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Different Tools Used for Treatment of Chronic Hepatitis B

Ukashah M[1]*, Qadir MI[2], Ijaz B[1] and Javed MK[2]

[1]Center for Agriculture Biochemistry & Biotechnology University of Agriculture Faisalabad, Pakistan

[2]Institute of Molecular Biology & Biotechnology Bahauddin Zakariya University Multan, Pakistan

Review Article

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***Corresponding author:** Muhammad Ukashah, Center for Agriculture Biochemistry & Biotechnology University of Agriculture Faisalabad, Pakistan; Email: kashanjaved01@gmail.com

Abstract

Currently different vaccines are available for cure and medicines are also available since 1988 but still 250 million people are infected with hepatitis B virus. The viruses of hepatitis B and hepatitis C causes liver cancer and also tuberculosis and malaria. The well developed and under developing countries both are very poor in care that can reduce the risk of hepatitis B. If we talk about United States only one third of those people who are infected with this virus are aware of their infection. The main reason for this un awareness is that the asymptomatic nature of hepatitis B virus as the symptoms are observed when it is at the chromic stage. The patients and care providers both lack knowledge regarding this disease. More attention has been focused from the previous 5 years in order to improve care linked to this disease, its proper diagnosis and proper care. There are also some novel compounds in trial phases to functionally cure this disease. There are also some professional organizations that provide knowledge and guidelines regarding this disease. These steps help those areas in which there is lack of knowledge regarding this disease and also they don't have proper cure of this disease. The findings of global experts are used to fulfill the gap that is occurring in this regard.

Keywords: Hepatitis B; Symptoms of HB; LNA; mi RNA; Chronic Stage

Introduction

The chronic infection hepatitis B is a greater threat to the people from all over the world. This virus is transmitted when any person is exposed to the infected body secretions or blood. The vertical transmission is the transfer of virus from mother to child and horizontal transmission is the transfer of virus from child to another child [1]. When the contaminated blood products are not sterilized than they can also serve the mode of transmission. The intravenous delivery of drugs is also the mode of transmission. The homosexuality is also mode of transmission but heterosexuality also serves as the mode of transmission if a person is sexing with many partners [2-4]. There are multiple modes of transmission of this disease so its occurrence in different regions of the world is different and it falls in the category of low, medium and high. Before the vaccination the occurrence of HBsAG was from 2% to 20%. The data was collected from different 161 countries that showed greater ration in Africa with 8.83%. It has also been shown that the persons in the age range of 48 to 52 years are more susceptible to this virus [5,6].

Natural History

The phases of infection of HBV and their history are being studied. If children get infected by HBV than this will be the chronic stage. The different phases of HBV are age dependent. The different phases of HBV are as follows [7]:

- Immunotolerant phase
- Immunoactive phase

- Reactivated phase

These phases also have other names like HBeAG positive, and HBeAG negative.

In case of young adults and children the rate of replication of virus is high while inflammation is low and the concentration of DNA in serum is high. When the rate of multiplication of HBV is very it is indicating the active phase of infection. In some cases, the disease regrets at the rate of 0.5 to 2% in every year [8].

In these patients the activity of virus can be judged due to the presence of HBcAG in the Treatments

The main goal of treatment in every case is to improve the survival of patients and their quality of life. In case of Hepatitis B treatment, the replication of HBV is stopped and the DNA of HBV is targeted to properly cure the disease. When the virus is suppressed than the chances of liver cancer are reduced. There are some treatment strategies which can be followed for the treatment of Hepatitis B and these treatments are as follows [9,10].

siRNA Therapy

There is another therapy that can be used for the treatment of this disease. This therapy uses a natural mechanism in which the foreign genes or the genes that are no longer required are suppressed. If in the body any viral gene is present its translation is stopped by this process. The greatest problem in this therapy is that there is also effect on the unneeded organs like kidney [11-14].

This therapy is given through injections as the siRNA gets digested in the gut. If the injections are given intravenous than there are chances of infusion reactions. Now the subcutaneous injections are given that target liver. These injections are used because they have lower side effects and there is no requirement of frequent dosing [15].

The stable siRNA do not activate the immune system of the host and the risk of off targets is also reduced. The genome of HBV is very compact and the siRNA molecules block many genes and the production of many proteins is also blocked. When we block the replication of HBV than the expression of HBeAG and HBsAG is also reduced [16-20].

