DACLATASVIR-SOFOSBUVIR COMBINATION THERAPY WITH OR WITHOUT RIBAVIRIN FOR **HEPATITIS C** VIRUS INFECTION: FROM THE CLINICAL TRIALS TO REAL LIFE

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REVIEW

Daclatasvir–sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life

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Abstract: The treatment of hepatitis C virus has changed dramatically with the rapid advent of numerous new antiviral agents, including direct-acting antivirals and agents with non-viral targets (cyclophilin inhibitors, interferon-lambda, vaccine therapy). Given the better safety profile and high antiviral potency of direct-acting antivirals, their combination in interferon-free oral regimens is becoming the standard of care for hepatitis C virus infection, tailored to individual patients according to the degree of disease progression (fibrosis), hepatitis C virus genotype and subtype, resistance profile, and prior therapeutic history. Results from clinical studies as well as preliminary real-life data regarding the combination of sofosbuvir (a nucleotide polymerase inhibitor) and daclatasvir, a first-in-class NS5A replication complex inhibitor, demonstrate that it is one of the most promising antiviral therapies, with once-daily oral dosing, a low pill burden, good tolerability, and limited drug–drug interactions, in addition to high antiviral potency, with >90% sustained virologic response rates. This combination has high pangenotypic antiviral potency regardless of the severity and patient characteristics. The combination of sofosbuvir and an NS5A inhibitor with ribavirin for 12 weeks appears to be a very good further treatment option in both cirrhotic and treatment-experienced patients whatever the stage of fibrosis.

Keywords: hepatitis C virus, direct-acting antivirals, sofosbuvir, daclatasvir

Introduction

Direct-acting antiviral agents (DAAs) have revolutionized the treatment of hepatitis C virus (HCV) infection over the last 5 years. As a result of our better understanding of the HCV life cycle, specific DAAs have been developed for HCV that are able to target the viral proteins implicated in replication of the virus, ie, the NS3/4A protease, NS5B polymerase, and multifunctional NS5A replication complex. The first-generation protease inhibitors significantly improved the sustained virologic response (SVR) in genotype 1-infected patients, but at the cost of increased side effects, a complex pattern of drug–drug interactions, and viral resistance. In addition, the first-generation drugs still required the use of PEGylated interferon (PEG-IFN) for 24–48 weeks. Oral IFN-free combinations containing at least two DAAs enabled less complex dosing, tolerable side effects, and fewer drug–drug interactions. This review summarizes the key safety and efficacy data from clinical studies concerning the combination of sofosbuvir, daclatasvir, with or without ribavirin in the treatment of HCV.

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Summary of pharmacology and pharmacokinetics

Daclatasvir

Daclatasvir is a first-in-class HCV NS5A replication complex inhibitor with pangenotypic activity and a pharmacokinetic profile allowing once-daily dosing. Reaching in vitro 50% effective concentrations (EC_{50}) in the picomolar range against HCV replicons representing six major HCV genotypes (1a, 1b, 2a, 3a, 4a, 5a), daclatasvir is one of the most potent HCV replication inhibitors reported to date.[1] Moreover, daclatasvir was generally well tolerated, with headache being the most frequently reported adverse event.[1]

In vitro resistance selection studies (with genotype 1a and 1b replicons) have identified daclatasvir resistance-associated mutations that map to the N-terminal region of NS5A and reduced susceptibility to daclatasvir which appear to have a low to medium barrier to resistance.[2] However, treatment with an appropriate dose of daclatasvir in combination with other agents is sufficiently potent to prevent emergence of resistance in most patients. In IFN-including and IFN-free regimens, daclatasvir has demonstrated a high level of antiviral efficacy and generally tolerable safety profile in treatment-naïve patients and in patients who have not previously responded to PEG-interferon/ribavirin.

While daclatasvir is a substrate and inhibitor of P-glycoprotein and a substrate of cytochrome P450 3A4, it is not a strong inhibitor or strong inducer of cytochrome P450 3A4 isozymes, suggesting it may have a low potential for drug–drug interactions. For example, no adjustment is needed when coadministered with tenofovir, and at 90 mg once daily with efavirenz and 30 mg once daily with atazanavir/ritonavir (300/100 mg), the exposure to daclatasvir is expected to be similar to that of daclatasvir 60 mg administered alone.[3] No clinically significant pharmacokinetic drug interactions were observed for ethinyl estradiol, norelgestromin, and norgestrel exposures.[4] In addition, as for most protease inhibitors, the metabolism of NS5A inhibitors is mainly hepatic, which allows their use without any dose adjustment in patients with chronic kidney disease.

