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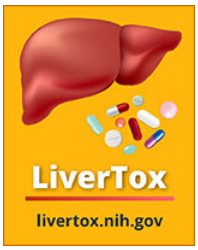


Telbivudine

Updated: October 20, 2020.

OVERVIEW

Introduction

Telbivudine is a nucleoside analogue and antiviral inhibitor of hepatitis B virus (HBV) replication which is used alone and in combination with other agents in the therapy of the hepatitis B. Telbivudine does not appear to be a significant cause of drug induced liver injury, but can be associated with flares of the underlying hepatitis B either during therapy or upon withdrawal.

Background

Telbivudine (tel biv' ue deen) is the L-enantiomer of deoxythymidine (LdT) and has antiviral activity against HBV replication both in vitro and in vivo. Telbivudine is phosphorylated intracellularly to the triphosphate which inhibits the HBV polymerase and competes with deoxythymidine for incorporation into the growing viral DNA, causing inhibition of polymerase activity and DNA chain termination. Telbivudine has little or no activity against HIV replication. Telbivudine was approved in the United States in 2006 as therapy of chronic hepatitis B, either alone or in combination with other agents. It was withdrawn from the United States market in 2016 largely for economic reasons. Telbivudine was previously available as 600 mg tablets under the brand name Tyzeka. The recommended adult dose was 600 mg orally once daily. Side effects of telbivudine are uncommon. Studies of telbivudine therapy during pregnancy suggest that it is safe for pregnant women and can lower the rate of maternal-infant transmission of hepatitis B if administered in the last trimester. It was never approved for this indication in the United States.

Hepatotoxicity

Telbivudine shares many features with the other L-nucleosides (lamivudine, emtricitabine) and has been linked to transient flares of hepatitis B during and after treatment of chronic hepatitis B. Serum ALT elevations above 3 times normal occurred in 5% to 10% of patients on telbivudine, which was comparable to other nucleoside analogues. Three types of flares can arise with nucleoside analogue therapy: transient and usually asymptomatic flares around the time of initiation of therapy (treatment flares), exacerbations of disease after development of antiviral resistance to telbivudine (breakthrough flares) and after stopping treatment (withdrawal flares). Cases of exacerbation of hepatitis B after development of antiviral resistance or upon telbivudine withdrawal can be severe and some cases have qualified as acute liver failure. No instances of lactic acidosis with hepatic steatosis have been reported with telbivudine therapy of hepatitis B, but isolated cases of suspected mitochondrial injury with myopathy have been reported. In trials of telbivudine therapy in pregnant women with HBsAg and HBeAg in serum and high levels of HBV DNA, therapy appeared to lessen if not eliminate maternal infant transmission, but withdrawal flares of hepatitis B occurred in some women with active disease and ALT elevations before

therapy. In women with "immune tolerant" hepatitis B with high levels of HBV DNA without serum aminotransferase elevations, withdrawal flares are uncommon and levels of HBV DNA rise to previous levels on stopping therapy but without a concurrent flare of disease.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The apparent absence of significant hepatotoxicity from telbivudine may be due to its lack of hepatic metabolism. In vitro, telbivudine has little activity against mitochondrial polymerase gamma, inhibition of which has been implicated in the syndrome of hepatic mitochondrial injury with lactic acidosis, steatosis and hepatic failure.

Outcome and Management

Flares of hepatitis B during and after telbivudine therapy can range in severity from mild, transient ALT elevations to severe acute liver injury resulting in hepatic failure and death. Flares occurring at initiation of therapy are usually mild and not associated with symptoms or jaundice. Flares associated with development of antiviral resistance and withdrawal flares can be severe. As a result, patients who develop evidence of antiviral resistance to telbivudine should be monitored carefully and switched to or have added another agent with a different pattern of resistance. Upon withdrawal of telbivudine, patients should be monitored carefully and promptly restarted on antiviral therapy if signs of severe injury arise.

Agents used in therapy of HBV infection include adefovir, emtricitabine, entecavir, lamivudine, telbivudine, tenofovir, interferon alfa and peginterferon.

