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Review Article

Management of Hepatitis C Infection with Direct Action Antiviral Drugs (DAA)**

Abstract

Several new direct action antiviral drugs (DAA) against the HCV virus (HCV) are approved and marketed. The combination of DAA with pegylated interferon and ribavirin (PR) is only recommended to patients with tolerance to interferon (IFN). IFN-free treatments are now considered elective drugs for patients with chronic HCV. More than 90% of patients infected with HCV genotype 1 or 4 (fewer with other genotypes) show sustained virological response, when treated with sofosbuvir combined with simeprevir, daclatasvir or ledipasvir, or by the combination of paritaprevir with ritonavir, ombitasvir and dasabuvir, with or without ribavirin.

The safety and efficacy of DAA therapy in HIV-HCV confection is now comparable with HCV monoinfection. DAA drugs are also efficient in patients with previous interferon/ribavirin, or protease inhibitors, treated patients as well as with hepatic transplanted patients.

The goal of this review is to clarify the current stage of DAA drugs already approved and available by January-2016. Another objective is to discuss the main drugs regimen recommended by international medical associations and drugs regulatory agencies, including Brazil's Health Ministry. In this review, the authors make an approach about: adverse effects of DAA; interactions with other drugs, efficacy in patients with compensated cirrhosis or comorbidities, different genotypes or subtypes, as well as the development of resistance associated to viral mutants and their possible clinical importance.

Introduction

The first direct action antiviral drugs (DAA), also referred to in the literature as C-STAT (specifically targeted antiviral therapy for HCV), which are also inhibitors of the NS3-4A serine protease proteins were telaprevir and boceprevir. These earlier drugs have many disadvantages, such as very serious side effects which require discontinuation of treatment around 10 to 15% of the times, as well as the inconvenience of having to associate interferon (INF) and ribavirin (RBV) to the treatment scheme. Furthermore, there are limiting factors such as requiring multiple daily doses; showing efficacy in only 40-50%, low genetic barrier, and lower efficacy in patients with cirrhosis. They are not efficient against other genotypes, acting only against genotype 1, and showing frequent relapses.

The new drugs that recently appeared, started a new era in HCV treatment. This has generated great expectations in effective control over this large global endemic problem.

Two events led to the advance in the development of these direct-action drugs. The first important milestone for the development of DAA was the discovery, in 1999, of a virus culture system developed in a hepatoma cell line [1]. After, in 2005, was possible the production of HCV in cell cultures from a cloned viral genome, thus allowing know the full replicative life cycle of the virus [2]. This knowledge was essential for understanding the function of viral proteins and how to stop the viral multiplication [3]. Potentially, each step of the viral cycle is a target for drug development.

These drugs are of different classes, developed almost simultaneously by the pharmaceutical industry, in impressive numbers, increasingly more effective, with reduced usage time and administered orally, and high tolerability to side effects, as disclosed in the major protocols that served as basis for registration in international drug regulatory agencies. Therefore, several IFN-free drugs combination with different viral targets, including NS3-A4 protease inhibitors, nucleoside/nucleotide analogues and non-nucleoside inhibitors of the RNA-dependent RNA polymerase, and NS5A inhibitors, are under development.

The safety and high efficacy of DAA therapy in HIV-HCV coinfection is now comparable with HCV monoinfection, and shows high efficiency in naïve or treatment-experienced patients, compensated cirrhotic patients, and hepatic transplant patients.

Awaits to brief new antiviral drugs of direct action, pangenomics, with a good security model and without cross-resistance.

Methodology

It was researched phase III clinical trials protocols in several different databases, and the guidelines of the European Association for the Study of the Liver (EAS-2015), American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA), up to date in December of 2015, and Brazil's Health Ministry Recommendations (2015). The Interest in Brazilian protocol recommendation lies in the fact that it was one of the first countries in world to make available the treatment universally.

Direct Antiviral Action Drugs (DAA): Table 1 shows the drugs

already approved in January 2016 and others in advanced stages of clinical trial. They are classified according to the antiviral action site.

Drugs already approved by the FDA*, EMA and ANVISA*****

FDA*: U.S.FOOD and Drugs Administration (USA); EMA**: European Medicines Agency; ANVISA***: Brazilian Health Surveillance Agency.

