlled Trials (RCTs)

The first studies were focused on highlighting any improvements, compared to previous therapy. Therefore, it was thought to demonstrate the efficacy and safety of new treatments with direct antivirals (using them with and without interferon and/or Ribavirin) in the follow-up of patients affected by the genotype 1 of the hepatitis C virus. In this regard, using the MEDLINE, related to PubMed, and others database, a meta-analysis (April 2015) takes into account 23 randomized and controlled clinical trials (RCTs, Randomized Controlled Trials) which present as outcomes: the sustained virological response (SVR) after 24 weeks of discontinuation of therapy; serious adverse events (SAE), defined as the side effects that lead to serious events; the suspension of treatment (DDR, Drug Discontinuation Rate), defined as the period of treatment interruption due to any event [2]. The analysis showed that only about 50% of patients achieved healing using the traditional approach using a weekly administration by injection of Peg-interferon accompanied by an oral administration of ribavirin. This data is associated with a high rate of SAE (10%) and DDR (9%).

First-generation direct antivirals (telaprevir and boceprevir) lead to an increase in sustained virological response levels of 60% and above (albeit with a considerable side effect profile). A higher increase is noted for those of the 2nd generation. The addition of DAA to the traditional treatment regimen shows an increase in the rate of recovery in terms of SVR from 50% to 75%. This increase reaches values of about 90% in the case in which 2nd generation direct antivirals are added. The impact on the degree of sustained virological response is even very much deep if two of the second generation are added. In the latter hypothesis, increments higher than 95% are obtained [12]. In his study Bansal finally found a global reduction in serious adverse events, from 10% up to even 1.5% with two DAAs while the suspension of treatment for any event, which goes from 9% to 0.9% with the use of two antivirals. Differences are more evident by relating patients who have not responded positively to previous treatments (NR, non-responders) with naive.

This type of data complies with the AASLD/IDSA guidelines (American Association for the Study of the Liver Disease/Infectious Diseases Society of America) for the treatment of HCV infections [3].

However these studies do not take care about the results of the most recent trials with DAAs that move in the direction of hepatitis C non-genotype 1 infections and take into account the more advanced stages of the disease, such as cirrhosis.

Efficacy

The development of drugs that are able to inhibit the fundamental steps of viral replication of HCV has guided the development principles of modern treatments with direct antivirals. The evaluation of the efficacy of the interferon-free regimes, including those that included the simultaneous use of two DAAs, was the subject of clinical trials after 2014, also evaluating the effects of Ribavirin, in relation to the SVR rate.

A more recent systematic analysis (March 2017), examines phase II and III clinical trials concerning patients affected by hepatitis C virus infection and above all belonging to any genotype (from 1 to 6) [4]. Forty-two publications were extracted from a larger group of 1796 literature citations, which emerged from the MEDLINE and EMBASE databases, concerning the treatment of hepatitis C infections with DAAs. A high degree of SVR was found for all direct antiviral treatment regimens approved by the FDA with some exceptions influenced by patient type and viral genotype. As proof of this, there are the low levels of SAE, that are below 10%; the same values relate to data on the loss of individuals during follow-up (< 10%), while the results on the treatment discontinuity are even lower (< 5%). Analysis of the clinical trials revealed that six different direct antiviral treatment regimens have a SVR rate higher than 95% for the majority of pharmaceutical combinations and for the types of patients treated. The high response to direct antivirals in individuals infected by genotype 1 of the hepatitis C virus is particularly important in light of the low SVR level observed in this category of patients following an interferon-based treatment [5].

In contrast, few DAA regimens are available for individuals affected by genotype 3 which is the second most prevalent in the world population (54 million infected individuals) [6]. However, by treating these patients with sofosbuvir in combination with an NS5a inhibitor (velpatasvir, daclatasvir) for 12 weeks, high levels of sustained virological response are achieved [7,8].

It has also been seen that individuals who are cirrhotic and infected by the genotype 3 of the virus may have a high degree of SVR if the combination of sofosbuvir-velpatasvir is added with ribavirin and the duration of the therapeutic treatment is lengthened [9]. Albeit relatively few studies enroll patients with genotype 2, 4, 5 or 6 infections, high levels of sustained virological response (> 92%) have been observed for all treatment regimens that last for at least 12 weeks; SVR levels are particularly high (99%) for patients with viral genotypes 2, 4, 5 or 6 treated with sofosbuvir-velpatasvir [19]. In particular, for the genotype 4, the regimen with paritaprevir-ritonavir-ombitasvir in combination with ribavirin has a high level of efficacy (SVR equal to 100%). This value decreases to 91% if ribavirin is eliminated from treatment.

