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Use of Daclatasvir in HCV/HIV-Coinfected Patients in a Real-Life Setting

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Abstract

The burden of HIV and HCV coinfection is estimated to affect 5-7 million people worldwide, with approximately 15-30% of people with HIV coinfected with HCV. The first oral direct-acting antivirals have shown to improve the response in patients with HIV/HCV coinfection, and more recently, other direct-acting antivirals that target various stages of the HCV life cycle have been developed, among them daclatasvir.

The objective of this article is to examine recent clinical studies investigating the efficacy and safety of daclatasvir in comparison with other antiretroviral drugs, focusing on its efficacy in the coinfected HIV patient and real-life data.

Daclatasvir is a direct-acting antiviral first-in-class HCV NS5A replication complex inhibitor, approved in June 2014 by the European Medicines Agency for use in combination with other medicinal products for the treatment of chronic HCV infection in adults, and in July 2015 by the Food and Drug Administration. Its efficacy was demonstrated in several trials, with a mean sustained virologic response 12 weeks after therapy completion above 90%. The majority of adverse events related to treatment were mild-to-moderate in severity, with no discontinuation of therapy because of an adverse event and no clinically significant interactions with most of HIV antiretrovirals. The efficacy of daclatasvir in HIV/HCV-coinfected patients was demonstrated in many studies, and confirmed by real-life data for patients with different genotypes, patients with cirrhosis, and in association with ribavirin, opening a new frontier in the treatment of these patients. **(AIDS Rev. 2017;19:24-34)**

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Key words

Daclatasvir. Efficacy. HCV-HIV coinfection. Safety.

HIV/HCV coinfection: Epidemiology and treatment options

The burden of HIV and HCV coinfection is estimated to affect 5-7 million people worldwide[1,2]. Approximately 15-30% of people with HIV are estimated to be coinfected with hepatitis C virus (HCV), and up to 90% of those with HIV secondary to injection drug use are coinfected[3]. HCV is ~10 times more infectious than HIV through percutaneous blood exposures, and HIV-infected persons who inject drugs represent the majority of HIV/HCV coinfections[4]. The HIV/HCV coinfection is associated with accelerated hepatic fibrosis progression and higher rates of liver decompensation and death compared to HCV monoinfection, and liver disease is a leading cause of non-AIDS-related mortality among HIV-infected patients[5]. HIV accelerates HCV-related fibrosis progression through multiple mechanisms: enhanced HCV replication, decreased rate of HCV

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clearance after an acute infection, accelerated fibrogenesis, increased frequency of liver decompensation and death, and diminished response to HCV antiviral therapy[5]. Suppression of HIV seems to reduce fibrosis progression and decrease rates of hepatic decompensation among coinfected patients[6,7]. In patients coinfected with HIV and HCV, treatment of HIV with antiretroviral therapy (ART) has been shown to delay the progression of cirrhosis, and those with undetectable HIV RNA tend to progress more slowly to cirrhosis than those with detectable viremia[6,8]. In addition, treatment of HIV is associated with reduced complications from end-stage liver disease, including hepatocellular carcinoma and death[7]. Successful HCV therapy is associated with a halting of fibrosis progression and decreased complications from end-stage liver disease, but historical rates of sustained virologic response (SVR) have been significantly lower among coinfected patients than those with chronic HCV monoinfection, so treatment uptake has remained low, given the limited efficacy and tolerability of current HCV regimens[9,10]. Peginterferon-alpha/ribavirin (PEG-IFN-α/ribavirin) treatment for chronic HCV infection is actually associated with an SVR (undetectable HCV RNA levels after treatment) in approximately 40% of patients with genotype 1 (GT 1) infection and 75% of patients infected with GT 2 or 3[11,12]. Adding the first oral direct acting antivirals (DAA) boceprevir or telaprevir has been shown to improve the response in patients with GT 1 infection[13,14]. However, the addition of boceprevir or telaprevir is limited to HCV GT 1 and is associated with adverse events (AE), complicated dose regimens, and viral resistance[15,16].

More recently, other DAAs that target various stages of the HCV lifecycle have been developed, among which is daclatasvir. Daclatasvir is a DAA first-in-class HCV NS5A replication complex inhibitor[17] with potent antiviral activity and broad genotypic coverage, administered orally once daily[18]. It is effective in patients infected with GT 1, 2, 3, or 4 when this treatment is combined with an interferon-free sofosbuvir regimen[19].

In June 2014 the European Medicines Agency (EMA) approved daclatasvir for use in combination with other medicinal products across genotypes 1, 2, 3 and 4 for the treatment of chronic HCV infection in adults[20] and in July 2015 the U.S. Food and Drug Administration (FDA) extended its approval for the use of daclatasvir and sofosbuvir for the treatment of HCV GT 3 infections, as the first drug that has demonstrated safety and efficacy to treat GT 3 HCV infections without the need for co-administration of interferon or ribavirin[21].

The objective of this article is to examine recent clinical studies investigating the efficacy and safety of daclatasvir in HIV/HCV-coinfected patients in a real-life setting.

