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DRUG EVALUATION

Efficacy and safety of alisporivir for the treatment of hepatitis C infection

Carol Stanciu[a,b], Anca Trifan[a,b], Cristina Muzica[b] and Catalin Sfarti[a,b]

[a]Department of Gastroenterology, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania; [b]Department of Gastroenterology, St. Spiridon, Emergency Clinical Hospital, Iasi, Romania

ABSTRACT

Introduction: Alisporivir (ALV) (previously known as Debio 025) is a potent, pangenotypic host-targeting antiviral oral agent acting on cyclophilin A, which is necessary for HCV replication.

Areas covered: This article reviews the therapeutic efficacy and safety of ALV for the treatment of HCV infection.

Expert opinion: Direct-acting antivirals (DAAs) have revolutionized the HCV antiviral treatment paradigm with success rates well above 95% for all HCV genotypes. However, challenges still remain in certain patient populations such as those who have developed resistance and have experienced multi-DAA failure. To cure HCV infection, a treatment regimen must combine antiviral potency and a high barrier to resistance. ALV fulfills this need as shown by the studies evaluating its clinical efficacy. Nevertheless, ALV missed the chance to be included in the HCV treatment armamentarium after the FDA halted clinical studies following reports of serious side effects (three cases of pancreatitis, one lethal). However, it is possible that ALV could still be considered for HCV-infected non-cirrhotic patients that are infected with a multiresistant virus or with HCV genotype 3, although it must be said that the drug industry would be reluctant to invest in new antivirals if the current clinical need is effectively met.

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KEYWORDS
Alisporivir; cyclophilin A; hepatitis C; side effects; treatment

1. Introduction

Hepatitis C virus (HCV) chronically infects approximately 71 million people worldwide [1,2], a significant proportion of whom will develop cirrhosis or hepatocellular carcinoma [3]. The goal of antiviral treatment is to achieve a sustained virologic response (SVR), defined as undetectable HCV RNA 3 months after the end of treatment.

Over the past 5 years, a new era in HCV therapy has opened by the arrival of direct-acting antivirals (DAAs) which dramatically increased the SVR rate (>95%) and decreased treatment duration to 8–12 weeks [4–7]. Nevertheless, some classes of DAAs (i.e. protease inhibitors) have lower effectiveness in patients with genotypes 2 or 3 and also a high mutation rate of HCV in response to therapy. Therefore, there was a need for drug therapy with a high barrier to resistance [8].

There are two classes of HCV antiviral agent which have different targets: 1) DAAs that target viral non-structural proteins including NS3/NS4A protease, NS5B polymerase and NS5A protein, 2) host-targeting agents which target various host proteins essential to HCV replication.

Alisporivir (ALV) is part of the second generation of host-targeting cyclophilin inhibitor devoid of immunosuppressive effect [9,10] acting against HCV, by blocking the interaction between cyclophilin A and the HCV nonstructural 5A (NS5A) protein [10,11]. ALV has excellent therapeutic characteristics such as being pangenotypic, had a high genetic barrier to the development of viral resistance, and a lack of cross-resistance to DAAs [11,12]. The capacity to block host proteins essential for viral replication is the main characteristic of ALV, unlike DAAs targeting certain viral proteins.

This review aims to summarize the data concerning the efficacy and safety of ALV for the treatment of HCV infection, based on phase 2/3 clinical trials.

2. Discovery of alisporivir

Cyclosporine A, an immunosuppressant used in organ transplantation to prevent rejection [13], was the first cyclophilin inhibitor which demonstrated in vitro anti-HCV activity, as well as the first reported to be more clinically effective when combined with pegylated interferon alfa (PegIFNα) than IFNα alone for the treatment of chronic HCV [14,15]. The first generation of cyclophilin inhibitors, by binding to calcineurin, forms a ternary complex that triggers a reduction in activity of the immune system [13]. The second generation of cyclophilin inhibitors, including ALV synthetized from cyclosporine A, was devoid of immunosuppressive effect, through chemical modifications which abolish its binding to calcineurin while enhancing affinity for cyclophilins [16].