SOFOSBUVIR (Sovaldi® -Gilead)

Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor of hepatitis C virus (HCV) polymerase —the key enzyme mediating viral RNA replication. It reveals highly promising features in combination with other DAA drugs (daclatasvir, simeprevir, ledipasvir). Sofosbuvir are active against all genotypes of HCV (pangenotipic) with a genetic high barrier, low interaction with other drugs, treatment with oral use (one tablet of 400 mg/day) and shorter duration (12-24 weeks). It was the first of new interferon-free drugs approved by the FDA (December 2013) [9-11]. Sofosbuvir and ribavirin is effective in co-infected HIV-HCV patients, compensated cirrhosis, including patients with hepatocellular carcinoma, and re-infected liver transplant recipients [12,13]. Treatment regimen and duration are dependent on both viral genotype and patient population. No response-guided therapy is required with sofosbuvir scheme.

Firstly tested in protocols in combination with RBV, without IFN, was effective by over 90% of sustained virological response (SVR) in genotypes 1, 2 and 4, and over 80% among patients with genotype 3 infection [14-17]. HCV genotype 3 infection causes faster injury, and shows high recurrence in previous treatments [18]. Sofosbuvir associate with ribavirin also show high SVR in HIV-co-infection [19], even in HIV-coinfected liver transplant recipients with recurrent hepatitis C virus infection [16]. However, the best results were achieved if associating sofosbuvir and daclatasvir for genotype 1,2,3,4 or simeprevir for genotype 1.

Sofosbuvir associated with daclatasvir reaches up to 95% efficacy against genotype 3 [20-22], filling an important therapeutic gap.

Sofosbuvir is highly metabolized in the liver and eliminated primarily by the kidneys. Using sofosbuvir is necessary to control renal function. Rigorously sofosbuvir shuld not be recommended in patients with severe renal impairment? Patients on haemodialysis, or after kidney transplantation, dose of sofosbuvir should be reduced to 200 mg daily or 400 mg every other day [23]. It presents the lowest risk of interaction with other drugs, although the manufacturer recommends no association with amiodarone. P-gp inhibitors in the intestine, such as rifampin, rifabutina, rifapentina, and St. John's wort, can reduce the effect of sofosbuvir.

Because sofosbuvir is used in combination with other antiviral drugs for treatment of HCV infection, it needs to consider the contraindications of the other drugs. Contraindications to peginterferon alfa and ribavirin also apply to sofosbuvir combination

Table 1: Direct-acting drugs registered or in final research phase.

1. Protease inhibitors - bind to the protein NS3-4A (... PREVIR)
1st wave: (suffix …previr) only for genotypes 1 and 4, serious side effects, low genetic barrier, NS3/4A inhibitor.
BOCEPREVIR (Merck), APPROVED TELAPREVIR (Jansen), APPROVED
2nd wave: (suffix …previr) higher genomic barrier, only for genotype 1, less serious side effects, NS3/4A inhibitor.
SIMEPREVIR (150 mg/tablet- Janssen), APPROVED FALDAPREVIR 120 mg/tablet -Boehringer), PHASE III PARITAPREVIR/RITONAVIR (12,5/50 mg/tablet - AbbVie) , APPROVED ASUNAPREVIR (Bristol), PHASE III DANOPREVIR (Roche), PHASE II SOVAPREVIR (associated with simeprevir), Achillion-Janssen (ACH-3102), Phase II VANIPREVIR (Merck), PHASE III GRASOPREVIR (MK 5172) (Merck), PHASE III [4-8]
2. RNA polymerase inhibitors (suffix...BUVIR), pangenotipcs, high genetic barrier, NS5B inhibitor.
1st wave: Analogue nucleosides SOFOSBUVIR (400 mg /tablet- Gilead), APPROVED
2st wave: Non-nucleoside analogue inhibitors (suffix... VIR): only for genotype 1, low genetic barrier. LOMIBUVIR (Vertex), PHASE II DESABUVIR (250 mg/tablet - AbbVie), APPROVED BECLABUVIR (Bristol), PHASE III
3. Polymerase inhibitors in the NS5A site (suffix... ASVIR)
1st wave: inhibit the release of particles of genotypes 1 and 4, minor action against genotypes 2 and 3, fast action, low barrier genetic, NS5A.
DACLATASVIR (60 mg/tablet- Bristol), APPROVED LEDIPASVIR (90 mg/tablet Gilead), APPROVED (in association with sofosbuvir) OMBITASVIR (75 mg/tablet - AbbVie), APPROVED
2st wave: pangenotipics 1, 2, 6, high genomic barrier, NS5A inhibitor
ELBASVIR (MK 8742 -Merck), PHASE III [4-8]
VELPATASVIR (GS-5816) (associated with sofosbuvir in one tablet, pangenotipic), Phase III
ODALASVIR (associated with simeprevir), Achillion-Janssen (ACH-3102), Phase I