In order to achieve this aim, combined automated and manual literature searches were performed on PubMed using the search terms “daclatasvir” AND “HCV” AND “HIV”. No other limits were applied. The search results were manually examined to select relevant clinical studies and reviews. The bibliographies of relevant reviews were also searched to find suitable papers for inclusion and references were supplied from the authors’ own libraries.

Daclatasvir and the other antiretroviral drugs

The drugs available for the treatment of HCV infection include the following: PEG-IFN-α, ribavirin, and the most recent DAAs sofosbuvir, sofosbuvir/ledipasvir, simeprevir, paritaprevir/ombitasvir/ritonavir, dasabuvir, and daclatasvir[22].

Efficacy

Since the discovery of HCV in 1989[23], strategies to cure the infection have evolved dramatically. A cure is defined as SVR and consists of undetectable levels of plasma HCV RNA at 12 (SVR12) or 24 (SVR24) weeks after therapy completion[24]. The combination of peginterferon and ribavirin has been the standard of care for patients with chronic hepatitis C, regardless of the strain of the virus (GT 1, 2, 3, 4, 5, or 6). This regimen results in SVR rates of 70-80% among patients with HCV GT 2 or 3 infection, and rates of 45-70% among patients with any of the other genotypes[25].

Very recently, newer DAAs have been licensed by the EMA and FDA to be used mainly as part of interferon-free combinations, offering high SVR rates (> 95%) and short treatment duration. These agents include the following.

Sofosbuvir

Sofosbuvir (Sovaldi, Gilead), the first nucleotide analogue NS5B polymerase inhibitor[26] in association with ribavirin for 12-24 weeks in HCV GT 1, evaluated in two evidence level 2B studies, achieved a response to treatment in treatment-naive patients of 68-84%[27,28].

Simeprevir

Simeprevir (Olysio, Janssen), a second-wave NS3/4A protease inhibitor, achieving SVR in 77-92% of GT

1 patients, compared to 46% under PEG-IFN plus ribavirin[29,30], and in 83% of patients with cirrhosis versus the historical control (70%)[31].

Ledipasvir/sofosbuvir

The co-formulation of the NS5A inhibitor ledipasvir with sofosbuvir (Harvoni, Gilead), that reached a high SVR in 94% of patients (95% CI: 87-97) for 12 weeks treatment of ledipasvir/sofosbuvir; 96% (95% CI: 91-99) for 12 weeks treatment of ledipasvir/sofosbuvir and ribavirin; 99% (95% CI: 95-100) for 24 weeks treatment of ledipasvir/sofosbuvir; and 99% (95% CI: 95-100) for 24 weeks treatment of ledipasvir/sofosbuvir and ribavirin[32].

Ombitasvir/paritaprevir/dasabuvir

The co-formulation of a ritonavir-boosted NS3/4A protease inhibitor, paritaprevir, with the NS5A inhibitor ombitasvir (Viekirax, Abbvie) and dasabuvir (Exviera, Abbvie), a non-nucleos(t)ide NS5B polymerase inhibitor. Non-cirrhotic patients with HCV GT 1b experienced SVR12 rates of 96-100% when ombitasvir/paritaprevir/ritonavir and dasabuvir were administered for 12 weeks, regardless of inclusion of ribavirin. SVR12 rates of 95-97% were seen in noncirrhotic patients with HCV GT 1a infection who received ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks[33].

Daclatasvir

The efficacy of daclatasvir (Dankliza, Bristol-Myers Squibb), a NS5A inhibitor, was demonstrated in several studies where treatment-naive and treatment-experienced patients with chronic HCV infection across various genotypes were treated, as reported in the EMA Assessment Report of 26th June 2014[19]. The clinical development of this drug started when PEG-IFN/ribavirin dual therapy was standard of care for all genotypes (AI444010[34], AI444042[35], AI444011, AI444014, AI444021, AI444022, AI444031[19]), so dose-ranging studies were performed in combination with these drugs, and the original phase II program was designed to define the best use/activity of daclatasvir with an interferon-based regimen and an interferon-free regimen in HCV and HIV/HCV patients.