Drug Class: Antiviral Agents, Antiretroviral Agents, Hepatitis B Agents

Other Drugs in the Subclass, Nucleoside Analogues: Abacavir, Adefovir, Didanosine, Emtricitabine, Entecavir, Lamivudine, Stavudine, Tenofovir, Zidovudine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Telbivudine – Tyzeka®

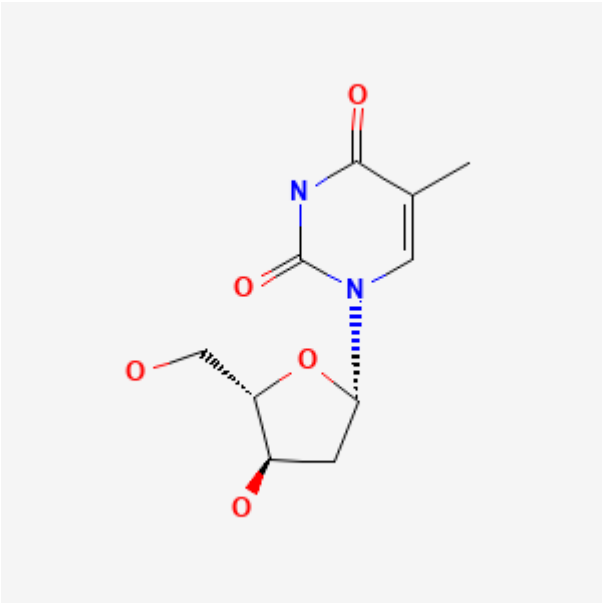
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Telbivudine	3424-98-4	C10-H14-N2-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2020

Núñez M. Hepatitis treatments. Hepatic toxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 511-2.

(Review of hepatotoxicity of antiviral agents; mentions the potential of severe flares of disease upon withdrawal of therapy in chronic hepatitis B).

Acosta EP, Flexner C. Antiviral agents (nonretroviral). In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1593-622.

(Textbook of pharmacology and therapeutics).

Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nature Med. 1995;1:417–22. PubMed PMID: 7585087.

(Review of mechanisms for mitochondrial injury by nucleoside analogues including inhibition of mitochondrial DNA polymerase gamma).

Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, et al. Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology. 2005;129:528–36. PubMed PMID: 16083710.

(One year course of telbivudine vs lamivudine vs combination of both in 104 patients with hepatitis B; ALT elevations >3 times ULN occurred in only 1 of 44 [2%] telbivudine-treated patients).

Chan HL, Heathcote EJ, Marcellin P, Lai CL, Cho M, Moon YM, Chao YC, et al. 018 Study Group. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. Ann Intern Med. 2007;147:745–54. PubMed PMID: 17909201.

(Trial of telbivudine vs adefovir for 52 weeks in 131 patients with chronic hepatitis B; rates of ALT elevations and flares of hepatitis were not provided).

Bridges EG, Selden JR, Luo S. Nonclinical safety profile of telbivudine, a novel potent antiviral agent for treatment of hepatitis B. Antimicrob Agents Chemother. 2008;52:2521–8. PubMed PMID: 18474576.

(Animal studies using high doses of telbivudine demonstrated no hepatotoxicity).

Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, Chen Y, et al; Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med. 2007;357:2576–88. PubMed PMID: 18094378.

(Trial of telbivudine [600 mg/day] vs lamivudine [100 mg/day] for 52 weeks in 1370 patients with chronic hepatitis B; ALT >3 times ULN occurred in 3.7% on telbivudine vs 6.3% on lamivudine; 1 patient on lamivudine developed antiviral resistance and liver failure requiring liver transplant).

Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X, Wang Y, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. Hepatology. 2008;47:447–54. PubMed PMID: 18080339.

(Trial of telbivudine vs lamivudine for 52 weeks in 332 patients with hepatitis B; ALT elevations >3 times normal occurred in 9.1% of lamivudine vs 5.4% of telbivudine treated subjects, usually associated with viral breakthrough; none fatal).

Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology. 2009;49(5 Suppl):S185–95. PubMed PMID: 19399802.

(Review of side effects of nucleoside analogues used to treat chronic hepatitis B).

Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, et al; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology. 2009;136:486–95. PubMed PMID: 19027013.

(2 year results from Globe trial [Lai, 2007]: ALT levels >3 times ULN occurred in 6.3% of telbivudine vs 11.6% of lamivudine-treated subjects; 1 patient on telbivudine with antiviral resistance developed liver failure, but survived).

Finsterer J, Ay L. Myotoxicity of telbivudine in pre-existing muscle damage. Virol J. 2010;7:323. PubMed PMID: 21083916.

(27 year old man with chronic hepatitis B developed myalgias 3 weeks after starting telbivudine [CPK 3243 U/L], improving upon stopping).