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treatment. No clinically significant pharmacokinetic interactions between sofosbuvir and antiretroviral [24].

Sofosbuvir should be used in combination with ribavirin in patients with hepatocellular carcinoma awaiting liver transplantation for up to 48 weeks or until liver transplantation, whichever occurs first.

OMBITASVIR-PARITAPREVIR-RITONAVIR with DASABUVIR -"3D Regimen Regimen" -Viekira Pak®-Abbvie) or without DASABUVIR – "2D Regimen"

This regimen interferon-free coformulated showed potent action against genotype 1 and 4, in treatment-naive and treatment-experienced patients [25-30]. Ombitasvir is a potent pangenotypic picomolar antiviral activity, NS5A inhibitor; paritaprevir is a nonstructural NS3/4A protease combined with ritonavir (a potent inhibitor of CYP3A4 enzymes and is used as a pharmacologic booster for paritaprevir without activity against HCV) and dasabuvir (a nonnucleoside NS5B RNA polymerase inhibitor). For genotype 1a, without chirrosis, is indicated to associate ribavirin for 12 weeks, and for genotype 1b without ribavirin for 12 weeks. Patients with compensated cirrhosis or liver transplant recipients with normal liver function and mild fibrosis, for genotype 1a for 24 weeks, and genotype 1b for 24 weeks, both with ribavirin [31].

Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.

For patients with HIV coinfection, using the same dosage. The 3D Regimen treatment regimen seems to be safe in patients with renal failure without the need for dose adjustments [32]. Ombitasvir-paritaprevir-ritonavir and dasabuvir is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated with severe hepatic impairment (Child-Pugh C). It needs dose adjustment in patients receiving immunosuppressive.

The formulated drug is marketed and has recently been licensed in Brazil. Adverse effects observed in clinical trials when used without ribavirin, and for patients with compensated cirrhosis, have had minimal risk for serious adverse effects. More often, causing fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Co-administration of 3D Regimen Regimen with inhibitors of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs, such as rifampicin, ergot derivatives, anticonvulsivants, St.John´s wort (hypericon perforatum), simvastatin, lovastatin, neuroleptics, antihyperlipidemics, ethinyl estradiol, triazolam, midazolam.

Hiv-Hcv Coinfection: Ombitasvir-paritaprevir-ritonavir and dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions. Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Should not be administered with efavirenz or with additional doses of ritonavir. Atazanavir, and darunavir require cautious monitoring.

DACLATASVIR (Daklinza ® - Bristol-Myers Squibb)

Daclatasvir is an inhibitor of non-structural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assembly. Daclatasvir is pangenotipic. Daclatasvir is also effective in compensated cirrhosis, including patients with hepatocellular carcinoma, and reinfected liver transplant recipients [33-37]. It is recommended oral dose of 60 mg/day for 12 or 24 weeks, according to genotype, cirrhosis or to treatment-experienced patients. Daclatasvir should not be administered with strong inhibitors of CYP3A4, as clarithromycin, erythromycin, rifampicin, corticosteroids, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, imidazole, rifampicin and others of the same class, calcium channel blockers verapamil, and phytotherapy. The use of amiodarone requires caution when is coadministered with sofosbuvir. Safety and efficacy of daclatasvir have not been established in patients with decompensated cirrhosis.

HIV-HCV Coinfection: Daclatasvir with sofosbuvir is effective in co-infected HIV-HCV patients [17]. The dose of daclatasvir should be reduced to 30 mg once daily when administered with atazanavir/ritonavir. Coad ministered with efavirenz should be increased to 90 mg of daclatasvir. No dose adjustment of daclatasvir and raltegravir is required. Associating daclatasvir with ritonavir, or nevirapine, may show potential interaction and need close monitoring.