The HBV mRNA is inhibited by this technique and the synthesis of its antigens is blocked. This technique is though effective for the treatment of chronic hepatitis B but in the next coming years the draw backs of this technique can be recovered. This technique will be used for clinical purposes in the next coming years [21,22].

The areas to be covered are improvement of the route of administration, safety profile and the combination of it with the other antiviral drugs. Many small interfering RNAs has been developed and some of them are ALN-HBV, ARC-520 and ARB-1467.

The ARC-520 knockdowns the HBV DNA and the viral drugs. Like the other techniques the mode of this treatment is different as it suppresses the DNA of virus along with its antigens. This one is also effective technique for the treatment of hepatitis B [23,24].

LNA Technology

An alternative technique to siRNA is LNA technology. This technique is also used to silence genes. The formation of different proteins is blocked by this technique. The advantage of this technique is that the risk of off target is reduced. The toxicity affects the target only. Now a days many treatments are being in use for the treatment of chronic hepatitis B. One of the methods is Taq man DNA technology but this method is old one and new technology is LNA technology. An experiment was performed by using this method in which 40 micro liters of PCR sample was taken and the composition of sample was 2 micro liter DNA sample, 400 micro liter DUTP, 200 nano mole of every primer, 200 micro mole of dGTP, dATP and dCTP, 2U of HotStarTaq DNA polymerase, 75nM of LNA probe, 0.5U uracil DNA glycosylase and 2 micro liter of DNA sample [25]. The amplification of that sample was performed in iCycler iQ5 and the protocol was:

First of all initially activate UDG at the temperature of 37C for the duration of 5 min. In the next step the UDG becomes inactivated. Than the HotStarTaq DNA polymerase becomes activated and the template is denatured at the temperature of 95C for the time period of 3min. Than 40 cycles are performed in two steps in which temperature of 95C is provided for 5sec and 60C is provided for 30 sec.

For every cycle the standard curves were created and the range of these curves was 40-4X107 IU/ml by the 1:10 serial dilutions of PUCm-T-HBV standard and all the samples were run duplicated. Than in order to create standard curves the threshold cycle was used as Y axis and at the x axis there was log of HBV DNA concentration and the examination of potential sample was performed by using Ct values that is corresponding to HBV DNA.

The efficiency of LNA technology is 100% and it was checked by taking 39 cases of known chronic hepatitis B and all of these were shown positive. The LNA technology is the new technology and it is basically the technology that is

based on nucleotide chemical modification. This modification is between O_2 and C_4 and this modification occurs through 2 methyl sugar link.

With this LNA modification the affinity and stability for the DNA molecules has been increased in PCR reactions. The melting temperature of oligonucleotide has been increased by 9.6C. This technology has made it possible to carry out the complicated experiments in a single test tube. These short probes are more sensitive towards single base mismatches. In order to test fetal DNA the LNA probes are more sensitive as compared to conventional DNA. The efficiency of PCR increases while using short probes rather than the large one and hence these probes are more useful in the PCR reactions [26].

In order to detect Salmonella we can also use LNA probes. In case of HBV DNA the detection performance of LNA probes is greater as compared to the common probes. The LNA probes have the detection limits of upto 40IU/ml. There are many more advantages of LNA technology and it is widely used for the treatment of chronic hepatitis B [27].

CRISPR/Cas9

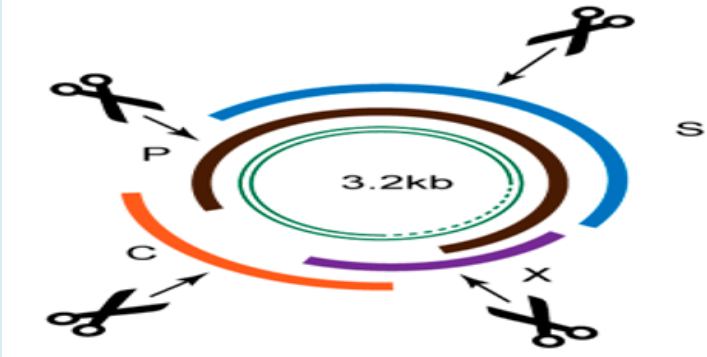
The problem related to other techniques is that they silence the genes during treatment but when the treatment is discontinued than the genes get activated again and again there is the production of proteins. These methods do not eliminate the virus. The solution is that the complete elimination of DNA of the virus.