Zou XJ, Jiang XQ, Tian DY. Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine. J Viral Hepat. 2011;18:892–6. PubMed PMID: 22093034.

(Among 200 patients with chronic hepatitis B treated with telbivudine for 3 years or more, 84% had at least one CPK elevation and 5% developed symptomatic myopathy [CPK more than 7 times ULN], but most abnormalities resolved spontaneously except in 3 patients in whom it resolved once they were switched to adefovir).

Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF, Yue X, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55:1215–21. PubMed PMID: 21703206.

(Controlled trial of telbivudine vs no treatment during the latter part of pregnancy [starting between weeks 20 and 33] in 229 Chinese women with HBsAg, HBeAg and high levels of HBV DNA in serum; transmission of HBV to the newborn occurred in 0% of newborns of telbivudine-treated vs 8% of those of untreated mothers; after withdrawal of telbivudine after delivery in 38 mothers, none had a flare of hepatitis with ALT elevations >10 times ULN).

Dang S, Gao N, Zhang X, Jia X. Rhabdomyolysis in a 48-year-old man with hepatitis B-induced cirrhosis. Am J Med Sci. 2011;342:73–5. PubMed PMID: 21642814.

(48 year old man with chronic hepatitis B and cirrhosis developed abdominal pain and swelling and was found to have ascites and elevated CPK [3110 U/L]; despite stopping therapy, he developed progressive rhabdomyolysis and died of renal failure).

Gane EJ, Wang Y, Liaw YF, Hou J, Thongsawat S, Wan M, Moon YM, Jia J, Chao YC, Niu J, Leung N, Samuel D, Hsu CW, Bao W, Lopez P, Avila C. Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B. Liver Int. 2011;31:676–84. PubMed PMID: 21457439.

(Further follow up of trial of telbivudine [Lai 2007] on safety in 399 patients treated for at least 3 years identified CPK elevations >7 times ULN in 55 [13%], myopathy in 22 [5%] and ALT flares >10 times ULN in 11 [3%]).

Chan HL, Chen YC, Gane EJ, Sarin SK, Suh DJ, Piratvisuth T, Prabhakar B, et al. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naïve patients with HBV-related decompensated cirrhosis. J Viral Hepat. 2012;19:732–43. PubMed PMID: 22967105.

(In a controlled trial of telbivudine vs lamivudine in 228 patients with chronic hepatitis B and hepatic decompensation, the mortality rate from end stage liver disease at 2 years was 16%, but no deaths were considered drug related; one patient on telbivudine developed myopathy).

Wang J, Wang M, Huang Y. Acute liver failure resulting from discontinuation of nucleoside analogues in chronic hepatitis B patients: A report of two cases. Scand J Infect Dis. 2013;45:158–60. PubMed PMID: 22830672.

(Two patients, 37 and 39 year old men, discontinued antiviral therapy [lamivudine and adefovir] on their own and developed acute on chronic hepatic failure [bilirubin 44.5 and 26.6 mg/dL, ALT 387 and 87 U/L, INR 2.47 and 2.44, HBV DNA 20,000-200,000 copies/mL], one died and one underwent emergency liver transplant despite restarting therapy with telbivudine).

Chen EQ, Zhou TY, Bai L, Wang JR, Yan LB, Liang LB, Tang H. Lamivudine plus adefovir or telbivudine plus adefovir for chronic hepatitis B patients with suboptimal response to adefovir. Antivir Ther. 2012;17:973–9. PubMed PMID: 22728692.

(Among 72 patients with chronic hepatitis B who had a suboptimal response to adefovir, lamivudine was added in 37 and telbivudine in 35 patients; no worsening of liver disease was reported).

Ahn SH, Kweon YO, Paik SW, Sohn JH, Lee KS, Kim DJ, Piratvisuth T, et al. Telbivudine in combination with adefovir versus adefovir monotherapy in HBeAg-positive, lamivudine-resistant chronic hepatitis B. Hepatol Int. 2012;6:696–706. PubMed PMID: 21989925.

(Among 42 patients with chronic hepatitis B who had lamivudine resistance, 21 were treated with adefovir alone and 21 with adefovir and telbivudine; 1 patient in each group had an ALT flare during therapy [ALT 1743 and 1362 U/L], but both evidently resolved without discontinuation).