SIMEPREVIR (Olysio®-Janssen)

Simeprevir belongs to a second wave of protease inhibitor drugs with strong activity against genotypes 1 and 4 especially against genotype 1b [38-41]. Simeprevir plus sofosbuvir is well tolerated in patients with advanced Child's B/C decompensated cirrhosis [42,43]. The effectiveness in combination with peginterferon Alfa (Peg-IFN-alfa) and ribavirin (RBV) is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV virus genotype 1a without the Q80K polymorphism. It presents risk of prior mutations in previously treated patients with telaprevir or boceprevir. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is recommended in the United States. However, this polymorphism is not very widespread in Brazil. Simeprevir is indicated for 12 weeks of treatment in patients without cirrhosis or 24 weeks for cirrhotic patients, and genotype 4 (combinated with interferon +ribavirina). Simeprevir is available in 150 mg capsules. The dosage of simeprevir is 150 mg PO once daily with food.

Simeprevir presents smaller adverse effects than other protease inhibitors, but it has described photosensitivity reactions (especially in interferon / ribavirin treatment regimen), cutaneous rash most frequently in the first 4 weeks of treatment, tiredness, weakness, headache, loss of appetite, nausea and vomiting, insomnia, pruritus, color changes in stools and increased bilirubin. Serious adverse events were seen in about 2% of the protocol patients. No dose adjustment of simeprevir is required in patient's renal or hepatic impairment. With the use of simeprevir with interferon + ribavirin, there is a rule to stop when the viral load is above 25 UI / mL in week four and

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detectable in week 12. If treatment with simeprevir and sofosbuvir is discontinued due to adverse reactions or inadequate virologic response in treatment, therapy simeprevir should not be restarted.

Simeprevir displays interactions with other drugs and cannot be used with: ledipasvir, calcium blocker, imidazole, sedatives, macrolides, and antiarrhythmics (if associate with sofosbuvir). Simeprevir undergoes oxidative metabolism from the CYP3A system (high interaction with drugs that suffer this metabolism) and subsequent excretion into the bile may cause jaundice and the elevation of ALT. In coinfection, HIV-HCV (only genotype 1) simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir (and probably dolutegravir), rilpivirine, and tenofovir [44].

SOFOSBUVIR + LEDIPASVIR or VELPATASVIR (Harvoni ® - Gilead)

Ledipasvir, a polymerase inhibitors in the NS5A site, formulated in association with the sofosbuvir showed, in protocols, close to 100% SVR against genotype 1, in patient naïves witout cirrhosis. It is also active against genotypes 4, 5 and 6, as well as compensated cirrhosis patients, in HIV co-infected, or liver transplant recipient's reinfected [45-49]. The drug is formulated in one tablet (400 mg sofosbuvir + 90 mg ledipasvir) PO, once daily. Treatment is recommended for 12 weeks or 24 weeks with ribavirin (if negative preditors). The concomitant use of sofosbuvir-ledipasvir and P-gp inducers (e.g., rifampin, St. John's wort, statin,) may significantly decrease plasma concentrations and may lead to a reduced therapeutic effect of da DAA.

HIV-HCV Coinfection: Because ledipasvir increases tenofovir levels, this drug should be avoided in patients co-infected with HIV and which have baseline creatinine clearance rate ≤ 60 mL/min.

Ledispavir (100 mg) will soon be replaced by velpatasvir, a NS5A inhibitor of second wave in the Harvoni® formula, due to higher efficacy with all genotypes, and high genetic barrier. Some recent trials show high efficacy (>95% SVR) against against all genotypes with dose diária for 12 weeks, in patients with or without previous treatment, including those with compensated cirrhosis [50-52]. In patients with decompensated cirrhosis the overall rates of sustained virologic response were until 94% among patients who received 12 weeks of sofosbuvir-velpatasvir plus ribavirin. Serious adverse events occurred in about 20% [53].

Resistance associated to viral mutants. **DAA Fail Retreatment**: The effectiveness of DAA is very high in all major clinical protocols, although there are some factors associated with treatment failure including cirrhosis (Child-Plough B/C), response to previous antiviral therapy, as well as viral factors such as genotype and subtypes or presence of previous viral mutants that could interfere with SVR.