Therapeutic regimens for patients who are poorly responsive or who cannot be treated with interferon are shown to be great effectiveness. Individuals who are also infected with hepatitis C virus and from what immunodeficiency or are forced to take immunosuppressive drugs (after liver transplant) have a sustained virological response rates comparable to that of patients without dysfunction immune. This suggests that these antivirals mitigate the effect of impaired immune response [10,11].

On the other hand, for subjects suffering from serious kidney disease, there are few therapeutic options with DAAs and, although high levels of SVR have been found (85 to 100%) in two different RCTs that recruit patients with HCV genotype 1 infections, there are no studies regarding genotype 2 or 3 infections, for which the interferon regimen is still the one of choice [12].

Furthermore, treatment possibilities remain limited for individuals with decompensated liver disease. This is because the liver metabolizes the current NS3 protease inhibitors, so they are contraindicated in this kind of patients; therefore, the experimentation was limited to the sofosbuvir with the addition of an NS5a inhibitor. The results produced a high SVR rate (> 85%) but the adverse events are present (from 10% to 52%). Problems also remain in the benefits for long-term treatment of HCV patients with major liver dysfunction [13].

Ribavirin continues to play a central role in increasing the degree of virological response sustained in some types of subjects, including those with genotype 1a or 3 infection, cirrhosis or those who have undergone previous therapeutic treatment; the same applies to individuals suffering from decompensated liver cirrhosis or liver transplantation. Albeit ribavirin has been associated with an increase in anemia, fatigue and insomnia, the degree of serious adverse events and discontinuation of therapy is similar in patients treated or not with it [14,15].

Safety

Although there are guidelines for the treatment of almost all HCV-infected patients, it becomes essential to understand the factors that pose a risk to individuals. These concern HCV-related complications (both liver and extrahepatic) and HCV transmission itself both.

A study conducted by a Canadian team [16] in 2017, takes into consideration eleven publications that include seven different clinical trials and a modeling study to evaluate the relationship cost-benefit. The so-called PRISMA protocol (Preferred Reporting Items for Systematic Review and Meta-Analysis) was used for the selection [17]. The aim is to establish the impact for each result obtained by each trial following the approach with the GRADE method (Grading of Recommendation Assessment, Development and Evaluation) [18].

The therapeutic regimens taken into account first, concerned the comparison between DAA and the duo ribavirin-peg-interferon. The follow-up with direct antivirals, in addition to determining a significant increase in SVR after 12, 24 and 72 weeks, causes a decrease in the frequency of treatment-related damage such as: anemia, psychological adverse events or withdrawal from the clinical trial due to the appearance of adverse events.

Moreover, using interferon-free direct antiviral therapeutic regimens, in particular sofosbuvir with ribavirin, a higher reduction in the frequency of some treatment-related problems is obtained such as flu-like symptoms, neutropenia, rash, psychological adverse events and withdrawal from the trial clinical due to the appearance of adverse events. The evaluation of health status in patients with hepatitis C treated with and without interferon showed that the perceived quality of life decrease in the HCV patients treated with IFN and improved after treatment with IFN-free therapeutic regimens [19].

While, based on the data emerging from the modeling study, the therapy performed with direct antiviral drugs is preferable to treatment with peginterferon-ribavirin to reduce long-term outcomes among which it is possible to include: hepatic mortality, hepatocellular carcinoma, hepatic decompensation and liver transplantation. More specifically, the advantages are double if treatment is started when the patient is in an early stage (F0 - F3 of the Metavir scale) compared to a late fibrosis (F - 4 on the Metavir scale, i.e. the one corresponding to cirrhosis).

Special populations

A consolidated therapeutic relationship between doctor and patient remains crucial for optimal results with direct-acting antiviral therapies, given that certain situations can affect access to drugs and the consequent possibility of delivering them to patients. Pre-treatment assessment and patient understanding of therapy goals as well as adherence and follow-up are essential.

Doctors need to know how to assess which patients need to be treated first. It is therefore important to understand the specific size of the disease from HCV as well as the natural history of special populations.

We know that in patients with advanced liver disease (Metavir F3 or F4 stage), the risk of developing complications, such as hepatic decompensation (Child-Turcotte-Pugh of class B or C) or hepatocellular carcinoma (HCC), is substantial and may occur in a relatively short period of time [20]. It is important to emphasize that people with advanced liver disease require long-term follow-up and surveillance of HCC regardless of treatment outcome. For those who have undergone liver transplantation, an effective therapy before transplantation prevents HCV recurrence after transplantation [21]. Furthermore, complete viral suppression of HCV prior to transplantation prevents relapse [22,23].