Sofosbuvir

Sofosbuvir is an orally administered HCV nucleotide polymerase NS5B inhibitor. It is given once daily, and has a good safety profile.[5,6] It has a high barrier to resistance, a pangenotypic antiviral effect, and few drug–drug interactions (although there is a recent US Food and Drug Administration warning concerning comedication with amiodarone or spironolactone).[7] Combination of sofosbuvir and daclatasvir with or without ribavirin has been well tolerated in previously treated or untreated HCV patients.[8]

Sofosbuvir + daclatasvir ± ribavirin: a pangenotypic combination

In the first study to assess the combination of an NS5A inhibitor and a nucleotide NS5B inhibitor, treatment-naïve patients with HCV genotype 1, 2, or 3 received daclatasvir 60 mg once daily + sofosbuvir 400 mg once daily (with or without lead-in) ± weight-based ribavirin for 24 weeks.[8] Patients with cirrhosis, hepatitis B, or human immunodeficiency virus (HIV) coinfection were excluded. This open-label, multicenter trial randomized patients to receive either sofosbuvir for 1 week then sofosbuvir + daclatasvir for 23 weeks, sofosbuvir + daclatasvir for 24 weeks, or sofosbuvir + daclatasvir + ribavirin for 24 weeks. The protocol was later amended to include 123 genotype 1-infected patients who were randomized to receive sofosbuvir + daclatasvir ± ribavirin (82 treatment-naïve patients for 12 weeks and 41 protease inhibitor non-responders for 24 weeks). The SVR rate 12 weeks following the end of treatment (SVR12) was 92% in patients infected with genotype 2 and 89% in patients infected with genotype 3. Neither adjunction of ribavirin nor the sofosbuvir lead-in phase provided any benefit. In genotype 1-infected patients, the SVR12 rate was 98%, regardless of viral subtype (genotype 1a 98%; genotype 1b 100%), interleukin-28B genotype (CC genotype 93%, non-CC genotype 98%), race (white 97%, black 96%, other 90%), ribavirin status (yes 94%, no 98%), or prior history of treatment (non-responders to protease inhibitors 98%). These high SVR rates also occur irrespective of duration of therapy (12 vs 24 weeks) in treatment-naïve patients. Fatigue, headache, and nausea were the most common adverse events. Thus, in the absence of cirrhosis, the combination of sofosbuvir and daclatasvir for 24 weeks is a highly efficient regimen in treatment-naïve patients infected with genotype 2 or 3 and in prior non-responding patients infected with genotype 1, and for 12 weeks in treatment-naïve patients infected with genotype 1, even in "difficult to treat" patients. Ribavirin is not required with every oral DAA regimen, including the sofosbuvir and daclatasvir combination which has a high antiviral potency and high resistance barrier. Ribavirin-sparing regimens are desirable, considering the risks of anemia and teratogenicity, but their role from a cost-effectiveness perspective (ie, allowing a reduction in treatment duration) cannot be excluded.

In the ALLY-3 study, 101 treatment-naïve and 51 treatment-experienced genotype 3-infected patients were

enrolled to receive open-label daclatasvir 60 mg + sofosbuvir 400 mg once daily for 12 weeks.[9] Some of the previously treated patients had been treated with sofosbuvir or alisporivir, but none had been treated with NS5A inhibitors (an exclusion criterion). SVR12 was achieved in 90.1% and 86.3% of treatment-naïve and treatment-experienced patients, respectively. Cirrhosis (present in 21.1% of the patients) was associated with lower SVR12 rates (62.5% in cirrhotic patients vs 96.3% in non-cirrhotic patients). There were 16 relapses (mainly in cirrhotic patients) and one treatment failure, but no case of virologic breakthrough. The same adverse events as those cited previously were most frequently reported. Thus, daclatasvir + sofosbuvir for 12 weeks achieved high SVR rates in both treatment-naïve and treatment-experienced genotype 3-infected patients without cirrhosis. Additional evaluation to optimize the treatment outcome with daclatasvir + sofosbuvir in genotype 3-infected patients with cirrhosis is underway, including addition of ribavirin for 12 weeks or extension of the daclatasvir + sofosbuvir combination to 24 weeks.