All the above-mentioned AI444 trials showed that treatment with daclatasvir (at the recommended dose of 60 mg once daily) offered a favorable benefit/risk ratio in patients infected by the four HCV genotypes (1, 2, 3, 4)[19]. In order to define the efficacy and safety of daclatasvir with an interferon-free regimen, it was also studied in a phase III trial in combination with the NS3/4A protease inhibitor asunaprevir, observing if an SVR could be reached in chronic hepatitis C without the use of interferon[36], and finally in a large phase IIb trial (AI444040)[37], the pilot study where the daclatasvir/sofosbuvir combination regimen, with or without ribavirin, was analyzed and demonstrated an efficacy measured as SVR12 after therapy completion across different HCV genotypes reaching 100%[19]. The efficacy of daclatasvir was also shown in the series of ALLY trials, namely ALLY-1[38], ALLY-2[39], ALLY-3[40]. The open-label ALLY-1 study assessed the safety and efficacy of a 60 mg once-daily dosage of daclatasvir in combination with sofosbuvir 400 mg once daily and ribavirin 600 mg/day for 12 weeks with a 24-week follow-up in two cohorts of patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or post-transplantation recurrence[38]. Results showed that in patients with cirrhosis, 82% (95% CI: 67.9-92.0) with GT 1 infection achieved SVR12, whereas the corresponding rates in those with GT 2, 3, and 4 were 80, 83, and 100%, respectively. In transplant recipients, SVR12 was achieved by 95% (95% CI: 83.5-99.4) and by 91% of patients with GT 1 and 3 infection[38]. The phase III study named ALLY-3 evaluated a 12-week regimen of daclatasvir plus sofosbuvir in patients infected with HCV GT 3[38]. Patients were either treatment-naive (n = 101) or treatment-experienced (n = 51) and received daclatasvir 60 mg plus sofosbuvir 400 mg once daily for 12 weeks; regarding endpoints, SVR12 rates were 90% (91/101) and 86% (44/51) in treatment-naive and treatment-experienced patients, respectively; no virological breakthrough was observed, and 99% of patients had a virological response at the end of treatment. The SVR12 rates were higher in patients without cirrhosis (96%; 105/109) than in those with cirrhosis (63%; 20/32)[38].

Daclatasvir efficacy and safety data were also available specifically for HIV/HCV-coinfected populations, both with and without interferon/ribavirin[39,35]. In the ALLY-2 trial, the SVR was 97% in treatment-naive and 98.1% in treatment-experienced patients[39], and these results were confirmed and surpassed in a recent study about interferon-free treatment with sofosbuvir/daclatasvir in HIV/HCV-coinfected patients with advanced liver disease, where the SVR12 reached directly 100%[41].

Safety

Patients treated with daclatasvir and sofosbuvir may experience headache, fatigue, and nausea. The majority of AEs with this combination were mild-to-moderate in

severity, with only two grade 3 and zero grade 4 AEs reported in ALLY-3. Additionally, there was only one serious AE, and no patient discontinued therapy because of an AE. The most common AEs (in at least 10% of patients) were headache (20%), fatigue (19%), and nausea (12%). Less than 2% of patients suffered from grade 3 or 4 neutropenia, lymphopenia, elevated international normalized ratio, and elevated lipase[39,42].

Interactions

Drug interactions between DAAs and other medications or other DAAs are of particular concern with the use of the protease inhibitors and should be reviewed prior to the initiation of HCV therapy[43]. This is of particular importance in HIV/HCV-coinfected patients, as a change of optimized ARV regimen could lead to serious AEs, including HIV viral breakthrough[44].

Daclatasvir is a substrate for CYP3A4 and P-glycoprotein, and moderately inhibits P-glycoprotein and OATP1B1.

Increases in daclatasvir levels are seen with the co-administration of strong CYP3A inhibitors (e.g. atazanavir/r and cobicistat-boosted regimens). In healthy volunteers atazanavir/r increases daclatasvir AUC ~2.1-fold, even if the magnitude of increase in daclatasvir exposure is not as high with darunavir/r (1.4-fold) or lopinavir/r (1.15-fold). For these reasons, a daclatasvir dose reduction to 30 mg once daily is recommended when used with atazanavir/r or cobicistat-boosted ARVs[45]. A reduction in daclatasvir exposure is seen when used with CYP3A inducers such as efavirenz: in particular, in healthy volunteers, daclatasvir AUC was reduced by 32% when co-administered with this drug. It is effectively recommended an increase in daclatasvir dose to 90 mg once daily to overcome this interaction[46]. The co-administration with rilpivirine does not require dose modification. Otherwise, co-administration of daclatasvir with etravirine and nevirapine is not recommended, due to the lack of data and the expected decrease in daclatasvir concentrations mediated by CYP3A4 induction. Furthermore, regarding the concomitant use of daclatasvir and dolutegravir, no significant interaction was observed[43], and there is no anticipated interaction between daclatasvir and raltegravir.

Finally, no significant interactions are reported between daclatasvir and tenofovir and no interactions are expected with the other N(t)RTIs[43]. It is noteworthy, moreover, that no significant interactions are reported with proton pump inhibitors and it can be administered with buprenorphine or methadone without dose adjustments[43].

Resistance

Resistance-associated variants (RAV) are an important factor to be considered in NS5A inhibitors. The NS5A inhibitor RAVs tend to be fit, allowing them to persist for a long time after failure of NS5A inhibitor therapy. These RAVs occur in a spontaneous manner in 15-20% of treatment-naive patients with HCV GT 1, and at higher rates in patients infected with other genotypes[47]. Although daclatasvir showed a moderate-to-high genetic barrier to resistance in clinical trials, some resistance variants emerged during daclatasvir monotherapy in patients with GT 1a and 1b[48,49]. These were mutations at L31F/V, P32L, and Y93H/N in genotype 1b. Genotype 1a presented more mutations that led to higher levels of resistance, with amino acid substitutions at M28T, Q30E/H/R, L31M/V, P32L, and Y93C/H/N. These resistant variants still had susceptibility to IFN-α and NS3 protease and NS5B (nucleoside and nonnucleoside) polymerase inhibitors, suggesting that variants will be susceptible to daclatasvir in combination therapies[50].

