RNA Interference: A Promising Approach for the Treatment of HBV Infection

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Abstract
Hepatitis B viral infection and associated sequelae is a public health concern as it is associated with high morbidity and mortality globally. The treatment modality currently available for patients with chronic condition cannot clear the viral DNA from infected hepatocytes and are associated with serious side effects and high rate of resistance. Thus, development of alternative therapeutic intervention with high rate of viral clearance, fewer side effects and that can target conserved regions of HBV genome remains a priority. Interestingly, RNA interference-based drugs have proven to be a promising therapeutic candidates and this article therefore reviews some of the potential benefits and how if refined can overcome current therapeutic hurdles against HBV.

Abbreviations: siRNA: Small Interfering RNA; cccDNA: Covalently Closed Circular DNA; NAG-MLP: N-acetyl Galactosamine Melitine-like Peptide; NUCs: Nucleoside Analogs; RNAI: RNA Interference

Introduction
Hepatitis B virus (HBV) infection is global health problem with over 350 million HBV carriers worldwide and over one million deaths occurring annually due to HBV-induced liver diseases [1]. Currently, HBV infection is treated with immunomodulatory agents (e.g. IFN-α) and nucleoside analogs such as lamivudine which are only partially effective [2]. Drawbacks of current therapies include Low efficacy, severe side effects and occurrence of resistance due to HBV mutations [1,3]. In view of the aforementioned challenges posed by current treatment regimen, there is the need for a better treatments option that can suppress viral replication within short duration, have high cure rates and fewer side effects [3,4]. RNA interference (RNAi) is a process by which small interfering RNA (siRNA) with specific sequences induce silencing of homologous genes by binding to their complementary mRNA and inducing the elimination of the mRNA [5]. RNAi has shown antiviral effect against HBV, Hepatitis C virus (HCV), Human Papillomavirus (HPV) and Human Immunodeficiency virus (HIV) [5,6]. Unlike HCV and HIV, the small size genome and presence overlapping reading frames (ORFs) in HBV makes it more susceptible to inhibition by RNAi [2,7,8].

Attributes of RNAi-Based Therapy

Figure 1: HBV Targets For siRNA Based Therapy.
siRNA mediated inhibition of gene expression does not require any viral DNA replication [3,4]. siRNA combinations have ability to target conserved regions of the viral genome [9,10]. Reduction of HBV DNA from infected hepatocyte [3]. Because RNAi-based drugs can be expressed from introduced genes, they offer the possibility for a sustained therapeutic response [11]. siRNA mediated inhibition is specific and potent [3,9,11] (Figure 1,2).

Methods of siRNA Synthesis

**Chemical synthesis:** This involves the production of sense and antisense strands, annealing of the strands, adding stable chemical entities and 2 nt overhangs at 3′ end.

**Ambion (Huston, TX) recommended the following guidelines for designing siRNAs:** Beginning with the AUG of the target gene transcript, search downstream for AA dinucleotide sequences, each AA and the 3′ adjacent 19 nt are potential siRNAs; blast the potential sequences against the species-specific genome database to eliminate cross-silencing phenomenon with non-target genes [12].

- a. Web-based software called siDirect algorithm incorporated the Ambion guidelines above for designing siRNAs [3]
- b. Endogenous vector Expression of Anti-HBV shRNA which involves the use of Plasmid to express shRNA that are converted into siRNA in cells [13,14].

**Delivery Strategies**

- a. Cationic liposome: This contains lipid with positively charged group (e.g. cholesteryl spermine) that form complexes with siRNA [15,16].
- b. Cationic polymer: like liposome, also form complexes with the negatively charged phosphate groups of the siRNA e.g. NAG-MLP [17].

**Challenges**

Delivery of the siRNA into the target organ [3,10].

Bioavailability and stability of siRNAs [18].

**What has been done to address these hurdles...**

Use of specific delivery methods such as cholesteryl spermine conjugation, formulation into liposomes and complexing with cationic polymers e.g NAG-MLP (Figure 3,4) [11,16]. In vivo stability of siRNA has been improved via chemical modification of backbone with 2′F, 2′O-Methyl, and 2′H to substitute 2′-OH residues required for nuclease activity [19,20].
ARC 520 Results

A single low dose of ARC-520 resulted in > 95% reduction of HBV RNA, proteins (e.g., HBeAg and HBsAg) and viral DNA with long duration of effect in mouse and chimpanzee models of HBV infection (Figure 5). In chimpanzee, Levels of HBV DNA, HBeAg, HBsAg only return to baseline after 43, 43, and 71 days respectively of dosing (Figure 5) [2]. ARC-520 has gone through phase-1-clinical trials. Results of a phase 1 from first-in-human safety and tolerability studies conducted among 36 patients with chronic HBV showed that the drug was reasonably safe and well tolerated. No dropouts for any reason and no serious adverse events [2].

Conclusion and Prospects for Clinical Application

The use of RNAi pathway as a new approach in antiviral drug discovery is promising as the genetic distance between mammalian and HBV genome represents an advantage in minimizing off-target hits and reducing possible side effects [21]. The ability of RNAi to effectively and durably halt viral protein production can lead to complete HBeAg loss and conversion to seronegative status; eliminates long treatments and patient compliance issues [2]. Although, RNAi-based therapeutic intervention against HBV infection has shown to be promising, improvements in safety and efficacy of delivery methods however remained important objectives for future studies to address [22-27].

References

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