

Lamivudine for Chronic Hepatitis B: Uses and Abuses

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Chronic Hepatitis B virus (HBV) infection remains a major public health problem in Pakistan. At an approximate carriage rate of 5%, there are potentially 3.5 million Pakistanis with chronic active HBV infection who are at risk of developing liver cirrhosis and therefore require treatment to eradicate the HBV infection. Similarly another 3.5 million people in the country are healthy HBV carriers who do not require treatment but are often the most desperate to get treated because they are denied marriages or jobs and visas to the Gulf countries. As a result numerous therapies promising complete HBV eradication have proliferated in the country, based on available allopathic agents, homeopathic recipes, Greek medicines and often home grown recipes. In such an uncontrolled milieu the introduction of a new promising compound like Lamivudine can lead to both beneficial uses and potentially dangerous abuses. Pakistan is the fourth country in the world, including United States, where Lamivudine has already been launched as treatment for chronic HBV infection. It is timely to review the information available for lam ivudine therapy for the benefit of our readers.

Lamivudine is a nucleoside analogue that has potent anti-viral effects against HBV by interfering with viral replication¹. The drug was initially used for HIV infection and then also found to be equally effective for HBV, which is not surprising given the similarities between the replicative processes of HIV and HBV. Larnivudine is now an established component of the multi-drug therapy used for HIV all over the world. Recently a lot of data has emerged regarding the efficacy of lamivudine for chronic HBV infection. Complete suppression of HBV DNA can be achieved in most patients with the use of 100 mg of lamivudine daily². Normalisation of serum ALT can be achieved in upto 70% of patients. After short courses of treatment (upto 12 weeks) however, most patients relapse and become HBV DNA positive again³. On the other hand, if treatment is extended to one year, a sustained response can occur in 16-35% patients as shown by loss of Hbe antigen and development of Hbe antibody⁴. These are figures very similar to those seen with interferon therapy for chronic HBV. Even better results are achieved if lamivudine treatment is extended upto two or three years, when the rates of HbeAg/HbeAb seroconversion can go as high as 75%⁵. The drug is generally free of side effects and well tolerated, with safety data now being available from over 700 patients treated world wide in clinical trials. How does lam ivudine compare with other treatments currently available for chronic hepatitis B infection? Lamivudine given for 1 year is as efficacious as interferon given for 4-6 months in causing HbeAg/HbeAb seroconversion and more efficacious than interferon if used for longer⁶. Most HbeAg positive patients will respond to lamivudine, irrespective of their clinical profile, whereas patient selection is of utmost importance in interferon treatment. A wider spectrum of chronic HBV hepatitis patients can thus be treated with lamivudine rather than interferon. It is almost free of side effects as compared to interferon, It has the ease of use, being given by mouth as compared to inteferon injections and it is substantially cheaper than interferon, adding to patient acceptance. However, due to these very properties, lamivudine is also at a higher risk of misuse.

Given such respectable efficacy and safety data, are there then any undesirable aspects of lam ivudine therapy for chronic HBV infection? There are at least two aspects which merit serious consideration. First is the issue of the development of mutant HBV strains during lamivudine therapy, specially with prolonged treatment. These mutations develop most commonly in the YMDD motif of the DNA polymerase gene of the virus and tend to occur usually after more than 6 months of treatment⁷. After 1 year of therapy, mutant HBV strains can be found in 14% of patients and with 2 years therapy this can rise to 40%⁴. The development of mutations is associated with a relapse and rise in serum HBV DNA

and ALT levels. However these flares in DNA and ALT are mild and generally settle with continued treatment with lamivudine. Some studies have reported severe flares in disease activity with acute hepatic decompensation but ultimate recovery in most cases⁸. This disease flare can even occur after stopping lamivudine, specially if therapy has been stopped prematurely before HbeAg seroconversion and hence the need for close follow up of patients. Secondly, lamivudine does not interfere completely in the complex replicative process of HBV. For example it has no effect on the intra-nuclear ccc HBV DNA, which in practical terms means that it is difficult to achieve complete viral eradication and patients will usually remain HBs antigen positive. This also means that the drug will not be effective in treating the HBV carrier patient, where the sole aim of therapy would be to achieve a negative HBs antigen status.

In summary, lamivudine is a promising advance in the treatment of chronic HBV hepatitis. Recent studies support the use of lamivudine in the treatment of HBe antigen positive patients with chronic hepatitis due to HBV infection. Lamivudine has to be used for an extended period of time and there is no role for short term treatment with this drug. The exact length of treatment is as yet undetermined but has to be based on the response of the patient, specially HbeAg to HbeAb seroconversion. Regular follow up is mandatory during and after treatment to detect flare of HBV infection. There is no role for lamivudine in the treatment of acute HBV hepatitis, as spontaneous recovery occurs in 95% of such patients. There is also no role for lamivudine in the healthy HBV carrier as the drug will not work in this situation. Medical practitioners are therefore urged to properly determine the need for therapy in the individual patient before commencing lamivudine for chronic HBV infection.

References

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