In patients at increased risk of fibrosis and rapidly progressive cirrhosis, the evolution of the disease varies over time between the different populations of individuals and within the individual. Many of the components that determine the progression of fibrosis and the development of cirrhosis in a subject are unknown. Co-infection with HIV (Human Immunodeficiency Virus) or hepatitis B virus (HBV), in addition to the prevalence of prevalent coexisting hepatic diseases, are elements contributing to disease progression. HIV co-infection

accelerates the progression of fibrosis among HCV-infected persons. In a recent biopsy study, 282 patients with HIV/HCV co-infection were prospectively evaluated [24] The 38% of patients showed a progression of at least 1-stage fibrosis of Metavir on average every 2.5 years and 45% of patients without fibrosis on the initial biopsy showed a progression in this direction. The control of HIV replication and the restoration of the number of CD4 cells can attenuate it to a certain extent [25]: hence, the treatment of HCV becomes necessary in this patient population regardless of the stage in which fibrosis is found.

The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and at 5% to 10% globally [26]. Patients with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk of disease progression as well as decompensated hepatitis and development of HCC. Individuals with HBV/HCV infection are susceptible to a process called *"viral interference*" in which a virus can interfere with the replication of the other virus. Treatment of HCV infection, in these cases, uses the same genotype-specific regimens recommended for HCV mono-infection. HBV infections for these subjects should be treated as recommended for HBV mono-infection [27].

Extrahepatic manifestations of chronic HCV infection may be associated with cryoglobulinemia, diabetes, fatigue or dermatological diseases. The relationship between chronic hepatitis C and diabetes is complex and to date not fully understood. However, the positive correlation between the amount of plasma viral RNA and insulin resistance markers confirms this relationship [28]. Insulin resistance and type 2 diabetes are factors correlated with the progression of accelerated liver fibrosis [29] and in addition, patients with type 2 diabetes and insulin resistance are at greater risk of hepatocellular carcinoma [30]. More recently, HCV anti-viral therapy has been shown to improve diabetes-related clinical outcomes. In a large Taiwanese prospective cohort, the incidence rates of end-stage renal disease, ischemic stroke and acute coronary syndrome were significantly reduced in patients with HCV infection with diabetes and undergoing antiviral therapy compared to the corresponding untreated controls [31]. Therefore, antiviral therapy can prevent progression to diabetes in HCV infected patients with prediabetes and may reduce renal and cardiovascular complications in those with HCV infection with established diabetes.

The Injectable Drug Use (IDU) is the most common risk factor for HCV infections in Europe and the United States with a seroprevalence rate of HCV between 10% and 70% [32]. The IDU is also the cause of most new HCV infections (about 70%) and is the main driving force in the perpetuation of the epidemic.

The use of lancing devices was also associated with a higher incidence of hepatitis C in patients who used it. Blood sampling from the finger has been reported as a cause of outbreaks of viral infection. The way in which blood sampling from the finger might have contributed to transmission of HCV in clinical setting remains unclear but reduction in the incidence of infection by HCV was observed after suspension of sampling from the finger especially with devices that include non-disposable parts [33].

Treatment of the infection with powerful therapeutic programs without interferon drastically reduces the incidence and prevalence of HCV [34]. However, strategies to prevent HCV transmission have yet to be investigated, including those to supplement hepatitis C treatment with other risk reduction strategies (e.g. opioid substitution treatment and needle and syringe exchange programs) [35].

Conclusion

Follow-up regimens with direct antiviral drugs are highly effective, well tolerated, relatively short and now available for all viral HCV genotypes, even for those patient populations that were historically considered difficult to treat.

DAAs contribute to the achievement of high levels of sustained virological response while maintaining a low rate of side effects (compared to the old treatment based on peginterferon-ribavirin) but above all limiting the progression of the disease (reduce hepatic mortality, carcinoma, hepatic decompensation and the need for organ transplantation).

The tendency is to simplify the regimen as much as possible by working on the way of administration. Until 2013, the sofosbuvir-ribavirin combinations were treated involved the use of seven pills/day at which an injection of interferon could be added. All that was replaced by the use of combinations, which have a follow-up regimen of one pill/day.

The ease of dosing, the safety profile and the efficacy of these drugs increase the number of treatable patients affected by HCV infections.

Today the challenge is to reduce the treatment regimen as much as possible, as demonstrated by the clinical trials recently conducted or still ongoing. If the results of the ongoing trials confirm the long-term efficacy of the treatments, which have given very comforting results for a period of only 8 weeks (contributing to a further increase in therapeutic adhesion), we will obtain not only a great advantage for patients but will also lead to a significant reduction in costs.

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Conflict of Interest

The authors declare no conflicts of interest.

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