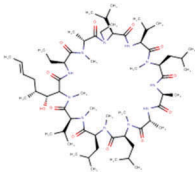
3. Overview of the market

Nowadays, all-oral interferon (IFN)-free DAAs regimens have the potential to achieve SVR in over 95% of patients with shorter treatment duration [4–7,17–19].

However, certain patient populations: cirrhosis with genotype 3 [20,21], patients harboring quasispecies with resistance

CONTACT Anca Trifan ancatrifan@yahoo.com Grigore T. Popa University of Medicine and Pharmacy, Str. Independentei nr 1, Iasi 700111, Romania

Box 1. Drug Summary Box.

Drug name	Alisporivir or Debio 025 or DEB-025
Phase	Phase III
Indication	Hepatitis C
Pharmacology description	Alisporivir (ALV) is a second generation of host-targeting cyclophilin inhibitor devoid of immunosuppressive effect acting against HCV, by blocking the interaction between cyclophilin A and the HCV nonstructural 5A (NS5A) protein
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	DEB-025-103 [26] DEB-025-HCV-203 – [37] DEB-025-HCV-205 (ESSENTIAL) – [38] DEB-025-HCV-207 – [39] CDEB025AA2211 (VITAL-1) [41] CDEB025A2210 (FUNDAMENTAL) [42] CDEB025A2301 (ESENTIAL II) [44]

associated substitutions [22,23], patients who failed a regimen containing a NS5A inhibitor, and those with cirrhosis and advanced chronic kidney disease [24] are still hard to treat. This niche remains an opportunity for the development of new HCV drugs.

4. Chemistry

ALV is a cyclic undecapeptide which differs from cyclosporine at position 3 which offers improved cyclophilin binding at position 4 which abolishes calcineurin binding, subsequently leaving the molecule without its immunosuppressive activity. ALV is not soluble in water, nor in non-polar solvents. (Box 1.) [12,25]

5. Pharmacokinetics and metabolism

Clinical pharmacokinetic studies have shown that ALV is rapidly absorbed (<2 hours) after oral administration [26], is metabolized by liver cytochrome P450 isoenzyme, which is then eliminated in the bile. Its half-life was estimated between the range of 60–90 h, which makes it suitable for once daily administration [26]. It presented a dose proportional increase in plasma exposure and 4–12 fold accumulation over 4 weeks of medication [27]. ALV has numerous drug-drug interactions, including those which inhibit Cytochrome P450 3A4 (CYP3A4), increase exposure to ALV and are inducers of CYP3A4, decreasing its activity [25].

6. Mechanism of action of ALV

Intracellular cyclophilin A is the essential element for HCV replication via its peptidyl-prolyl isomerase [28,29]. ALV is an oral, non-immunosuppressive, host-targeting antiviral agent that inhibits HCV replication by binding to host cyclophilin A and blocking its peptidyl-prolyl *cis/trans* isomerase activity [30–32]. Cyclophilin A binds to the non-structural 5A (NS5A) protein of all HCV genotypes, a process which is essential for HCV replication [33]. Thus, ALV, by inhibiting this action, has pangenotypic activity both in vitro and in clinical studies, and has a high barrier to the development of viral resistance [34,35]. Moreover, ALV in combination with DAAs has both an additive or synergetic effect with them and prevents the selection of HCV variants resistant to those agents [36].

7. Clinical efficacy – main clinical trials

7.1. Phase I

The DEB-025–103 study is the only phase 1 double-blinded, randomized, placebo controlled trial, evaluating short term efficacy of ALV administered as monotherapy in patients coinfected with human immunodeficiency virus (HIV-1) and HCV. ALV was administered as two daily doses of 1200 mg in 16 subjects for 14 days. In 15 of them, the HCV viral load decreased more than 2 $\log_{10}$ while in 3 patients became undetectable after 8–15 days. All 3 genotypes identified in the study (1, 3 and 4) responded well to ALV and no breakthrough occurred during treatment suggesting a high barrier to resistance. Interestingly, ALV was found to be more potent in patients infected with genotype 3 than in those with genotypes 1 and 4 [26].

7.2. Phase II

Phase II studies have been conducted on ALV and different combinations of ALV and PEG-IFNα2a and ribavirin. However, these studies were on hold via the FDA because some patients developed serious complications (3 cases of pancreatitis, one lethal).

