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REVIEW

New era for management of chronic hepatitis C virus using direct antiviral agents: A review

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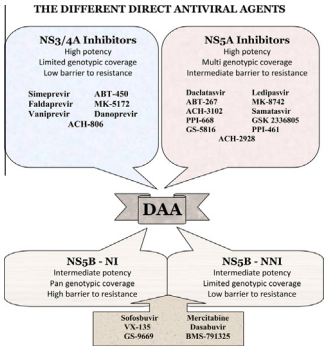
GRAPHICAL ABSTRACT



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ABSTRACT

The pegylated interferon regimen has long been the lone effective management of chronic hepatitis C with modest response. The first appearance of protease inhibitors included boceprevir and telaprevir. However, their efficacy was limited to genotype 1. Recently, direct antiviral agents opened the gate for a real effective management of HCV, certainly after FDA approval of some compounds that further paved the way for the appearance of enormous potent direct antiviral agents that may achieve successful eradication of HCV.

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Introduction

The first generation of protease inhibitors included boceprevir and telaprevir. Combined with pegylated interferon and ribavirin, they improved the overall rates of sustained virological response (SVR). This included treatment naïve as well as experienced patients [1–10]. However, this efficacy was limited to patients with hepatitis C virus genotype 1 infection, was associated with numerous side effects and needed a frequent dosing schedule [11].

With recent advances, many direct antiviral agents (DAA) developed and led to a more promising future for HCV infected patients. Excellent advantages were related to their high potency, pangenotypic coverage and intermediate to high barrier to resistance [12]. They paved the way to the possible application of oral interferon-free regimens. In addition, these regimens can be taken once daily and may result in global HCV eradication in near future [13].

Three major classes of DAA dominated the scenario at different stages of development and clinical practice: NS3/4A protease inhibitors, NS5B polymerase inhibitors and NS5A direct inhibitors (Figs. 1 and 2). NS5B polymerase inhibitors are further categorized into two distinct groups: the nucleoside polymerase inhibitors (NIs) and the nonnucleoside polymerase inhibitors (NNIs). NIs interact with the catalytic site for NS5B affecting viral RNA synthesis. They are characterized by their high barrier of resistance [14,15]. NNIs bind to different allosteric sites on the NS5B protein and prevent effective viral RNA synthesis. Their efficacies differ according to HCV genotypes and subtypes. They have a lower barrier of resistance [16].

NS5A inhibitors showed promising results among the different DAA drug studies due to their multigenotypic efficacy, high potency but low to intermediate barrier to resistance. Such DAA are used in combination with interferon and ribavirin to prevent virologic breakthrough and subsequent resistance. Similarly, they synergize with other DAA to suppress the development of resistant virus strains [17–19].

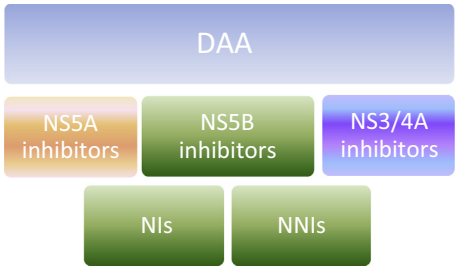

Fig. 1 Different classes of direct antiviral agents (DAA).

The most important direct antiviral agents

Sofosbuvir

Sofosbuvir is a prodrug of 20-deoxy-20-fluoro-20-C-methyluridine monophosphate. It is a specific nucleotide analog inhibitor of the HCV NS5B polymerase acting as a false substrate for the RdRp and ending at chain termination after incorporation into the newly produced RNA chain [20]. It is characterized by its broad antiviral activity against all HCV genotypes [21]. Sofosbuvir is a 400 mg once-daily capsule, which can be taken with or without food. It is mainly excreted by the kidneys at a rate of 76% with a median half life ranging from 0.48 to 0.75 h [22]. Metabolism of sofosbuvir and the other related drugs of the same family have no relation with the CYP3A4 pathway. So, they have a low potential for drug-drug interaction [23,24].

S282T mutation is determined as the common mutation occurring in replicon studies with sofosbuvir [25]. This mutation has reduced replicative capacity as compared to the wild type containing replicons [26,27]. In a study using sofosbuvir containing regimen, patients who failed to achieve SVR showed undetectable S282T mutation, either at baseline or later [28].