How do these results in limited series translate to real-world experience? Some answers were given at the 2015 European Association for the Study of the Liver meeting. Indeed, although real-life results for the sofosbuvir + simeprevir combination have been extensively reported in genotype 1-infected patients (TARGET and TRIO American cohorts),[10,11] there have been few or no data for the sofosbuvir + daclatasvir combination in patients infected with genotype 1, 3, or 4.

More than 3,000 patients were given the new oral antivirals in 32 centers of the French ANRS CO22 HEPATHER observational cohort in January 2015. Data on demographics and history of liver disease were collected at entry into the study cohort. Clinical, adverse event, and virologic data were collected during treatment and follow-up post-treatment.

In total, 409 patients monoinfected with HCV genotype 1 were given sofosbuvir 400 mg/day + daclatasvir 60 mg/day without ribavirin (n=318) or with ribavirin (1–1.2 g/day, n=91).[12] Three hundred and eighteen patients had cirrhosis and 306 were previously treated with PEG-IFN + ribavirin (n =134) or PEG-IFN + ribavirin + a first-generation protease inhibitor (n=172).[12] The overall SVR4 rates were 81.6%, 93.9%, 100%, and 96.6% in those given sofosbuvir + daclatasvir and sofosbuvir + daclatasvir + ribavirin for 12 and 24 weeks, respectively. The overall SVR4 rate differed according to prior history and fibrosis stage. Sofosbuvir + daclatasvir + ribavirin for 12 weeks achieved a 100% SVR4 rate in patients with cirrhosis, with no additive effect on extension of treatment to 24 weeks with or without ribavirin (95.7% and 92.5%, respectively) and this was also true in experienced patients; all patients without cirrhosis achieved a 100% SVR4 at 12 weeks, indicating that combination of sofosbuvir + daclatasvir for 12 weeks is a good therapeutic option. Serious adverse events were reported in 9% and adverse-event-related treatment discontinuation in 3.1%.

Forty-seven genotype 4-infected patients from the same HEPATHER database were given a combination of sofosbuvir 400 mg/day + daclatasvir 60 mg/day, including 15 patients with ribavirin 1–1.2 g/day for 12 (n=11) or 24 weeks (n=36).[13] The overall SVR4 rate was high at 86%–100% according to the baseline characteristics and therapeutic schedule. There was an additive effect in cirrhotic or treatment-experienced patients of either extension of treatment duration from 12 to 24 weeks or addition of ribavirin for the two combinations, sofosbuvir + daclatasvir and sofosbuvir + simeprevir. The 12-week combination of sofosbuvir + daclatasvir + ribavirin achieved a 100% SVR4 rate in patients with cirrhosis, with no additive effect of extension of the treatment to 24 weeks, and this was also observed in experienced patients. All non-cirrhotic patients achieved a 100% SVR4. The 12-week combination of sofosbuvir + daclatasvir was generally well tolerated.

In summary, the sofosbuvir + daclatasvir combination is associated with a high rate of SVR4 in difficult-to-treat patients infected with genotype 1 or 4. Combination with ribavirin increases the SVR rate in cirrhotic and treatment-experienced patients with no additive effect of extension of treatment from 12 to 24 weeks.

Data are limited in patients with HCV genotype 3. The combination of daclatasvir and sofosbuvir for 12 weeks was associated with high SVR rates in genotype 3 patients without cirrhosis, but with only a 65% SVR rate in cirrhotic patients in the ALLY-3 study (see the earlier discussion). Interim results from a French multicenter compassionate use program of daclatasvir + sofosbuvir ± ribavirin in patients with chronic HCV genotype 3 infection have been reported.[14] Six hundred and one patients with HCV genotype 3 and severe fibrosis (F3), cirrhosis (F4), extrahepatic HCV manifestations, post-liver transplant recurrence of HCV, or an indication for liver or kidney transplantation were enrolled in this program. Patients were not randomized and received daclatasvir + sofosbuvir once daily for 12 or 24 weeks, with or without ribavirin, according to the physician's decision. Most of the patients were male (75%), monoinfected with HCV

(83%), cirrhotic (77%), and treatment-experienced (73%). The median age was 54.3 (27–83) years. Sixty-four percent and 15% received daclatasvir + sofosbuvir for 24 weeks with and without ribavirin, respectively, and 4% and 17% received daclatasvir + sofosbuvir for 12 weeks with and without ribavirin, respectively. The baseline median HCV RNA level was 6.07 (1.20–7.62) log10 IU/mL, the platelet count was 118.5 (31–387) $\times 10^9$/L, and albumin was 39.0 (13–56) g/L. Treatment discontinuation was related to adverse events in one patient, death in two patients, and patient's decision in one case. The preliminary analysis shows that 12 weeks of daclatasvir + sofosbuvir was not an optimal way to treat cirrhotic patients with HCV genotype 3 (SVR12 76% as compared with 92% in non-cirrhotic patients), but extension to 24 weeks improved the SVR rate to 88%, suggesting that this treatment duration is optimal for these patients.