Regarding combination therapy, in a *post hoc* analysis of the HALLMARK DUAL trial, conducted to determine the efficacy and safety of daclatasvir plus asunaprevir in Korean and Taiwanese patients, the presence of key baseline NS5A resistance-associated polymorphisms Y93H and/or L31M/V was found to be significantly predictive of SVR12 (NS5A RAVs absent vs. present in Asian patients; OR: 19.64; 95% CI: 4.72-81.75; $p < 0.0001$)[51]. Other important results regarding resistance wererederived from studies whose results were presented at recent international congresses; the most relevant are the following.

In a phase III, open-label study of daclatasvir plus asunaprevir in Asian GT 1b IFN-ineligible or -intolerant patients, there was a 100% concordance between SVR12 and SVR24 and 13/13 patients with virologic failure had NS5A RAVs (L31F/M/V and/or Y93H) or NS3 RAVs (D168E/T/V/Y) at treatment failure. The baseline NS5A RAVs (L31M or Y93H) were present in 19 patients (12%); 8/19 (42%) achieved SVR24, 137/139 (99%) patients without baseline NS5A RAVs achieved SVR24 (43/44 (98%) with cirrhosis, and 94/95 (99%) without cirrhosis)[52].

In a study regarding the impact of NS5A baseline RAVs on SVR12 rates in GT 1b patients using a dual regimen in China, Korea, Japan and Taiwan, data were pooled from six clinical studies in which patients with GT 1b infection received daclatasvir plus asunaprevir for 24 weeks. Only patients with GT 1b infection who

had baseline NS5A sequence data were included; all patients received the recommended doses of daclatasvir (60 mg once daily) and asunaprevir (200 mg tablet [phase II] or 100 mg soft-gel capsule [phase III] twice daily). The efficacy endpoint was SVR12, defined as HCV RNA < 25 IU/ml (non-Japanese studies) or < 15 IU/ml (Japanese studies) at PT12. For SVR12 analyses, non-virologic failures were censored. A total of 735 patients were included in the analysis of baseline NS5A polymorphisms at L31 and Y93H and a total of 729 patients were included in the SVR12 analyses. Results showed that in the absence of BL L31F/I/M/V and/or Y93H, SVR12 rates were high irrespective of prior treatment status and results were similar across national groups[53]. Among all GT 1b-infected patients, SVR12 rates in the absence of the RAVs L31F/I/M/V and/or Y93H at baseline were high (SVR12 range: 88.0-93.9%); neither baseline L28M nor R30Q had any relevant effect on SVR12 in the absence of NS5A polymorphisms at amino acids 31 or 93, and SVR12 in daclatasvir plus asunaprevir treatment was 94% in the absence of baseline L31F/I/M/V and/or Y93H (the SVR12 rate was 39% where either or both of these polymorphisms were present at baseline)[54].

The all-oral, ribavirin-free regimen of daclatasvir plus asunaprevir was highly efficacious for treatment of GT 1b without baseline NS5A-L31 or NS5A-Y93H resistance-associated polymorphisms, with SVR12 rates of up to 100% across subgroups including the elderly (> 65 years of age) and patients with cirrhosis. In the light of these findings, Authors suggested that pretherapy screening for NS5A polymorphisms at L31 and Y93H may be beneficial.

Regarding daclatasvir plus asunaprevir regimens, a recent study demonstrated that 100% of GT 1a and GT 1b patients with baseline NS5A RAVs at amino acid positions associated with daclatasvir resistance achieved SVR12 when treated with daclatasvir plus sofosbuvir with or without ribavirin for 12 weeks[55]. In the same population, all HCV-mono-infected and HIV/HCV-coinfected GT 1a patients achieved SVR12, irrespective of the presence or absence of baseline NS5A RAVs, and one of 31 post-transplant GT 1a patients did not achieve SVR12, while all 34 HCV-mono-infected and HIV/HCV-coinfected GT 1b patients achieved SVR12, irrespective of the presence or absence of baseline NS5A RAVs.

Moreover, when using the combination of an NS5A inhibitor with another DAA having a high barrier to resistance, such as sofosbuvir, the issue of NS5A inhibitor resistance can be erased: in the ALLY-3 trial where patients, mostly cirrhotic, were treated with daclatasvir combined with sofosbuvir, resistance mutations emerged in some HCV GT 3-infected patients.

Regarding SVR in patients infected with HCV GT 2 with baseline NS5A polymorphisms treated with daclatasvir-based regimens, a recently published study by Zhou, et al. showed that high SVR rates were achieved in patients infected with GT 2 treated with daclatasvir-based regimens, irrespective of GT 2 subtype or baseline NS5A polymorphisms. In particular, of 13 GT 2 subtypes identified from 426 NS5A sequences, the most prevalent were GT 2a (32%), GT 2b (48%) and GT 2c (10%), and the most prevalent NS5A polymorphism was L31M (GT 2a 88%; GT 2b 59%; GT 2c 10%). Substitutions identified in 96% of GT 2 NS5A sequences exhibited daclatasvir EC50 values ranging from 0.005 to 20 nM when tested *in vitro* and a similar range in daclatasvir EC50 values was observed for 16 diverse GT 2 patient-derived NS5A sequences (EC50: 0.005-60.0 nM). Depending on the daclatasvir-based regimen studied (daclatasvir/interferon-based or daclatasvir/sofosbuvir-based), the SVR rates ranged from 90 to 100% in GT 2 patients with the most prevalent baseline NS5A-L31M polymorphism, compared with 96-100% without this polymorphism[56].