Pre-existant resistance to direct-acting antiviral (DAA) agents against HCV infection by the selection of mutations at different positions in the NS3 protease, NS5B polymerase and NS5A proteins could reduce SVR [54-58]. Resistance to DAAs is a complex scenario, with eventual clinical implications. The relevance of pre-existing resistance mutations for responses to DAA therapies is unclear for most treatment regimens and requires further study.

Due to the development of viral mutants by all known direct-acting drugs does not recommend the use of DAA monotherapy.

The presence of resistance associated variants may also impact therapy during retreatment with DAAs.The optimal retreatment strategy for chronic hepatitis C virus patients who fail DAA-based treatment has not been extensively studied. Because of the high barrier to resistance and potency, retreatment with SOF seems to be much safer than with other DAAs. One small open-label trial showed effectiveness (~80%) of sofosbuvir plus peguilated interferon and ribavirin in patients infected with HCV genotype 1 who had previously failed to achieve SVR with investigational DAA scheme [59]. In other small nonrandomized (SPARE Study) of patients with genotype1 (most 1a) who failed 24 weeks of SOF plus RBV and were retreated with 12 weeks of sofosbuvir e ledipasvir. All reached SVR after completion of therapy [60].

The baseline resistance tests have no clear indication so far in clinical practice [61,62]. But could be one valuable option at the retreatment of patients who failed DAA-containing regimens. In this context, long-term resistant variants persistence after failure should be taken into account [63].

Main chronic hcv treatment recommendations (2015)

The regimens of recommendations for the treatment of chronic HCV in adult patients by EASL, AASLD, IDSA, are very similar. Small variations can be observed for suggesting higher effectiveness. The direct-acting drugs now occupy a central position in the treatment of HCV. However, addition of ribavirin to sofosbuvir + simeprevir and sofosbuvir + daclatasvir schemes could be carried out especially in patients with negative predictors (advanced fibrosis, liver failure and comorbidities).

The Brazilian protocol is much more concise, and limited. Does not make formal distinction between sub genotypes 1a and 1b. Pharmacoeconomic factors were also considered as well. The DAA drugs are available free to cirrhotic mono infected or coinfected HIV-HCV patients, compensated cirrhotic and hepatic transplanted patients.

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All protocols recommend quantitative HCV viral load testing at the end of treatment and 24 weeks or longer following the completion of therapy (Rating: Class I, Level B).

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Table 2: EASL Recommendations (2015)64: monoinfected or HCV/HIV coinfected patients.

HCV genotype	no cirrhosis	compensated cirrhosis (Child-Pugh A)
1	SOF + DACLA: 12 weeks. SOF + SIM: 12 weeks. 3D: 1a: 12 weeks with ribavirina; 1b: 12 weeks without ribavirin. SOF+ LEDI: 12 weeks. - Tolerant patients to interferon. SIM+ RBV +PEG-IFN: 12 weeks (naïves or relapsers) and 24 weeks (partial or null responders) or SOF+ RBV + IFN: 12 weeks.	SOF+DACLA: 12 weeks with ribavirin or 24 weeks without ribavirin. SIM+ SOF: 12 weeks with ribavirin or 24 weeks without ribavirin. 3D Regimen: 1a: 24 weeks with ribavirin; 1b: 12 weeks with ribavirin. SOF+ LEDI: 12 weeks with ribavirin or 24 weeks with ribavirin (if negative predictors). - Tolerant patients to interferon. SIM+ RBV +PEG-INF: 12 weeks (naïves or relapsers) and 24 weeks (partial or null responders). SOF+ RBV +PEG-INF: 12 weeks
2	SOF + DACLA: 12 weeks SOF+ R: 12 weeks. - Tolerant patients to interferon. SOF + RBV +PEG-IFN: 12 weeks.	SOF and DACLA: 12 weeks without RBV. SOF+ RBV: 16-20 weeks. - Tolerant patients to interferon: SOF+ RBV +PEG-IFN: 12 weeks.
3	SOF + DACLA: 12 weeks without RBV. SOF+ RBV: 24 weeks. - Tolerant patients to interferon: SOF+ RBV +PEG-IFN: 12 weeks.	SOF+ DACLA: 24 weeks with RBV. - Tolerant patients to interferon: SOF+ RBV +PEG-IFN: 12 weeks.
4	SOF+ DACLA: 12 weeks. SOF+ SIM: 12 weeks. 2D Regimen: 12 weeks with RBV. SOF+ LEDI: 12 weeks. - Tolerant patients to interferon. SIM: 12 weeks (naïves or relapsers) and 24 weeks (partial or null responders). SOF+ RBV +PEG-IFN: 12 weeks.	SOF+ DACLA: 12 weeks with RBV or 24 weeks without RBV. SOF+ SIM: 12 weeks with RBV, or 24 weeks without RBV. 2D Regimen: 24 weeks with RBV. SOF+ LEDI: 12 weeks with RBV, or 24 weeks without RBV (if negative predictors). - Tolerant patients to interferon. SIM: 12 weeks (naïves or relapsers), and 24 weeks (partial or null responders). SOF+ RBV +PEG-IFN: 12 weeks.
5,6	SOF and DACLA: 12 weeks. SOF and LEDI: 12 weeks. -Tolerant patients to interferon. SOF+ RBV +PEG-IFN: 12 weeks.	SOF and DACLA: 12 weeks with RBV or 24 weeks without RBV. SOF and LEDI: 12 weeks with RBV or 24 without RBV (if negative predictors). - Tolerant patients to interferon. SOF+ RBV +PEG-IFN: 12 weeks.