Preliminary results of German data under real life (SOFGER trial) about the use of DAAs in prioritized patients are available.[15] In a national cohort, 790 patients were treated in six large German liver centers with sofosbuvir-based therapies. A total of 221 patients received sofosbuvir + daclatasvir for 12 weeks, most (71%) were genotype 1 and 23% were genotype 3, 67% had fibrosis (F4), and 66% were treatment-experienced (including 21% who had failed protease inhibitors). The interim analysis was presented at the most recent European Association for the Study of the Liver meeting, and with the sofosbuvir + daclatasvir combination without ribavirin for 12 weeks, 84% of the 161 patients who reached follow-up week 4, mostly difficult-to-treat patients (prior non-responders and cirrhotics) achieved an SVR4.

Specific populations

Advanced cirrhosis

The efficacy and safety of daclatasvir + sofosbuvir for 12 weeks is being assessed in cirrhotic patients (ALLY-1 trial) whatever the genotype (from 1 to 6), and the results are awaited. As reported for the 12-week and 24-week course of sofosbuvir + ledipasvir (another NS5A inhibitor coformulated with sofosbuvir in a single-tablet regimen) + ribavirin, we can expect a high SVR12 rate (87% and 89%, respectively), without a major impact of duration of treatment in Child-Pugh B patients (87% and 89%, respectively) and in Child-Pugh C patients (86% and 89%, respectively).[16] However, these excellent results in difficult-to-treat patients are below those reported for Child-Pugh A patients who failed prior PEG-IFN + ribavirin and PEG-IFN + ribavirin + first-generation protease inhibitors (96% with sofosbuvir + ledipasvir + ribavirin and 97% for 24 weeks of sofosbuvir + ledipasvir in the SIRIUS study).[17]

Patients with HIV coinfection

The daclatasvir + sofosbuvir combination (for 8 or 12 weeks) was evaluated in 203 genotype 1–4 patients with HIV coinfection in the ALLY-2 trial.[18] After 12 weeks of treatment, an SVR12 was achieved in 97% of patients: 97% in genotype 1-infected patients and 100% in genotype 2-infected and 3-infected patients (n=32), 97% in treatment-naïve and 98% in treatment-experienced patients. After 8 weeks of treatment, the SVR12 rate was 72%. There seemed to be no impact of cirrhosis, but only 25 patients were cirrhotic. Rates of relapse were increased in patients who had a shorter duration of treatment (8 weeks), those who had baseline HCV RNA levels >2 M IU/mL, and those who received coadministration of ritonavir-boosted darunavir + daclatasvir at lower doses (30 mg/day). Thus, the association of sofosbuvir with daclatasvir for 12 weeks achieves high rates of SVR12 in HIV-HCV genotype 1-infected patients, with good tolerance and no impact on HIV immunosuppression.

Liver-transplanted patients

Recurrent HCV infection following liver transplantation can lead to accelerated allograft injury that is difficult to treat with PEG-IFN-based regimen, involving poor tolerance, modest efficacy, and possible interactions with immunosuppressive agents.

As reported previously in a patient with recurrent cholestatic hepatitis C,[19] the combination of sofosbuvir + daclatasvir is efficient in liver transplant recipients.[20,21] Pellicelli et al evaluated this combination in 12 patients (including three with fibrosing cholestatic hepatitis and nine with cirrhosis) treated for 24 weeks with sofosbuvir and daclatasvir, in association with ribavirin for six patients.[20] Nine patients (five of whom received ribavirin) completed 24 weeks of treatment, with undetectable HCV RNA at the end of treatment. Seven patients experienced severe liver disease-related adverse events, three of whom died. All five patients for whom post-treatment (week 4 and week 8) was available had undetectable HCV RNA. There was no interaction with immunosuppressants. Thus, this association shows high virologic efficacy, but optimal outcomes require initiation of treatment before decompensation. Whereas the mean Model For End-Stage Liver Disease score did not improve in patients who completed the 24 weeks of treatment in that study, the CUPILT study reported not only high rates of SVR12 with good tolerance and no drug–drug interactions