When considering treatment-experienced patients with HCV GT 3 infection and advanced fibrosis or compensated cirrhosis, daclatasvir/sofosbuvir/ribavirin for 12 or 16 weeks is an efficacious and well-tolerated regimen. This combination used for 12 or 16 weeks achieved 89% SVR12, with a response independent of previous IFN-based treatment outcomes and comparable across subgroups. All five treatment-experienced patients with baseline NS5A-Y93H or A30K achieved SVR12, including one with A30K and prior relapse following sofosbuvir plus ribavirin. Overall, 3/5 patients with prior relapse following sofosbuvir plus ribavirin achieved SVR12, with no treatment-related deaths, serious AEs, or AEs leading to discontinuation reported[57].

In another study, the pan-genotypic all-oral regimen of daclatasvir/sofosbuvir ± ribavirin has provided high SVR rates across diverse groups of GT 3-infected patients. Prevalence of baseline NS5A variants was ≈30% higher with a sequencing cut-off of ≥ 1% versus ≥ 10%, and similar SVR12 rates were observed in GT 3-infected patients with baseline variants whether using ≥ 1% or ≥ 10% sequencing cut-offs. Emergent NS5A minor variants detected in GT 3-infected patients with treatment failure did not persist, showing generally that baseline NS5A minor variants do not appear to impact overall SVR rates in GT 3-infected patients[58]. In order

to overcome the problem of RAVs, suggestions could be a careful assessment of patient history, disease severity, and viral genotype/subtype. All these strategies may help in the selection of the more efficient drug combination and the optimal duration of treatment, especially in a small number of difficult to treat patients such as those with cirrhosis. For all the other patients, baseline or following treatment RAVs seemed to not preclude SVR.

Efficacy of daclatasvir in HIV/HCV-coinfected patients

In the AI444043 study, 301 treatment-naive patients with HCV GT 1 infection and HIV coinfection (10% with compensated cirrhosis) were treated with daclatasvir in combination with PEG-IFN/RBV. The dose of daclatasvir was 60 mg once daily, with dose adjustments for concomitant ARV use. Patients achieving virologic response (HCV RNA undetectable at weeks 4 and 12) completed therapy after 24 weeks, while those who did not achieve virologic response received an additional 24 weeks of treatment with PEG-IFN/RBV, to complete a total of 48 weeks of study therapy. An SVR12 was achieved by 74% of patients in this study (GT 1a: 70%, GT 1b: 79%)[59].

The combination of daclatasvir and sofosbuvir in patients coinfected with HIV-1 was studied in the ALLY-2 trial, an open-label study involving 151 treatment-naive and 52 treatment-experienced patients[19]. Previously untreated patients were randomly assigned in a 2:1 ratio to receive either 12 weeks or eight weeks of daclatasvir at a standard dose of 60 mg daily (with dose adjustment for concomitant ARV medications) plus 400 mg of sofosbuvir daily. Previously treated patients were assigned to undergo 12 weeks of therapy at the same doses. The primary end point was an SVR at week 12 after the end of therapy among previously untreated patients with HCV GT 1 who were treated for 12 weeks. Patients had HCV GT 1 through 4 (83% with GT 1), and 14% had compensated cirrhosis; 98% were receiving ART. Treatment-experienced patients were largely treated with an interferon- and ribavirin-based regimen (71%). Among patients with GT 1, SVR was reported in 96.4% (95% CI: 89.8-99.2) who were treated for 12 weeks and in 75.6% (95% CI: 59.7-87.6) who were treated for eight weeks among previously untreated patients, and in 97.7% (95% CI: 88.0-99.9) who were treated for 12 weeks among previously treated patients. Treatment-naive patients with GT 2, 3, or 4 treated for 12 weeks had higher rates of SVR12 than those treated for eight weeks (100 vs. 78%, respectively). Regardless of treatment status, patients treated with 12 weeks of therapy had higher SVR rates versus those treated with eight weeks of therapy across all subgroups, with one exception. In patients with a baseline HCV RNA < 2 million IU/ml, 100% (n = 18) of patients achieved SVR12. Rates of SVR across all genotypes were 97.0% (95% CI: 91.6-99.4), 76.0% (95% CI: 61.8-86.9), and 98.1% (95% CI: 89.7-100), respectively. The HIV-1 suppression was not compromised.

Real-life data about use of daclatasvir in HIV/HCV-coinfected patients

Literature on real-life data about the use of daclatasvir, both in HCV-monoinfected patients and in HIV/HCV-coinfected patients, is lacking at the moment because, as already said, this drug has been approved very recently by the EMA and FDA (see Introduction). Some information is available from results presented in 2015 at National and International Congresses about liver or infectious diseases.