Sofosbuvir has been studied in different combinations (Table 1). The value of adding sofosbuvir to the combination

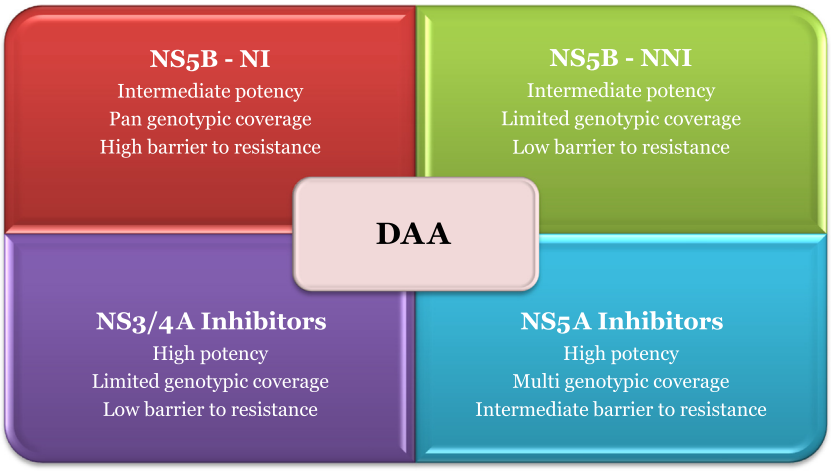

Fig. 2 Differences between the different DAA classes.

of Peg-IFNα in genotype 1 patients was first addressed in two phase II trials (PROTON and ATOMIC) [29,30]. The first study (PROTON) tested the addition of 400 mg sofosbuvir versus placebo to the combined IFN/RBV regimen for 12 weeks followed by an additional 12 or 36 weeks of Peg-IFNα and RBV. The 91% SVR12 in sofosbuvir arm compared to the 40% figure in placebo group was striking. The other trial (ATOMIC) evaluated the role of maintenance therapy after the initial 12 week response. SVR rated between 90% and 94%. This occurred regardless of the use of maintenance therapy. This based the 12 week triple therapy regimen for phase III NEUTRINO study [31]. In this study, 327 naïve patients with different genotypes (1, 4, 5 and 6) were treated for 12 weeks in an open-label single-arm design with sofosbuvir 400 mg and RBV 1000–1200 mg daily in addition to weekly Peg-IFNα 180 μg. The historic SVR12 of 60% was used for comparison. According to the treated HCV genotype, the results were 89% in HCV type 1, 96% in HCV type 4 and 100% in seven patients with HCV types 5 and 6. The overall response was 90%.

Sofosbuvir was the first drug to test the concept of "interferon free" regimens. Many phase II studies were conducted to evaluate the efficacy of various sofosbuvir combination regimens [32,33]. The sofosbuvir based interferon free regimens were either: sofosbuvir plus RBV, sofosbuvir plus another DAA or sofosbuvir plus another DAA and RBV for different treatment durations (8–24 weeks). Studies that tested for sofosbuvir in genotype 1 included QUANTUM and ELECTRON studies. Fifty naïve patients were treated with sofosbuvir and ribavirin for 12 weeks. SVR12 rates were 56% and 88% respectively [34,35]. No obvious improvement in SVR was noted when treatment duration extended up to 24 weeks in a subgroup of patients in the QUANTUM and NIH SPARE studies [34–36]. Results of FUSION trial that used the same duration (24 weeks) in genotypes 2 and 3 led to significant improvement of SVR from 56% to 73% [37].

Impressive results are shown in studies that used sofosbuvir combined with other DAA. Most of studies proved that ribavirin use will be of no value [32,36]. Many regimens with different DAA were used with either a non-nucleoside polymerase inhibitor or a NS5A inhibitor with no significant differences in response. The addition of one of the nucleotide analogs (GS-0938) to sofosbuvir for 12 weeks resulted in SVR12 in 88% while SVR4 after 12 weeks of a combination of sofosbuvir and daclatasvir (NS5A inhibitor) or ledipasvir (GS-5885) was as high as 98% and 100% [38,39]. Shortening of treatment duration in LONESTAR trial that used sofosbuvir and ledipasvir for 8 weeks resulted in 95% SVR8 [38].