Abbreviations: SOF: Sofosbuvir; SIM: Simeprevir; 3D Regimen: Paritavir/ Ritonavir-boosted, Ombitasvir, and Dasabuvir; 2D Regimen: Paritavir/ Ritonavir-boosted, and Ombitasvir; LEDI: Ledipasvir; RBV: Ribavirin PEG-IFN: Peguilated Interferon.
Note –EASL (2015) recommends for retreatment:

1. Patients who failed after PegIFN-α and Ribavirin combination treatment must be retreated like treatment-naive patients, according to the above recommendations by HCV genotype. (Class I, level A).
2. Patients infected with HCV genotype 1 who failed after a triple combination regimen of PegIFN-α, ribavirin and either telaprevir or boceprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, sofosbuvir and daclatasvir, with ribavirin for 12 weeks. (Class I,level A).

Table 3: AASLD/IDSA Recommendations65 (Up to date December 2015) monoinfected or HCV/HIV coinfected patients.

HCV genotype	NAÏVE PATIENTS	
1a	DACLA + SOF: 12 weeks (no cirrhosis), Class I, Level B; or 24 weeks with/without RBV (cirrhosis), Class IIa, Level B. SOF + LEDI: 12 weeks, Class I, Level A 3D Regimen + RBV: 12 weeks (no cirrhosis), Class I, Level A; or 24 weeks (cirrhosis), Class I, Level A. SIM + SOF: 12 weeks (no cirrhosis), Class I, Level A; or 24 weeks (cirrhosis without Q80K) with or wSithout RBV, Class I, Level A.	
1b	DACLA + SOF: 12 weeks (no cirrhosis), Class I, Level B; or 24 weeks with/without RBV (cirrhosis), Class IIa, Level B. SOF + LEDI: 12 weeks, Class I, Level A. 3D Regimen: 12 weeks, Class I, Level A. SIM + SOF: 12 weeks (no cirrhosis), Class I, Level A; or 24 weeks with/without RBV (cirrhosis), Class I, Level A.	
2	DACLA + SOF: 12 weeks, Class IIa, Level B. SOF + RBV:12 weeks, Class I, Level A;; or 16 weeks (cirrhosis), Class IIb, Level C	
3	DACLA + SOF: 12 weeks (no cirrhosis), Class I, Level A; or 24 weeks with/without RBV (cirrhosis), Class IIa, Level C . SOF + RBV + PEG-IFN: 12 weeks (if IFN-eligible), Class I, Level A. SOF + RBV: 24 weeks, Class I, Level A.	
4	SOF + LEDI: 12 weeks, Class IIb, Level B. 2D Regimen + RBV: 12 weeks, Class I, Level B. SOF + RBV: 24 weeks, Class IIa, Level B. SOF + RBV + PEG-IFN: 12 weeks, Class II, Level B.	
5 and 6	SOF + LEDI: 12 weeks, Class IIa, Level B. SOF + RBV + PEG-IFN: 12 weeks, Class IIa, Level B.	
RETREATMENT IN PERSONS WHOM PRIOR THERAPY HAS FAILED		
HCV genotype	no cirrhosis	compensated cirrhosis