A Comparative Assessment of Utilization of Antiviral Therapies in Hepatitis C and Effectiveness of Daclatasvir-containing Regimens in Real-life Clinical Care in Europe (CMPASS-EU) started in December 2014 and is currently recruiting participants. This observational cohort study aims to collect information on the current treatment patterns for hepatitis C in participating countries. There is also a focus on patients receiving a daclatasvir-containing treatment regimen who will be followed prospectively for 12 months after treatment initiation to collect real-world data on effectiveness and safety of the treatment. The current primary outcome measure is to quantify the effectiveness of a daclatasvir-containing regimen overall and in subgroups (GT 1, non-GT 1 and cirrhotic patients) by measuring SVR12; time frame, up to week 12 after the end of HCV treatment (SVR12), defined as a documented undetectable viral load on or after week 12 following the end of treatment. Estimated primary completion date of the study is set for December 2016[60].

Cirrhosis

Clinical practice data about the use of DAAs in patients affected by HCV and cirrhosis were recently shown at international and national congresses in the USA and Europe.

Results of a multicenter European compassionate use program about the use of daclatasvir plus sofosbuvir

with or without ribavirin for the treatment of chronic HCV in patients coinfected with HIV were presented at the 66th Annual Meeting of the American Association for the Study of Liver Diseases by Rockstroh, et al.[61]. The primary objective of these Authors was to provide access to daclatasvir to patients with life-threatening chronic HCV infection who have no other treatment options, monitoring efficacy (SVR12 achievement) and safety (clinical AE, serious AE, AE leading to discontinuation and death- and laboratory abnormalities) endpoints. All patients (52) were HIV/HCV-coinfected, most (95%) of them were also cirrhotic; 38 were treated with daclatasvir/sofosbuvir, while 14 were on a daclatasvir/sofosbuvir/ribavirin regimen. Results demonstrated that, in a real world setting, daclatasvir/sofosbuvir/ribavirin was generally safe and well tolerated in patients with HIV/HCV coinfection, including patients with advanced liver disease. The SVR12 rate was high (92%) in 49 patients with HIV/HCV coinfection, including 46 with compensated or decompensated cirrhosis. Similar SVR12 was observed in patients treated with or without ribavirin. Similarly high SVR12 rates were reached across a wide range of concomitant ARV regimens, and control of HIV disease indicators was maintained during HCV therapy. No treatment-related serious AEs were found and only few treatment-emergent grade 3 or 4 lab abnormalities were registered.

Other important findings in this field were presented at the 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention of Vancouver, Canada (19-22 July 2015). Lacombe, et al. described results of an interim analysis of a French multicenter compassionate use program about daclatasvir plus sofosbuvir with or without ribavirin in patients with HIV/HCV-coinfection[62]. Of 562 patients enrolled, 395 (71.0%) were cirrhotic and 460 (82.6%) were treatment-experienced. All patients received daclatasvir/sofosbuvir once daily for 12 or 24 weeks, with ribavirin added at the physician's discretion. Also in this program, the daclatasvir/sofosbuvir/ribavirin regimen was well tolerated and demonstrated high SVR12 rates in HIV/HCV-coinfected patients with advanced liver disease. Overall, SVR4 was obtained in 90.2% (148/164) and SVR12 in 95.9% (94/98) of the cases. Among patients treated with daclatasvir/sofosbuvir for 12 or 24 weeks, 96.0% (24/25) and 95.1% (58/61), respectively, achieved an SVR12, compared to 100% (6/6) and 100% (6/6) for patients receiving daclatasvir/sofosbuvir/ribavirin. Neither duration of treatment nor cirrhosis status and genotype influenced the rate of SVR12.

Salmon-Ceron, et al. followed a real-life prospective French national cohort, carrying out an interim analysis on 245 patients[63]. Of them, 69% were cirrhotic and 71% had failed to respond to previous treatment. The HCV genotype distribution was as follows: GT 1, 58%; GT 2, 4%; GT 3, 13%; GT 4, 25%. A total of 133 patients reached the end of treatment (54%) and 62 patients SVR12 (25%). HCV RNA was undetectable at the end of treatment in 99% of the patients (95% CI: 96-100) and global SVR12 was 90% (95% CI: 80-96). Overall, end of treatment response was 100% in both non-cirrhotic and cirrhotic patients.

Finally, a group of Italian infectivologists evaluated the efficacy and safety profile of DAAs, including daclatasvir, in 68 patients with advanced liver disease or cirrhosis and HIV/HCV coinfection. Daclatasvir was given in combination with sofosbuvir ± ribavirin in eight (12%) patients. Moderate efficacy of DAA regimens at four weeks of therapy and a good tolerability were observed, with mild-to-moderate AEs in absence of permanent suspension of treatment for them[64].