DEB-025-HCV-203, a preliminary phase IIa multicenter randomized study, via a monoinfected HCV population, investigated the appropriate dose of ALV in combination with PEG-IFNα. The results of this study suggested ALV was suitable doses for all genotypes at either 600 mg or 1000 mg daily. ALV in combination with PEG-IFN significantly reduced viral load in all treatment-naïve hepatitis C patients. This effect was more powerful in HCV-genotypes 2 or 3 than in those infected with genotype 1 or 4 [37], confirming the results of a phase 1 study [26].

DEB-025-HCV-205 (ESSENTIAL) is a study which evaluated the efficacy and safety of ALV combined with PEG-IFNα and ribavirin in treatment-naïve patients infected with HCV-genotype 1 and showed that once daily ALV plus PEG-IFNα and ribavirin significantly increased SVR rates [38]. Regarding side effects, a significant increase of serum total bilirubin was observed during the first weeks of treatment with ALV.

DEB-025-HCV-207 is a phase II trial, which evaluated different combinations of ALV with PEG-IFNα2a and ribavirin for 29 days in HCV-genotype 1 non-responders to previous PEG-IFNα2a and ribavirin therapy. This study showed that such combination therapy is effective in the treatment of HCV-genotype 1 non-responders [39].

CDEB025AA2211 (VITAL-1), a phase IIb study evaluated the efficacy and safety of ALV administered either alone, or ALV plus ribavirin, or ALV plus ribavirin plus PEG-IFN in 340 treatment–naïve patients infected with HCV-genotype 2 or 3 [40]. The authors found that ALV was well tolerated and improved the rate of SVR. Among 70 patients receiving only IFN-free therapy (ALV plus ribavirin), 95% had end-of-treatment-response, and 88% achieved SVR12, demonstrating that ALV plus ribavirin is an effective IFN-free therapy for HCV-naive patients infected with genotype 2 or 3. It should be underlined, that this was the first international multicenter trial that included HCV-genotype 2 and 3 patients demonstrating that an all oral IFN-free regimen could cure the HCV infection [40,41].

CDEB025A2210 (FUNDAMENTAL) is a double-blind placebo, randomized, controlled, phase II study which evaluated efficacy and safety of different doses of ALV in combination with PEG-IFNα and ribavirin in 491 HCV-genotype 1 patients who relapsed or did not respond to prior therapy with PEG-IFNα and ribavirin [42]. All ALV treatment groups showed a higher SVR rate compared to PEG-IFN and ribavirin. However, serious adverse effects were more frequent in ALV-treated patients. One case of pancreatitis, although which fully recovered, occurred with ALV/PEG-IFN+ribavirin. In April 2012, the FDA decided to put a partial clinical hold on the global ALV clinical trial programme in the United States, but all patients in this study received at least 31 weeks of randomized treatment and completed 48 weeks of PEG-IFN+ribavirin. In patients who received more than 40 weeks of randomized treatment, the SVR12 score was 89% for ALV *vs* 30% for PEG-IFN+ribavirin alone [43]. Of note, between the years of 2010–2013 when this study was performed, this SVR rate for non-responder HCV-genotype 1 patients was revolutionary.

7.3. Phase III

CDEB025A2301 (ESENTIAL II) is the single phase III double-blind, randomized, placebo controlled study which included a large number (1081) of HCV- genotype 1 naïve patients, and aimed to evaluate the efficacy and safety of two different doses of ALV (600 mg once daily and 400 mg twice daily) plus PEG-IFN and ribavirin for 24 or 48 weeks (response-guided therapy) compared with PEG-IFN and ribavirin alone for 48 weeks. Due to the FDA clinical hold, only 70% of patient completed their scheduled duration of double-blind treatment. Despite premature discontinuation of ALV, the rate of SVR12 was higher in all ALV treated patients (69%) than in PEG-IFN and ribavirin arms. Interestingly, the rate of SVR12 increased with the duration of ALV therapy, the highest proportion of SVR (90%) being obtained in patients who received ALV 400 mg twice daily with PEG-IFN and ribavirin for more than 24 weeks [44]. The idea of including ALV in IFN-free combination regimens was still attractive in 2012–2013.