Treatment experienced patients were the target group in many sofosbuvir trials. In ELECTRON study, 12-week sofosbuvir plus RBV were tested in 10 genotype 1 patients with previous treatment failure and led to high relapse rates [32]. It differed when another DAA was used with sofosbuvir for 12 weeks in this difficult to treat group of patients. The SVR results in these DAA combination studies ranged 90–100%. Many DAA were used in combination with sofosbuvir as NS5A inhibitor ledipasvir or daclatasvir, the protease inhibitor simeprevir or the non-nucleoside polymerase inhibitor GS-9669 [33,38,39].

ELECTRON study assessed the use of sofosbuvir plus ribavirin in genotypes 2 and 3 for 12 weeks with/without Peg-IFNα [32]. The nonsignificant value of added interferon paved the way for further interferon free trials.

For genotypes 2 and 3, interferon free regimens were assessed in phase III trials (FISSION, FUSION and POSITRON) where combined sofosbuvir and RBV were given

Table 1 Different sofosbuvir studies.

Name of study	Design	Genotype	SVR (%)
PROTON	Sof, IFN/RBV	1	91
ATOMIC	Sof, IFN/RBV	1,4,6	90–94
NEUTRINO	Sof, IFN/RBV	1,4,5,6	89–100
ELECTRON	Sof, RBV	1	88
	Sof, RBV, Ledipasvir		100
	Sof, RBV, GS-9669		92
QUANTUM	Sof, RBV	1	56
FISSION	Sof, RBV	2,3	67
FUSION	Sof, RBV	2,3	56–73
POSITRON	Sof, RBV	2,3	61–93
LONESTAR	Sof, RBV, Ledipasvir	1	95–100

for 12 weeks. The efficacy of such combination was tested in the FISSION study in 256 naïve patients with SVR reached about 67% [31]. The 16 week instead of 12 week duration was tested in the FUSION study that recruited previous treatment failure patients. The overall SVR rates were 50% in the 12 week and 73% in the 16 week arms [40]. The POSITRON trial studied the effectiveness of 12 weeks of combination of sofosbuvir and RBV in patients with HCV type 2 or 3 who are ineligible for Peg-IFNα-based therapies due to contraindications, unacceptable previous adverse events or unwillingness to receive Peg-IFNα therapy. The overall SVR rates were 61–93% according to RBV dose [37].

Daclatasvir

Daclatasvir, produced by Bristol-Myers Squibb, is the first-in-class NS5A inhibitor that demonstrated a satisfactory multiphase rapid HCV RNA decline without significant adverse events. It is highly effective against genotypes 1–4 [41,42]. Several clinical trials assessed the efficacy of daclatasvir with different compounds.

Using daclatasvir with interferon and ribavirin, Suzuki et al. managed HCV patients who were treatment naïve, prior null or partial responders. Two Different concentrations of daclatasvir were used (10 and 60 mg) versus a placebo group. SVR24 reached 66.7–90% in naïve group versus 62.5% in placebo group and much less satisfactory results in prior null responders (22–33.3%) [43]. Better results were achieved by Izumi and colleagues. Naïve group had SVR24 89–100% while null responders group 50–78% [44].

Other trials looked for daclatasvir combinations with asunaprevir. A phase III trial was accomplished in 24 Japanese centers to manage genotype 1b HCV patients who were either interferon ineligible/intolerant or nonresponders. SVR24 was 87.4% in interferon ineligible versus 80.5% in null responder patients. Cirrhotic patients achieved 90.9% SVR24. Side effects included nasopharyngitis, elevated liver enzymes, headache, diarrhea and pyrexia [45]. Another study found 90.5% SVR in null responders while 63.6% in ineligible/intolerant patients [46]. Moreover, further results were published by Lok et al. who used different combinations of daclatasvir with asunaprevir (Dual), ribavirin (Triple) or interferon and ribavirin (Quad) in genotype 1 null responder patients. Dual twice daily asunaprevir and the quad therapy were effective (SVR 78% and 95% respectively). Neither dual (once daily asunaprevir) nor triple therapy was sufficiently effective for such patients [47]. Ongoing studies added BMS791325 to daclatasvir and asunaprevir. SVR results were recorded as 94–100% according to treatment period (12 or 24 weeks) [48].