Genotype

Results shown in April 2015 at the International Liver Congress in Vienna demonstrated that the daclatasvir/sofosbuvir combination is effective amongst HCV GT 1-monoinfected patients. These results are significant because, whilst other combinations have been widely reported on, there have been few data until now regarding the use of the daclatasvir/sofosbuvir combination in real-world situations. Overall, the SVR4 for daclatasvir/sofosbuvir was 81.6% after 12 weeks of treatment and 93.9% following 24 weeks of treatment. The SVR4 rate for daclatasvir/sofosbuvir/ribavirin was 100 and 96.6% after 12 and 24 weeks, respectively. The 12-week combination of daclatasvir/sofosbuvir/ribavirin achieved a 100% SVR4 rate in cirrhotic patients without the additive effect of extension of the treatment to 24 weeks with or without ribavirin (95.7 and 92.5%, respectively), and this was also true in experienced patients. All non-cirrhotic patients achieved 100% SVR4 at 12 weeks, demonstrating that the 12-week combination of daclatasvir/sofosbuvir is a proven therapeutic option. Importantly, the SVR12 rate was 100% for daclatasvir/sofosbuvir/ribavirin after both 12 and 24 weeks[65].

Treatment of HCV GT 3-infected patients is a challenge, with urgent need of effective antiviral therapies[66]. Interim findings on the combination of daclatasvir/sofosbuvir/ribavirin in HCV GT 3-infected patients with advanced liver disease enrolled in a European compassionate use program (CUP; study AI444-237),

including 15% of patients with HIV coinfection, were the following: in a real-life clinical setting, daclatasvir/sofosbuvir/ribavirin achieved high SVR rates (87%) in HCV GT 3-infected patients at high risk of hepatic decompensation or death (87% SVR12 in cirrhotic patients) and comparable SVR12 rates with or without ribavirin in the regimen; improvements in liver function were observed as well. Daclatasvir/sofosbuvir/ribavirin was generally safe and well tolerated: few discontinuations due to AEs, treatment-related serious AEs, or grade 3/4 laboratory abnormalities were registered[67].

These findings suggest that daclatasvir/sofosbuvir/ribavirin is an effective and well-tolerated oral treatment for patients with GT 3 infection, including those with most advanced disease.

Another compassionate use program for treatment of GT 3-infected patients with advanced liver disease with daclatasvir/sofosbuvir/ribavirin was recently carried out in France (ATU - Temporary Authorization for Use). About 15% of the population were HIV/HCV-coinfected patients. In this real-world setting, daclatasvir/sofosbuvir/ribavirin for 12 or 24 weeks was well tolerated and achieved high SVR12 in GT 3 patients with advanced liver disease (97% in non-cirrhotic patients mostly with advanced fibrosis, 87% in Child-Pugh A cirrhosis, and 82% in all cirrhosis). Twenty-four weeks of daclatasvir/sofosbuvir resulted in 86% SVR12 in cirrhotic patients. Ribavirin use had no impact on SVR for 24 weeks of treatment (81% SVR12 with ribavirin), whilst the role of ribavirin in daclatasvir/sofosbuvir treatment < 24 weeks requires randomized evaluation in a larger dataset[68]. These results show that the pan-genotypic, all-oral regimen of daclatasvir/sofosbuvir/ribavirin is an effective and well-tolerated option even for patients with GT 3 infection and advanced liver disease.

An Italian real-life experience described the efficacy and safety of an anti-HCV regimen of daclatasvir/sofosbuvir without ribavirin in three cases of HIV/HCV-coinfected patients virally suppressed for HIV, treated with ARV (atazanavir 400 mg), one of which was infected with GT 3 HCV.

The coadministration of daclatasvir at standard dose of 60 mg/day with atazanavir non-boosted with ritonavir was also safe in terms of tolerability and without AEs on $CD4^+$ cell count, HIV RNA levels, and renal functionality. The Authors only suggest a frequent monitoring of bilirubinemia in case of modifying the atazanavir dosage[69].

A Sicilian real-life experience evaluated the efficacy of DAA treatment in 13 patients coinfected by HCV and HIV, of which four were GT 3. Every patient was experienced to previous treatment with PEG-IFN+RBV, stopped for intolerance, or non-responder, and five of them were relapsers. All coinfected patients were on HAART; the average CD4 count was 460/mmc, and all of them had undetectable viremia. The combination of daclatasvir/sofosbuvir was administered with or without ribavirin. Results showed a high response rate and all patients that completed treatment achieved the end-of-treatment response. All the therapies were well-tolerated[70].

Association with ribavirin

The interim results focused on HIV/HCV-coinfected patients of the CUP study AI444-237 found that, in a real-world setting, treatment with daclatasvir/sofosbuvir ± ribavirin achieved a high SVR12 rate (92%) in 49 patients with HIV/HCV coinfection, including 46 with compensated or decompensated cirrhosis. A similar SVR12 was observed in patients treated with or without ribavirin. Only one virologic failure (relapse, treated with daclatasvir 30 mg) was observed. Similarly high SVR12 rates across a wide range of concomitant ARV regimens and control of HIV disease indicators was maintained during HCV therapy. Improvements in alanine transaminase and total bilirubin were also observed between baseline and post-treatment (week 12). Daclatasvir/sofosbuvir ± ribavirin was generally safe and well tolerated and no treatment-related serious AEs were found (only few treatment-emergent grade 3 or 4 laboratory abnormalities were registered)[61].