8. The safety profile of alisporivir

The safety analysis of all ALV containing regimens highlighted the most frequent adverse effects (AEs) as headache, anemia, neutropenia, thrombocytopenia, fatigue, pyrexia, alopecia, hypertension, hyperbilirubinemia and hypertriglyceridemia. The overall incidence of AEs was generally similar across treatment arms containing both PEG-IFN plus ribavirin and ALV with the highest rates seen in the ALV 400 mg BID group [42]. Serious AEs (SAEs) were also more frequent in 400 mg BID group, the most common being hypertension, chest pain, anemia, pyrexia, pneumonia, appendicitis, dyspnea and loss of consciousness. In the Essential II study, the highest number of acute pancreatitis were reported with five in patients receiving ALV and PEG-IFN plus ribavirin and two in the group without ALV. The overall frequency of pancreatitis was indifferent between the ALV containing group (0.6%) and in PEG-IFN and ribavirin group (0.8%) [44]. In two cases, pancreatitis occurred in patients with a high level of triglycerides which was considered a contributing factor. In the above mentioned study, one patient with pancreatitis died because of the development of multiorgan failure despite supportive measures being taken, and the investigator considered that the event was related to ALV. It is worth noting that an external review committee of pancreatitis experts disagreed with this conclusion [42,44].

In the PEG-IFN containing therapy, ALV seemed to exacerbate safety concerns known to be associated with PEG-IFN and ribavirin including hematological side effects and the elevation of serum triglycerides. The side effects added by ALV seemed to be hypertension (many, as single episodes), transient hyperbilirubinemia due to inhibition of the uptake organic anion-transporting polypeptides (OATP1B1 and OATP1B3) and efflux transporter type multi-drug resistance proteins [34]. Concerning acute pancreatitis, no patient on ALV without PEG-IFN presented this side effect [45].

The pooled analysis of the ALV development program, performed by Griffel et al. on 2,153 patients showed that IFN-free ALV treatment had a better overall safety profile compared to IFN-containing treatments. Thus, in the IFN-free ALV group, the rate of AEs was lower (1.9%) than in the ALV-PEG-IFN and ribavirin triple therapy (7.7%) group, and in PEG-IFN and ribavirin control group (4.7%) [45].

It seems plausible that ALV alone has few mild side effects itself that only when in combination with PEG-IFN and ribavirin, does it then contribute to increased rates of AEs and SAEs. From a safety point of view, ALV alone could be an attractive candidate for combinational treatment regimens not containing IFN, because its characteristics ability for restoring the host's innate immune response to HCV [46]. It is, however, not known if ALV in combination with DAAs could lead to other adverse events.

9. The future of alisporivir in HCV therapy

After several years of development and the release of DAAs for the treatment of HCV infection, currently approved regimens are efficient (95% viral cure), ribavirin free, pangenotypic and safe. The market is full of IFN-free regimens and it is true that the clinical need is largely fulfilled. The question, therefore, is whether ALV still has any place in today's HCV drug armamentarium. Indeed, whether or not ALV should be investigated in new clinical trials for the treatment of HCV patients is debatable.

Despite extraordinary results, the current DAA regimens have some limitations in several special groups of patients: those with genotype 3 cirrhosis, those with advanced renal insufficiency with decompensated liver cirrhosis, and null responders to DAAs. Moreover, the implementation of the World Health Organization (WHO) strategy on viral hepatitis with its ambitious goals, already adopted by many countries [47] will tremendously increase the use of DAAs regimens (original drugs and different generics) without a stewardship program for viral resistance. Thus, in the future, it is possible to witness the emergence of different genetic variants of HCV multi-resistant to existent antivirals, and a window could open for new antivirals with different mechanisms of action, such as is the case of ALV. Meanwhile, the existent DAAs fulfill the requirement of efficacy, safety, easiness of administration as of now. Yet, presently, with numerous real-life studies that have evaluated the efficacy of different DAAs regimens and which have shown a SVR rate well above 95% [4–7], it is hard to believe that a drug company is ready to invest in new HCV drugs.

ALV missed the chance to be included among the present DAAs regimens, when the FDA decided in April 2012 to put on hold all ALV clinical trials following reports of serious adverse effects (pancreatitis) which later had not been scientifically demonstrated. It should be underlined that at that time, ALV therapy was among the first (if not the first) drug which proved the concept of all-oral IFN-free regimen (ALV plus ribavirin).