Excellent results were further published by Sulkowski et al. [49]. Daclatasvir was combined with sofosbuvir for treatment naïve and treatment experienced patients infected with HCV genotypes 1, 2 and 3. The best results were achieved with genotype 1 patients (98% SVR12 for both naïve and prior null responder patients). As for genotypes 2 and 3, SVR was achieved in 92% and 89% of patients respectively. Response rates were similar whether patients were taking ribavirin or not. In another phase II study, SVR12 was recorded in all genotype 1 naïve and treatment experienced patients (100%) while patients with genotype 2 or 3 succeeded to have 91% SVR [50].

Simeprevir

Simeprevir is a new direct acting antiviral drug and a second generation NS3/4A serine protease inhibitor. It was introduced by Janssen and Medivir for the oral treatment of patients with genotype 1 and/or genotype 4 chronic HCV infections [51]. *In vitro*, it is active against all six genotypes with lesser efficacy against genotype 3a [52,53]. Simeprevir proved to have several advantages such as its high efficacy, short treatment duration (12–24 weeks), better safety profile than first generation drugs and the decreased pill burden being taken once daily [54].

The PILLAR study is a phase IIb trial that was performed to test the efficacy of combined simeprevir, interferon and ribavirin in HCV G1 infected patients who were naïve and noncirrhotic. They were compared to another group taking interferon and ribavirin alone. SVR rates in the combined group reached 74.7–86.1% compared to 64.9% in the second group. Patients who met the RGT criteria had the best SVR rates (91%). Reversible hyperbilirubinemia was recorded as a side effect of simeprevir. Discontinuation rates were 8–16% in the simeprevir group versus 15% in the control group [55].

The ASPIRE trial is another phase II trial that was designed for treatment experienced HCV G1 patients. Triple therapy (simeprevir, interferon and ribavirin) led to 85% SVR as compared to 37% only in control group (interferon and ribavirin). More detailed, partial responders had a SVR 75% versus 9% while prior nonresponders recorded 51% versus 19% SVR [56].

A phase III trial for treatment experienced HCV genotype 1 patients, named PROMISE study, was performed with randomization of patients to simeprevir, interferon and ribavirin versus placebo, interferon and ribavirin. Results were 79% SVR12 versus 39% in placebo group. QUEST-1 and QUEST-2 studies also randomized to same regimen. Higher SVR12 rates were recorded in simeprevir group (80–81%) compared to the placebo group (50%) [57–60].

In parallel, important randomized clinical trials were performed in Japan. In the DRAGON study, 92 naïve patients infected with genotype 1 HCV were enrolled for simeprevir (12–24 weeks) with pegylated interferon and ribavirin (24–48 weeks) versus lone pegylated interferon and ribavirin for 48 weeks. Statistically significant difference was observed between simeprevir group (SVR 77–92% with relapse rate 8–17%) and the other group (SVR 46% with relapse rate 36%) [61]. CONCERTO-1 study for treatment naïve G1 HCV patients found SVR 88.6% versus 61.7%. CONCERTO-2 (for nonresponders) and CONCERTO-3 (for relapsers) concluded SVR12 rates as 35.8–52.8% for prior nonresponders and 95.9% for prior relapsers [62,63]. Most recently, CONCERTO-4 study for both treatment naïve and experienced patients with chronic HCV genotype 1 infection was published. The highest SVR12 was achieved by the treatment naïve patients (91.7%) and prior nonrelapsers (100%) while the prior nonresponders scored an SVR rate 38.5% only [64].

Ledipasvir

Ledipasvir is another NS5A inhibitor that showed promising results in different trials that evaluated its combination to sofosbuvir. It provided high potency against HCV genotypes 1a,

1b, 4a and 6a while it was less efficacious against genotypes 2a and 3a [65]. It cannot be used alone due to quick development of resistance [66].

The LONESTAR clinical trial evaluated the use of sofosbuvir and ledipasvir with and without ribavirin for HCV G1 patients, either treatment naïve or experienced. SVR was really successful (98%) [67]. ELECTRON trial is a similar trial that announced 100% SVR12 for both treatment naïve and prior nonresponder G1 patients [68]. These results are further proved in another large clinical trial using fixed doses for untreated G1 patients. Ledipasvir combined with sofosbuvir led to 99% SVR of total 865 patients (16% had liver cirrhosis) [69]. Concerning the previously treated patients (n = 440), SVR ranged 94–99% according to duration of therapy (12–24 weeks) and whether taken with or without ribavirin [70]. Reducing the duration of therapy to 8 weeks led to 93–94% SVR compared to 95% if the regimen was taken for 12 weeks [71].