but also clinical and biochemical improvement.[21] Twenty-one patients with fibrosing cholestatic hepatitis were treated for 24 weeks: 12 with sofosbuvir + daclatasvir, one with sofosbuvir + daclatasvir + ribavirin, two with sofosbuvir plus ribavirin with PEG-IFN and six with sofosbuvir plus ribavirin. The SVR12 was 88% in the sofosbuvir + ribavirin group and 100% in the sofosbuvir + daclatasvir + ribavirin group. SVR rates and tolerance are being further assessed in this setting with the combination of daclatasvir + sofosbuvir without ribavirin for 12 weeks in the ongoing ALLY-1 trial.

International guidelines

Daclatasvir was recently approved in Europe and in Japan for use in combination with other DAAs such as sofosbuvir, with or without ribavirin, and is currently being reviewed in the USA. Because daclatasvir is not available on the USA market, the American Association for the Study of Liver Disease proposed a daclatasvir-free regimen for treatment-naïve and treatment-experienced patients (prioritized for patients with advanced fibrosis, cirrhosis, liver transplantation, or severe extrahepatic HCV manifestations).[22]

The European Association for the Study of the Liver guidelines recommended sofosbuvir + daclatasvir ± ribavirin, among other options, prioritized as follows: patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis, those with HIV or hepatitis B virus coinfection, those with an indication for liver transplantation, those with HCV recurrence after liver transplantation, those with clinically significant extrahepatic manifestations, those with debilitating fatigue, and individuals at risk of transmitting HCV (active injectable drug users, men who have sex with men and high-risk sexual practices, women of child-bearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals).[23]

For HCV-monoinfected or HCV/HIV-coinfected patients with chronic HCV without cirrhosis, including treatment-naïve patients and patients who have failed treatment based on PEG-IFN-alpha and ribavirin, the combination of sofosbuvir + daclatasvir for 12 weeks without ribavirin should be proposed for genotypes 1–6. HCV or HCV/HIV patients with compensated cirrhosis can be treated with sofosbuvir + daclatasvir + ribavirin for 12 weeks or sofosbuvir + daclatasvir without ribavirin for 24 weeks in genotypes 1, 4, 5, and 6, with sofosbuvir + daclatasvir without ribavirin for 12 weeks in genotype 2, and with sofosbuvir + daclatasvir + ribavirin for 24 weeks in genotype 3. Patients with decompensated cirrhosis can be treated with a combination of sofosbuvir + daclatasvir + ribavirin for 12 weeks or without ribavirin for 24 weeks, regardless of genotype. Finally, for retreatment of HCV-monoinfected or HCV/HIV coinfected patients with chronic HCV who have failed to achieve an SVR on prior antiviral therapy containing one or several DAAs, there are limited data to support firmly these retreatment recommendations; sofosbuvir + daclatasvir + ribavirin for 12 or 24 weeks can be chosen depending on the first combination, the fibrosis score, and the genotype.

Conclusion

The field of HCV treatment has changed dramatically with the advent of a number of new antivirals, including DAAs and agents with non-viral targets (cyclophilin inhibitors, IFN-lambda, vaccine therapy). Given their better safety profile and improved antiviral potency, combinations of these agents in IFN-free regimens are becoming the standard of care for HCV infection. All oral treatments will be tailored to individual patients according to the degree of disease progression (fibrosis), HCV genotype and subtype, resistance profile, and prior therapeutic history. Results from clinical studies as well as preliminary real-life data demonstrate that the combination of sofosbuvir and an NS5A inhibitor, including the first-inclass agent daclatasvir, belongs to one of the most antiviral therapies with once-daily oral dosing, a low pill burden, good tolerability, and limited drug–drug interactions, in addition to high (>90%) SVR rates. Such a combination has pangenotypic high antiviral potency. Regardless of the severity of the underlying liver disease and the baseline characteristics of the patients, combination of sofosbuvir with an NS5A inhibitor for 12 weeks appears to be a very good option when used in combination with ribavirin in cirrhotic and treatment-experienced patients whatever their fibrosis stage. Future challenges to be addressed, over and above the already increased efficacy, will be to further improve the safety, adherence, and costs of these new oral combinations, particularly in patients with chronic renal failure or transplantation and in complex clinical settings. Beyond the competition between companies, the next step is to improve screening and access to these therapies, which have shown good safety and efficacy for most patients.

Disclosure

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