A real practice monitoring of the safety of daclatasvir combination regimens was recently carried out in an Infectious Disease Department in Sardinia, Italy. Ninety patients were followed, seven of which were HIV/HCV coinfected. Daclatasvir was given in combination with sofosbuvir, and with sofosbuvir and ribavirin. Results showed a good tolerability of DAAs; more common AEs were asthenia, headache, itching and insomnia as in all phase III clinical trials. Nevertheless, none of patients suspended treatment because of AEs[71].

Conclusion

The efficacy of daclatasvir in HIV/HCV-coinfected patients was demonstrated in many studies, and confirmed by real-life data for patients with different genotypes, patients with cirrhosis, and in association with ribavirin, opening a new frontier in the treatment of these patients. The achievement of SVR can help in reducing liver disease progression and solving the

Table 1. Summary of recommendations about daclatasvir for patients in whom previous treatment has failed

Genotype 1a PEG-IFN/ribavirin treatment-experienced patients without cirrhosis – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a recommended regimen for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.

Genotype 1a PEG-IFN/ribavirin treatment-experienced patients with compensated cirrhosis - Alternative: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an alternative regimen for patients with HCV genotype 1a infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.

Genotype 1b PEG-IFN/ribavirin treatment-experienced patients without cirrhosis – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a recommended regimen for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.

Genotype 1b PEG-IFN/ribavirin treatment-experienced patients with compensated cirrhosis – Alternative: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is an alternative regimen for patients with HCV genotype 1b infection, who have compensated cirrhosis, in whom prior PEG-IFN/ribavirin treatment has failed.

Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/ribavirin treatment-experienced patients without cirrhosis – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who do not have cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.

Genotype 1 HCV nonstructural protein 3 (NS3) protease inhibitor (telaprevir, boceprevir, or simeprevir) plus PEG-IFN/ribavirin treatment-experienced patients with compensated cirrhosis – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a recommended regimen for patients with HCV genotype 1 infection, regardless of subtype, who have compensated cirrhosis, in whom prior treatment with an HCV protease inhibitor plus PEG-IFN/ribavirin has failed.

Genotype 2 PEG-IFN/ribavirin treatment-experienced patients without cirrhosis – Alternative: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is an alternative regimen for patients with HCV genotype 2 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.

Genotype 2 PEG-IFN/ribavirin treatment-experienced patients with compensated cirrhosis – Alternative: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is an alternative regimen for patients with HCV genotype 2 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.

Genotype 2 Sofosbuvir plus ribavirin treatment-experienced patients – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 weeks is a recommended regimen for patients with HCV genotype 2 infection, regardless of cirrhosis status, in whom prior treatment with sofosbuvir and ribavirin has failed.

Genotype 3 PEG-IFN/ribavirin treatment-experienced patients without cirrhosis – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a recommended regimen for patients with HCV genotype 3 infection, who do not have cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.

Genotype 3 PEG-IFN/ribavirin treatment-experienced patients with compensated cirrhosis - Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a recommended regimen for patients with HCV genotype 3 infection, who have compensated cirrhosis, in whom prior treatment with PEG-IFN/ribavirin has failed.

Genotype 3 Sofosbuvir and ribavirin treatment-experienced patients – Recommended: Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with weight-based ribavirin for 24 weeks is a recommended regimen for patients with HCV genotype 3 infection, regardless of cirrhosis status, in whom prior treatment with sofosbuvir and ribavirin has failed.

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
Adapted with permission from AASLD/IDSA[73].

HCV-related complications not directly affecting liver, with less liver-related and overall mortality. Guidelines published until now are useful for the management of these kinds of patients but, in accordance to other Authors[72], the economic viewpoint should be considered for each setting in order to choose the best balance between efficacy and price of each therapy. From a safety viewpoint, daclatasvir did not present any particular issues, neither about drug interactions. Considering this last point, daclatasvir presents even more advantages as it allows dosage flexibility. Nevertheless, regarding treatment in HIV/HCV-coinfected patients, it should be remembered that when prescribing the most appropriate anti-HCV drug, interactions should always

Table 2. Key points about daclatasvir

Topic	Results
Efficacy	Demonstrated in a relevant number of clinical trials and confirmed by real-life data or patients with different genotypes, patients with cirrhosis, and in association with ribavirin.
Safety	No particular adverse effects evidenced.
Drug interactions	Drug-drug interactions are manageable with the benefit of dosage flexibility.
Resistance	No particular cases observed, except for a small number of difficult to treat patients such as those with cirrhosis.

be avoided, enabling patients to follow the anti-HIV treatment already started.

For a summary of recommendations about daclatasvir for patients in whom previous treatment has failed, see table 1.

Declaration of interest

Massimo Puoti has received research grants and/or personal fees as a member of temporary advisory boards and/or speaker in own events and/or in internal courses from Abbvie, BMS, Janssen, Gilead sciences, Roche, MSD, ViiV.

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