Drug Update

Tenofovir Alafenamide

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ABSTRACT

Tenofovir alafenamide (AF), an oral prodrug of tenofovir, was developed to optimize the antiviral potency and clinical safety of the active moiety tenofovir diphosphate (selective reverse transcriptase nucleotide inhibitor). In phase III trials in treatment-naive and -experienced adult patients with HepatitisB eantigen (HBeAg)-positive or -negative chronic hepatitis B virus (HBV) infection, once-daily tenofovir AF 25 mg provided effective and sustained viral suppression.Tenofovir AF was noninferior to once-daily tenofovir disoproxil fumarate (DF) 300 mg.

Given the bone and renal safety concerns associated with long-term tenofovir DF treatment, the more favourable pharmacological profile of tenofovir AF permits a marked reduction in the dosage of this tenofovir prodrug and thereby reduces systemic exposure to tenofovir.Tenofovir AF is an important emerging first-line option for the treatment of chronic HBV infection in adults and adolescents (aged =12 years and with a bodyweight of =35 kg).

Introduction

Chronic hepatitis B virus (HBV) infection is one of the leading causes of cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC). An estimated 257 million people are positive for hepatitis B surface antigen (HBsAg) globally.[1] Due to interaction among various host, environmental, and viral factors, chronic HBV infection can range from chronic infection with active viral replication but relatively normal biochemical profiles to chronic hepatitis with elevated ALT.[2,3] Serial monitoring of ALT, HBV DNA level, and hepatitis B e antigen (HBeAg) sero-status is essential for characterization of the phase of infection.[4]

There are currently two classes of treatment options for chronic HBV infection : pegylated interferon and nucleos(t)ide analog. Treatment with pegylated interferon involves immune system control of HBV infection, and thus is limited to patients who can better respond to interferon, such as patients with HBV genotype A/B, wild type pre-core and basal core promotor sequences, low HBV DNA, and higher ALT levels at baseline or those who are younger.[5,6,7] Interferon-based therapies are also contraindicated in the presence of hepatic decompensation and should be used with caution in patients with cirrhosis. Nucleos(t)ide analogs inhibit HBV replication and are generally well tolerated; however, lamivudine, telbivudine, and adefovir are no longer recommended because of the high risk of resistance.[2,4] Entecavir and tenofovir disoproxil fumarate (TDF), are recommended by most management guidelines as the first line oral agents and can be used for patients with hepatic decompensation and post transplant patients.[2,4,8] Long-term nucleos(t)ide analog treatment has been shown to be effective in the suppression of HBV replication, histologic improvement and reducing the incidence of HCC although the loss or seroconversion of HBsAg is very rare.[9,10] In this context, long-term treatment is required in almost all cases. As such, long-term safety of therapy is a matter of concern.

Consequent to these safety concerns, tenofovir alafenamide (TAF), a prodrug of tenofovir, was developed to optimize the antiviral potency and clinical safety of tenofovir. The favourable pharmacological profile of tenofovir AF compared with tenofovir DF reduces systemic exposure to the active moiety tenofovir diphosphate and, consequently, may improve bone and renal safety. This review discusses the clinical use of oral tenofovir AF in treatment-naive and experienced patients with HBeAg-positive or negative chronic

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HBV infection and summarizes the pharmacological properties of tenofovir AF.

Mechanism of action and pharmacokinetics

TAF, like TDF, is a phosphonate prodrug of tenofovir (TFV), specifically developed to have enhanced antiviral potency with an improved safety profile to address the renal and bone toxicities associated with TDF. Both TAF and TDF are initially metabolized to TFV in the plasma, which in turn is metabolized, in target viral infected cells, to the active metabolite tenofovir diphosphate (TFV-DP). Levels of circulating plasma TFV are associated with renal and bone toxicity. TAF has greater plasma stability than TDF, enabling more efficient delivery of the active metabolite TFV-DP intracellularly at much lower doses.[11,12] When TAF is given at a dose of 25 mg, circulating concentrations of plasma TFV are about 90% lower than with the approved daily dose of 300 mg TDF.[13,14] This difference underpins the better safety profile of TAF compared with TDF.

