Commentary: Thomas G. Evans

Investigating a functional cure for hepatitis B

Hepatitis B virus (HBV) is a complex, small DNA virus that goes through a unique ribonucleic acid (RNA) intermediate life cycle that requires reverse transcription. After transmission through infected blood, contaminated body fluids or perinatal transfer, the virus infects the liver and can then either integrate into the hepatocyte DNA or can exist in the nucleus outside the host DNA as a stable covalently closed circular DNA (cccDNA). Once HBV infection takes place, it results in chronic liver disease in 5-10% of infected adults, whereas the rate for perinatal transmission is the opposite, with around 90% of infected neonates progressing to chronic disease. Chronic disease is defined as not clearing a detectable virus within six months.

After chronic hepatitis B infection is established, the rate of natural clearance is minimal. The virus persists in the cccDNA form and then integrates into various regions of the host chromosomal DNA, where it continues to be a source for some viral proteins, especially a surface protein known as surface antigen (HBsAg). Chronic hepatitis B infection frequently results in the death of liver cells with resultant ongoing liver damage, which may lead to cirrhosis and liver cancer.

In contrast to chronic hepatitis B infection, hepatitis C is an RNA virus that exists and replicates in the cytoplasm. Drugs that target the RNA polymerase and associated replication machinery lead to a cure in almost all cases. Such was the case with Gilead Science's Harvoni and other combinations. Similar products can target the HBV RNA to DNA reverse transcription replication efficiently but have minimal effect on the HBV DNA. Thus, when these agents are stopped, in most cases there will be a rebound effect since the DNA is still making RNA copies which can become new viruses.

Highly effective vaccines to prevent established infection from hepatitis B virus were implemented in the early 1980s; however these vaccines are completely ineffective once a chronic infection is established. Despite the wide use of prophylactic vaccines, there are an estimated 257 million chronic hepatitis B carriers and over 880,000 related deaths per year worldwide. Two classes of antiviral therapies have been approved and recommended for the treatment of hepatitis B: interferons, which work through immune stimulation, and nucleotide analogues, which target the RNA to DNA replication. It is uncommon for patients on either therapy to achieve what is known as a 'functional cure,' which is defined as the loss of detectable HBV DNA in the plasma and evidence that DNA to RNA transcription has been shut down. This is signalled by having no detectable HBsAg in a serum sample.

Many research programmes are ongoing to develop new treatment concepts that focus on achieving this functional cure in a significant proportion of patients. The principal aim is to be able to stop any treatment without incurring a risk of virological relapse, and therefore a decreased risk of liver disease damage and liver cancer. Most experts believe that to reach a functional cure, a combination approach may be needed. The first part of the combination would result in lowering the cccDNA amount, and the second would be to restore or augment the immune responses against HBV. This immune clearance and control of chronic hepatitis B is likely to depend on the use of specific modalities that induce cells known as CD8+ T cells. This is the aspect of the cure combination on which our immunotherapeutic, Vaccitech VTP-300, is based.

The VTP-300 vaccine developed by Oxford University and Vaccitech uses a platform approach that has induced remarkably high levels of CD8+ T cells in humans, including CD8+ T cells against HBV. VTP-300 uses a single intramuscular injection of a non-replicating adenovirus 'prime' followed by a different viral vector 'boost' using a non-replicating pox virus (modified vaccinia virus Ankara (MVA). These vectors have been widely and safely used in millions of people and are licensed in some countries for the prevention of Covid-19, smallpox and Ebola infections.

Most attempts at using an immunotherapeutic therapeutic vaccine in HBV have failed, but unlike VTP-300 they have not elicited a meaningful CD8+ T cell response. Also, there is T cell exhaustion in many chronic infections, and this may require the use of compounds alongside the CD8+ T cell induction to allow the T cells to function at their site of action. Vaccitech has employed this strategy of using the VTP-300 with the checkpoint inhibitor nivolumab. This has been observed to have overcome some of the exhaustion. At the 2022 EASL International Liver Congress in June, the company reported additional interim results on 39 patients, with three months of follow-up, from its ongoing clinical trial of VTP-300.

The results showed that VTP-300 as a monotherapy or in combination with low-dose nivolumab, had no treatment-related serious adverse events. Meaningful and durable reductions of HBsAg were seen in some patients. In all patients who had an HBsAg decline greater than 0.5 log10, the reductions of HBsAg were durable by up to eight months after the last dose. A robust T cell response against all encoded antigens was observed following VTP-300 administration, notably for marked CD8+ T cell predominance. Enrolment in the HBV002 study is complete with 55 patients registered. An updated interim analysis for all patients at the six-month follow-up is expected at the end of 2022.

Finally, another approach under investigation for VTP-300 is to combine it with a compound that profoundly reduces the initial levels of hepatitus B surface antigen, known as a siRNA (AB-279 from Arbutus). This combination is also being tested in an ongoing clinical trial.

This commentary was written by Dr Thomas G. Evans, Chief Scientific Officer of Vaccitech Plc.