Still, several challenges still remain despite excellent efficacy and safety of currently used IFN-free approved regimens [48,49]. HCV-genotype 3 cirrhosis is considered to be the most difficult-to-cure genotype with DAA-based therapy and those with multi-failure to DAAs regimens who have developed resistance remain unsolved [50–54]. Regarding HCV-genotype 3 therapy, they do have the lowest SVR rates with DAAs regimens. Consequently, ALV might be an option in future regimens due to its high response rates in those phase II studies undertaken [40,41]. However, new and large clinical trials are needed to define the best treatment strategies for the special patient populations mentioned above.

Until now, among cyclosporin A derivates with non-immunosuppressive activity, only two molecules (alisporivir/Debio 025 and SCY-635) have shown clinical efficacy in patients with HCV infection treated with both IFN-based and IFN-free regimens [41,55]. However, safety limitations have delayed the clinical development of ALV and therefore, further studies are needed to evaluate the role of this compound in the management of patients with HCV infection. Gallay et al described recently a new cyclosporine A inhibitor, named CPI-431–32 (now called CRV431) that simultaneously blocks HCV and HIV replication with a higher in vitro efficiency than ALV, and thus, this compound may be used in the treatment of patients with HIV/HCV coinfection [56]. As of now, ALV is not included is new clinical studies and one can wonder about the positioning of ALV in any anti-HCV therapy.

10. Conclusion

ALV is a host-targeting antiviral agent with a mechanism of action that differs from those of DAAs, is pangenotypic, and in combination with PEG-IFN and ribavirin, has high efficacy in treatment-naïve patients, relapsers, and nonresponders. Of note, ALV, when combined with ribavirin (as a IFN-free regimen) is highly effective in the treatment of HCV-naive genotype 2 and 3 patients. However, because of reported serious side effects (cases of pancreatitis), the FDA decided to put a clinical hold on the global ALV trial program, and consequently, ALV missed the chance to be included with DAAs as part of the HCV treatment armamentarium.

11. Expert opinion

Alisporivir is a second generation host-targeting cyclophilin inhibitor with excellent therapeutic characteristics such as being pangenotypic, having high genetic barrier to the development of viral resistance, and has a unique mode of action by blocking host proteins essential for viral replication, differing from DAAs that block certain viral proteins. Alisporivir has been tested in over 2,000 HCV patients and had demonstrated efficacy with an acceptable safety profile, with the promise of being a useful additional tool to the current treatment armamentarium of HCV infection. Due to its high genetic barrier to resistance and lack of cross-resistance, ALV can be used as the "backbone" of all-oral, IFN-free regimens in HCV therapy.

DAAs have become the standard of care for HCV therapy, and currently approved regimens are efficient (a 95% viral cure), are ribavirin free, pangenotypic and safe. It should be underlined that current DAAs regimens, despite extraordinary results, have some limitations in several special groups of patients: with genotype 3 cirrhosis patients, those with advanced renal insufficiency, those with decompensated liver cirrhosis and null responders to DAAs. The question is whether ALV still has any place in the today HCV drug armamentarium. Particularly, ALV may still have a chance as a treatment for HCV naive patients infected with genotype 3 HCV as was shown in phase II studies as well as in those patients with multiple failures with DAAs regimens due to having developed resistance. Phase II clinical trials demonstrated an interferon-free combination of ALV with ribavirin that achieved a very high SVR rate (~90%) in treatment naive patients with HCV genotype 2 and 3 [40,41], with low virological breakthrough, low post-treatment relapse, a favorable safety profile, giving a major advantage over NS5A inhibitors (ledipasvir, daclatasvir etc.) in treating HCV-genotype 3 patients [57]. Nevertheless, to prove this supposition, new clinical trials are needed to further demonstrate their efficacy in these subgroups and when currently DAA regimens are very effective and safe, the drug industry is reluctant to invest in new HCV drugs.

The predictions made by some experts 5 years ago that ALV will be approved for the treatment of naïve patients with HCV-genotypes 1, 2, and 3 never came through and we, the authors, believe that ALV will most likely be out of the reckoning as a HCV treatment in the near future if not forever.

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