TAF leaves the plasma and enters hepatocytes primarily by passive diffusion, with some uptake by the hepatic uptake transporters organic aniontransporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3). TAF is then primarily hydrolysed by carboxylesterase 1 (CES1) to form TFV, which undergoes phosphorylation to form the pharmacologically active metabolite TFV-DP.[12] Potent inhibition of HBV replication occurs when HBV reverse transcriptase incorporates TFV into HBV DNA resulting in HBV DNA chain termination. TAF exhibits linear and dose-dependent pharmacokinetics, in patients with chronic HBV, characterized by efficient absorption ($t1/2 < 1$ h) and rapid plasma elimination ($t1/2 < 45$ min).[13] TAF is a substrate for P-glycoprotein (P-gp) and so potential drug interactions can be expected with P-gp inducers such as carbamazepine, phenobarbital, rifabutin, rifampicin, rifapentine. Coadministration of these drugs with TAF is expected to decrease TAF plasma concentrations, which may result in loss of therapeutic effect, and is therefore not recommended. Excretion is largely in the faeces, with very little intact TAF. No clinically relevant differences in those with severe renal impairment (CLCR > 15 but TAF pharmacokinetics have not been studied in patients with a creatinine clearance (CLCR) < 15 ml / min but there are no clinically relevant differences in those with severe renal impairment (CLCR > 15 but < 30 ml / min) compared with healthy subjects with normal renal function.[14]

Doses and administration

Oral Tenofovir AF is indicated for the treatment of chronic HBV infection in adults and adolescents (aged > 12 years and with a body weight of > 35 kg].[15] The recommended dosage is 25 mg once daily. In HBeAg positive patients without cirrhosis, treatment should continue for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or until there is a loss of efficacy. Regular reassessment is recommended after treatment discontinuation to detect virological relapse. In HBeAg-negative patients without cirrhosis, treatment should be given until HBs seroconversion or until there is evidence of a loss of efficacy. Hepatic function should be monitored closely with both clinical and laboratory follow-up for > 6 months in patients who discontinue anti-hepatitis B therapy. No dosage adjustment is required in patients with an estimated CLCR of > 15 mL/min or patients with a CLCR of < 15 mL/min who are receiving dialysis.[15] Tenofovir AF is not recommended in patients with an estimated CLCR of < 15 mL/min who are not receiving haemodialysis. There are no efficacy or safety data in HBV-infected patients with decompensated liver disease and who have a Child Pugh score.[16] Data relating to the use of tenofovir AF in renal impairment are currently limited[15]; Although data from pregnant women treated with tenofovir AF are limited, extensive data from pregnant women treated with tenofovir DF (1000 exposure outcomes) indicates no malformative or fetal / neonatal toxicity was associated with the use of tenofovir DF.[15]

Phase III clinical trials[17,18]

Table 1. Primary and secondary efficacy endpoints at 48 and 96 weeks of treatment with tenofovir alafenamide or tenofovir disoproxil fumarate for chronic hepatitis B virus patients.

	HBeAg positive (n = 873)			HBeAg negative (n = 425)		
	TAF 25 mg (n = 581)	TDF 300 mg (n = 292)	p-value	TAF 25 mg (n = 285)	TDF 300 mg (n = 140)	p value
Week 48						
HBV DNA < 29 IU/ml	371/581 (64%)	195/292 (67%)	0.25	268/285 (94%)	130/140 (93%)	0.47
ALT normalization* central laboratory AASLD criteria	384/537 (72%) 257/572 (45%)	179/268 (67%) 105/290 (36%)	0.18 0.014	196/236 (83%) 137/276 (50%)	91/121 (75%) 44/138 (32%)	0.076 0.0005
HBeAg loss	78/565 (14%)	34/285 (12%)	0.47	NA	NA	
HBeAg seroconversion	58/565 (10%)	23/285 (8%)	0.32	NA	NA	
HBsAg loss	4/576 (0.7%)	1/288 (0%)	0.52	0/281 (0%)	0/138 (0%)	-
HBsAg seroconversion	3/576 (0.5%)	0/288 (9%)	0.22	0/281 (0%)	0/138 (0%)	-
Week 96						
HBV DNA < 29 IU/ml	423/581 (73%)	218/292 (75%)	0.47	258/285 (90%)	127/140 (91%)	0.84
ALT normalization central laboratory AASLD criteria	405/537 (75%) 299/572 (52%)	181/268 (68%) 121/290 (42%)	0.017 0.003	191/236 (81%) 86/121 (71%)	139/276 (50%) 55/138 (40%)	0.038 0.035
HBeAg loss	123/565 (22%)	51/285 (18%)	0.2	NA	NA	
HBeAg seroconversion	99/565 (18%)	35/285 (12%)	0.5	NA	NA	
HBsAg loss	7/576 (1%)	4/288 (1%)	0.88	1/281 (0.4%)	0/138 (0%)	0.72
HBsAg seroconversion	6/576 (1%)	0/288 (0%)	0.078	1/281 (0.4%)	0/138 (0%)	0.72