Abt-450/ritonavir, ombitasvir and dasabuvir

ABT-450, new product of Abbvie Company (North Chicago, USA), is a potent inhibitor of NS3/4A protease. It has been studied with several drugs aiming to provide a possible interferon free/ribavirin free "all oral" drug regimen in a shorter duration of therapy [72]. Ombitasvir (ABT-267) is a pangenotypic inhibitor of NS5A with excellent potency, metabolic stability and pharmacokinetics [73].

Different studies provided optimistic results for a future of HCV eradication. The AVIATOR study used the combination of ABT-450/r, ombitasvir (ABT-267), dasabuvir (ABT-333) plus ribavirin for 8, 12 or 24 weeks in noncirrhotic G1 HCV patients (either naïve or previous treatment failure). Treatment naïve patients had a successful SVR (97.5%) as well as treatment experienced patients (93.3%) [74].

In another clinical trial performed by Zeuzem et al., they managed HCV G1 infected patients with ABT-450/r-ombitasvir and dasabuvir with ribavirin. 286 of 297 patients (96.3%) achieved SVR12. Enrolled patients were treatment relapsers, partial responders or null responders [75]. Feld et al. used the same drug regimen for treatment naïve patients and scored 96.2% SVR [76]. Moreover, Poordad and colleagues focused their clinical trial on cirrhotic patients, used the same regimen and finally concluded a successful SVR12 rate in such difficult to treat patients (91.8%) [77].

In a trial to exclude ribavirin, Ferenci et al. used the same drug regimen excluding ribavirin and found that the rates of virologic failure were higher in the ribavirin free group (7.8% versus 2%) [78]. Finally, Andreone et al. concluded a 97–100% SVR with or without ribavirin in treatment experienced patients with HCV G1 infection with well tolerability as evidenced by the low rates of discontinuation and the mild adverse events [79].