Kim EH, Park H, Lee KH, Ahn SH, Kim SM, Han KH. Two cases of telbivudine-induced myopathy in siblings with chronic hepatitis B. Clin Mol Hepatol. 2013;19:82–6. PubMed PMID: 23593614.

(28 and 25 year old brothers developed muscle weakness 5 and 12 months after starting telbivudine for hepatitis B [bilirubin 0.9 and 0.4 mg/dL, ALT 26 and 57 U/L, CPK 788 and 2992 U/L], improving upon switching to entecavir).

Wang Y, Thongsawat S, Gane EJ, Liaw YF, Jia J, Hou J, Chan HL, Papatheodoridis G, Wan M, Niu J, Bao W, Trylesinski A, Naoumov NV. Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B. J Viral Hepat. 2013;20:e37–46. PubMed PMID: 23490388.

(Further follow up of controlled trials of telbivudine for chronic hepatitis B with safety data on 655 patients reported cumulative CK elevations in 104 [16%], myopathy in 4 [1%] and ALT flares in 42 [6%], 13 being early on treatment flares and 42 breakthrough flares).

Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology. 2014;60:468–76. PubMed PMID: 25187919.

(Among 648 HBeAg positive pregnant women with 52 weeks of follow up, treated with telbivudine, lamivudine or no therapy during the last trimester, 16% on telbivudine, 4% of lamivudine and 3% of untreated women had an on treatment flare of ALT, but all were asymptomatic and less than 5 times ULN; no mention of withdrawal flares).

Marcellin P, Wursthorn K, Wedemeyer H, Chuang WL, Lau G, Avila C, Peng CY, et al. Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. J Hepatol. 2015;62:41–7. PubMed PMID: 25152207.

(Among 159 HBeAg positive adults with chronic hepatitis B treated with telbivudine, peginterferon or both, neuropathy arose in 14% of those on both agents vs 2% on telbivudine alone and none of the peginterferon alone group, which led to the early discontinuation of the trial).

Wu Q, Huang H, Sun X, Pan M, He Y, Tan S, Zeng Y, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. Clin Gastroenterol Hepatol. 2015;13:1170–6. PubMed PMID: 25251571.

(Among 279 HBeAg positive women with chronic hepatitis B and high levels of HBV DNA treated with telbivudine during the last trimester, rates of transmission were 0% compared to 15% of subjects who refused antiviral therapy; no serious adverse events occurred and there was no mention of on treatment or withdrawal ALT flares).

Han GR, Jiang HX, Yue X, Ding Y, Wang CM, Wang GJ, Yang YF. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2015;22:754–62. PubMed PMID: 25641421.

(Among 454 HBeAg positive pregnant women with chronic hepatitis B and normal ALT levels despite high levels of HBV DNA treated with telbivudine or given no therapy starting in the 2nd or 3rd trimester, rates of transmission were none vs 9% [8/86] and 46 of 236 women [20%] who discontinued therapy one month postpartum had a withdrawal flare, although in only 3 [1.3%] did levels rise about 5 times ULN and no woman required therapy as all levels eventually fell into the normal range).

Tsai MC, Chen CH, Tseng PL, Hung CH, Chiu KW, Wang JH, Lu SN, et al. Comparison of renal safety and efficacy of telbivudine, entecavir and tenofovir treatment in chronic hepatitis B patients: real world experience. Clin Microbiol Infect. 2016;22:95.e1–95.e7.

(Among 587 Chinese patients positive chronic hepatitis B [~50% with cirrhosis] treated with tenofovir, entecavir or telbivudine for at least one year, viral resistance developed in none on tenofovir, 3.4% on entecavir and 23% of telbivudine, while renal function was stable except in those on tenofovir in whom a decrease occurred by year 5 and rates of hepatocellular carcinoma were highest among those with cirrhosis treated with telbivudine).

Hu Y, Xu C, Xu B, Hu L, Liu Q, Chen J, Liu J, et al. Safety and efficacy of telbivudine in late pregnancy to prevent mother-to-child transmission of hepatitis B virus: A multicenter prospective cohort study. J Viral Hepat. 2018;25:429–37. PubMed PMID: 29193547.

(Among 328 HBeAg positive pregnant Chinese women who were treated with telbivudine during the last trimester or elected not to receive therapy, there were similar rates of ALT elevations in the postpartum period [21% vs

20%], whereas none of the 128 infants born to treated mothers developed HBV infection compared to 2 of 156 [1.5%] infants of controls).