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1a	SOF + LEDI: 12 weeks, Class I, Level A. 3D Regimen + RBV: 12 weeks, Class I, Level A. SOF + SIM: 12 weeks, Class IIa, Level B. SOF + DACLA: 12 weeks, Class IIa, Level B	SOF + LEDI: 24 weeks, Class I, Level A. 3D Regimen + RBV: 24 weeks, Class I, Level A. SOF + LEDI + RBV: 12 weeks, Class I, Level B. SOF + DACLA with/without RBV: 24 weeks, Class IIa, Level B. SOF + SIM with/without RBV: 24 weeks, Class IIa, Level B.
1b	LEDI + SOF: 12 weeks, Class I, Level A. 3D Regimen: 12 weeks, Class I, Level A. SIM + SOF:12 weeks, Class IIa, Level B. SOF + DACLA: 12 weeks, Class IIa, Level B	3D Regimen: 12 weeks, Class I, Level A. SOF + LEDI: 24 weeks, Class I, Level A. SOF + LEDI + RBV: 12 weeks, Class I, Level B. SOF + DACLA with/without RBV: 24 weeks, Class IIa, Level B. SOF + SIM with/without RBV: 24 weeks, Class IIa, Level B.
2 (with or without cirrhosis)	SOF + RBV: 16 or 24 weeks, Class I, Level A. SOF + RBV + PEG-IFN: 12 weeks, Class IIa, Level B (If IFN-eligible).	
3	no cirrhosis	compensated cirrhosis
	SOF + DACLA: 12 weeks, Class I, Level A. SOF + RBV + PEG-IFN: 12 weeks, Class IIa, Level B (If IFN-eligible).	SOF + RBV + PEG-IFN: 12 weeks, Class I, Level A. (If IFN-eligible). SOF + DACLA + RBV: 24 weeks, Class IIa, Level C.
4 (with or without cirrhosis)	SOF + LEDI: 12 weeks, Class II a, Level B. 2D Regimen: 12 weeks, Class II a, Level B. SOF + RBV + PEG-IFN: 12 weeks, Class IIa, Level B (If IFN-eligible). SOF + RBV: 24 weeks, Class II a, Level B.	
5 and 6 (with or without cirrhosis)	SOF LEDI: 12 weeks, Class II a, Level C. SOF + RBV + PEG-IFN: 12 weeks, Class IIa, Level C (If IFN-eligible).	

Abbreviations: SOF: Sofosbuvir, SIM: Simeprevir, 3D Regimen:Paritavir/Ritonavir-boosted, Ombitasvir, and Dasabuvir, 2D Regimen: Paritavir/Ritonavir boosted, and Ombitasvir LEDI: Ledipasvir, RBV: Ribavirin, PEG-IFN: peguilated Interferon.

Table 4: The Brazil's Health Ministry protocol (2015)66 for DAA usage, monoinfected or HCV/HIV coinfected patients.

HCV genotype	naïve patients	Child-Ploug B/C; treatment-experienced; HIV-HCV coinfection
1	SOF+ DACLA or SOF+ SIM: 12 weeks; Class I, Level A.	SOF + DACLA: 24 weeks; Class I,Level B.
2	all patients	
	SOF+ RBV: 12 week;, Class I, Level A.	
3	no tolerant patients to interferon	tolerant patients to interferon
	SOF+ DACLA with or without RBV: 12 weeks; Class I Level B.	SOF+RBV + PEG-IFN: 12 weeks (If IFN-eligible); Class I Level B.
4	SOF + DACLA: 12 weeks; Class I Level C.	SOF + DACLA+ RBV + PEG-IFN:12 weeks (If IFN-eligible); Class I Level A.

Abbreviations: SOF: Sofosbuvir, SIM: Simeprevir, LEDI: Ledipasvir, R: Ribavirin, RBV: Ribavirin; PEG-IFN: peguilated Interferon.

Table 5: Main Drug interactions between Direct-Acting Antivirals and Antiretroviral drugs*.