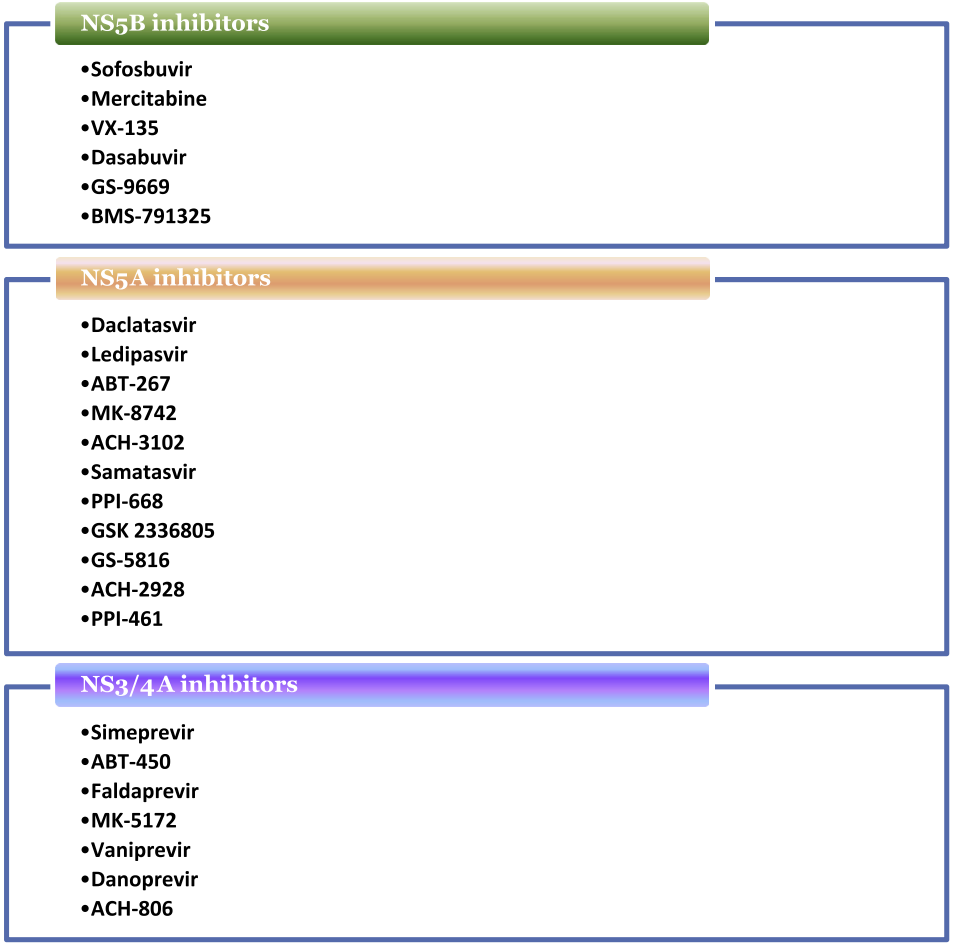

Fig. 3 The different direct antiviral agent drugs.

Faldaprevir

Faldaprevir is a new NS3/4A protease inhibitor that has an acceptable tolerability and safety at all dose levels. Several studies used it with different drug combinations. SILEN-C1 (for naïve G1 HCV patients) and SILEN-C2 (for prior nonresponders) were enrolled on 429 and 290 patients respectively. Faldaprevir was used in combination with pegylated interferon and ribavirin. SVR rates in naïve, prior partial responders and null responders were 72–84%, 32–50% and 21–35% respectively. SILEN-C3 is a phase II trial for 160 naïve G1 infected patients. Faldaprevir was taken for 12–24 weeks with 24–48 weeks of pegylated interferon and ribavirin. SVR rates were 67% (if 12 weeks) and 74% (if 24 weeks) [80–82].

Zeuzem et al. used a different drug combination. In a phase Ib trial (SOUND-C1), faldaprevir was taken with deleobuvir and ribavirin. Studied patients were treatment naïve G1 infected persons. Two out of 32 managed patients suffered from virological breakthrough that was successfully treated with interferon containing therapy. SVR24 was 73% (deleobuvir 400 mg) and 94% (deleobuvir 600 mg) [83]. In another phase IIb trial by Zeuzem et al., SVR12 was 52–69% according to the drug regimen using 120 mg once daily faldaprevir with deleobuvir 600 mg (2–3 times daily) and ribavirin (16, 28 or 40 weeks) [84].

MK-5172, MK-8742 and vaniprevir

MK-5172 is an NS3/4A protease inhibitor with a high potency and barrier to resistance. It is taken once daily. MK-5172 is active against multiple genotypes associated with resistance to first generation protease inhibitors [85,86]. It has been tested in combination with pegylated interferon and ribavirin to manage patients infected with genotype 1 HCV. Achieved SVR24 ranged between 86% and 93% according to the used dose (100, 200, 400 or 800 mg). The combination was generally well tolerated [87]. Vaniprevir (MK-7009) is another NS3/4A protease inhibitor that reached phase III clinical trials. Vaniprevir monotherapy showed potent antiviral activity in genotype 1 HCV patients. It is generally well tolerated without serious adverse events [88]. Despite the efficacy of both MK-5172 and vaniprevir, emergence of resistance reduced their effectiveness against viral replication [89]. MK-8742 is an NS5A inhibitor, currently in phase IIb clinical trials as an all oral, interferon free regimen for management of HCV [90]. Being combined with MK-5172, they led to a breakthrough therapy for HCV therapy. This study named C-WORTHY study treated genotype 1 (1a and 1b) and declared 89–100% SVR12 for patients using this combination with or without ribavirin [91]. Still more progression is ongoing to provide further MK compounds with retained high potency and pangenotypic activity [92].

Other compounds

Apart from the previously discussed major compounds, there are numerous drugs and molecules at various stages of production and different phases of trials (Fig. 3). Phase II clinical trials include NS3/4A inhibitors such as danoprevir [93–95] and NS5A inhibitors such as ACH-3102 [96], samatasvir [97], PPI-668 [98], GSK 2336805 [99] and GS-5816 [100,101]. Similarly, phase I clinical trials include NS3/4A inhibitors such as ACH-806 [102] and NS5A inhibitors such as ACH-2928 [103] and PPI-461 [104].

Conclusions

The last few years witnessed the development and appearance of many drugs that led to potent changes in the management of HCV. Still the future will evidence the development of much more compounds that will provide 100% efficacy within very short periods of therapy and the dream of HCV eradication seems to be possible in the near future.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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