There are different therapies which can be used for the modification of DNA like deacetylase activation and demthylation but the problem in these methods is the risk of off targets. The more beneficial method is the use of CRISPR/Cas9 which involves the cleavage of DNA. In case of bacteria the CRISPR/Cas9 present in it destroys the genetic material by combining with gRNA. In case of humans their genomes can be edited by the use of CRIPR/Cas9. We can take the example of sickle cell anemia as it is a genetic disorder and it can be cured by using CRISPR/Cas9.

In case of Hepatitis patients this technique reduces the level of DNA and the proteins produced by the host are also reduced. The CRISPR/Cas9 can also be combined with other gene editing tools like siRNA and the DNA is effectively reduced. When we are using this technique we have to follow many challenges and these challenges need to be overcome before we safely apply this to the patients. In this technique there are the chances of off target toxicities. The challenges which we are facing in this technique are overcome than this technique can be applied as the complete treatment of CHB. The chances of reactivation of virus are also reduced in this technique. In this technique the DNA will be completely removed and this can be used as the 100% efficient system. The CRISPER/Cas9 is basically a prokaryotic immune system. This technique is gene editing. In CRISPER many spacer and short regions are present. The type 2 system of CRISPER is widely studied system.

Many of the new spacer regions have been added in the CRISPER as these are more beneficial in case of invading viruses. As the HBV DNA replicates in liver so the CRISPER is than added into the liver. This double stranded DNA of HBV is converted into the single stranded DNA and this one is present on to the surface of liver cells. The complete removal of HBV DNA is very important. The double stranded DNA of HBV is being cut by the CRISPER.

Due to CRISPER the HBV DNA loses its biological activity or even it can be degraded. Its cell content is also reduced. This technique has been checked on the humanized mouse. This CRISPER/Cas9 technique is now used effectively for the treatment of chronic hepatitis B Figure 1 [28].



SBV-specific RNA Targeting Regions

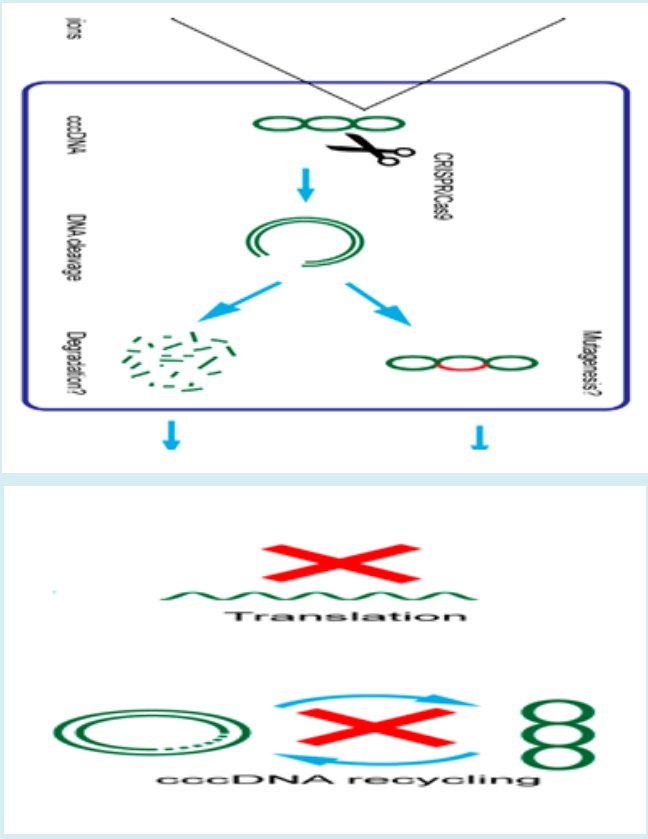


Figure1: Hepatitis B Treating Method of Targeting of Specific ssRNA ToolByCRISPR/Cas9.

Conclusion

Many techniques can be used for the treatment of hepatitis b like siRNA, CRISPER/Cas9 and LNA technology. Each technique has its own benefits and drawbacks. CRISPR/Cas9 can be the tool that we can use for the treatment of CHB (Chronic Hepatitis B).

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