	SOFOSBOVIR	DACLATASVIR	PARITAPREVIR, RITONAVIR, OMBITASVIR plus DESABUVIR (PrOD)	SIMEPREVIR	LEDIPASVIR
Ritonavir-boosted atazanavir	–	Daclastavir ↑	Paritaprevir ↑ Atazanavir ↑	–	Ledipasvir ↑ Atazanavir ↑
Ritonavir- boosted darunavir	Sofosbovir ↑ Darunavir ↔	Daclatasvir ↑ Darunavir ↔	Paritaprevir ↑/↓ Darunavir ↓	Simeprevir ↑ Darunavir ↔	Ledipasvir ↑ Darunavir ↔
Ritonavir- boosted lopinavir	–	Daclatavir ↑ Lopinavir ↔	Paritaprevir ↑ Lopinavir ↔	–	–
Ritonavir- boosted tipranavir	–	–	–	–	–
Efavirenz	Sofosbovir ↔ Efavirenz ↔	Daclatasvir ↓	No Pharmacokinetic data	Simeprevir ↓ Efavirenz ↔	Ledipasvir ↓ Efavirenz ↓[a]
Rilpivirine	Sofosbovir ↔ Rilpivirine ↔	–	Paritaprevir ↑ Rilpivirine ↑	Simeprevir ↔ Rilpivirine ↔	Ledipasvir ↔ Rilpivirine ↔
Etravirine	–	Daclatasvir ↓	–	–	–
Raltegravir	Sofosbovir ↔ Raltegravir ↔	–	PrOD ↔ Raltegravir ↑	Simeprevir ↔ Raltegravir ↔	Ledipasvir ↔ Raltegravir ↔
Cobicistat- boosted elvitegravir	Sofosbovir ↑ Cobicistat ↑	–	–	–	Ledipasvir ↑ Cobicistat ↑
Dolutegravir	–	Daclatasvir ↔ Dolutegravir ↑	Paritaprevir ↓ Dolutegravir ↑	–	Ledipasvir ↔ Dolutegravir ↔
Maraviroc	–	–	–	–	–
Tenofovir disoproxil fumarate	Sofosbovir ↔ Tenofovir disoproxil fumarate ↔	Daclatasvir ↔ Tenofovir disoproxil fumarate ↔	Paritaprevir ↔ Tenofovir disoproxil fumarate ↔	Simeprevir ↔ Tenofovir disoproxil fumarate ↔	Ledipasvir ↑ Tenofovir disoproxil fumarate ↑

**Adapted from: AASLD/IDSA. Unique Patient Populations: Patients with HIV/HCV Coinfection. 2015.http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection.

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The Tables 2, 3 and 4 show the recommendations to chronic HCV treatment by EASL, AASLD/IDSA and the Brazil's Health Ministry, respectively.

Infection Hiv-Hcv

The efficacy of DAA therapy in HIV-HCV coinfection is similar with HCV monoinfection. Table 5 shows the main interactions of DAA with antiretroviral drugs. It is recommended to avoid drugs administration without clarify of drug interactions. Sofosbuvir and daclastavir are more adequate to treat coinfection, due to lower interaction with other antiretroviral drugs.

Comments

The effectiveness of the new DAA against the HCV virus is very high, almost revolutionary, certainly offering therapeutic solution to thousands of patients. However, the use of these drugs requires a more thorough evaluation in treatment of patients in real life [67,68]. Multiple aspects were not considered in the pivotal protocols, or in other minor further studies. Some aspects already are obvious enough, such as: comorbidities, more clear indications for decompensated cirrhotic patients, or liver pretransplant; use in children; further knowledge of the implications of antiviral drug resistance, interactions of DAA with other drugs; the need of further research about patients that reach sustained virologic response; better schemes and new drugs for the treatment of patients with genotype 3.

Because clinical trials are conducted under very special conditions, adverse reaction rates observed may be lower than in routine medical practice.

The high cost of DAA is an important limiting factor for their use in most countries. That will require intense price negotiations, or use of generic drugs traded between the pharmaceutical industry and governments.

The recommendations of international medical societies and by Brazilian government protocol should occur in short intervals, in order to include new knowledge acquired in studies and the incorporation of new drugs.

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