*Central laboratory: ALT ≤ 43 U/l for males aged 18–69 years and ≤35 U/l for males aged ≥69 years; ALT ≤ 34 U/l for females aged 18–69 years and ≤32 U/l for female aged ≥69 years. AASLD criteria: ALT ≤ 30 U/l for males and ≤19 U/l for females.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable.

Overall, at week 96, no resistant isolates were detected in the TAF or TDF groups in either study.[19]

Safety and tolerability

Both phase III studies showed TAF to be well tolerated in patients with chronic hepatitis B with most adverse events being mild in severity. At week 48, discontinuation of treatment due to adverse events was uncommon (< 1%) in both treatment groups.[17,18]

Bone safety - Patients receiving TAF had significantly smaller reductions in bone mineral density (BMD) compared with patients receiving TDF. No treatment-related fractures were reported in either group. At 96 weeks, the reduced effects on BMD decline with TAF versus TDF, continued with a pooled analysis of the treatment populations showing patients receiving TAF had significantly smaller decreases compared with TDF-treated patients, at the hip (-0.33% versus -2.52%) and the spine (-0.75% versus -2.59%). Furthermore, the magnitude of the difference in BMD decreases between the TAF and TDF groups was significantly greater at week 96 compared with the difference in decline observed at week 48 ($p < 0.001$) when assessed at hip but not at spine received continuous TAF at week 144 ($p = 0.016$).[19] Antiviral efficacy was maintained in both groups and TDF patients

switching to TAF at week 96 had increased rates of ALT normalization at week 144.[20] Various surrogate biomarkers for bone metabolism were evaluated in the phase III trials found reduced impact of TAF on bone safety compared with TDF. These included markers of bone resorption [C-type collage sequence (CTX)] and formation [procollagen type 1 N-terminal propeptide (P1NP), bone-specific alkaline phosphatase (bsAP), osteocalcin]. TAF recipients showed significantly smaller changes in these biomarkers from baseline, than those receiving TDF[17,18]

Renal safety

TFV nephrotoxicity primarily occurs in the proximal tubule cells. There were no significant between-group differences in urine-protein-to-creatinine or albumin-to-creatinine ratio (UACR) but significant differences were observed when more sensitive markers of proximal tubular dysfunction were assessed.[19] Median percentage changes from baseline in both urine retinol-binding-protein-to-creatinine (RBP:CR) ratio and urine-β-2-microglobulin-to-creatinine (β2M:CR) ratio favoured TAF over TDF at week 48 ($p < 0.001$).

Discussion :

Two large, multinational, phase III trials have demonstrated sustained antiviral efficacy of TAF that is non-inferior to TDF in patients with both HBeAg-positive and HBeAg-negative chronic HBV infection. In conclusion, TAF is more efficient than TDF at delivering TFV into target hepatocytes with reduced impact on renal function and bone mineralization. Although the phase III renal safety data are encouraging, these studies did not enrol patients with clinically significant renal impairment (eGFR < 50 ml/min) and the majority of patients were under 65-years old without comorbidities. Similarly, there are no efficacy or safety data for patients with decompensated or advanced liver disease (Child-Pugh class B and C). The efficacy of TAF in patients with resistance mutations associated with older nucleos(t)ide analogues is unclearTAF has been included in the 2017 European Association for the Study of the Liver guidelines as a first-line agent for the treatment of chronic HBV infection in adults, and the recently updated 2018 AASLD and APSL guidance also recommends TAF amongst preferred antiviral therapies in adults.[21,22] These guidelines support a role for TAF in the management of chronic hepatitis B and as encouraging as the phase III data for TAF is, substantially longer follow up will be required to determine if and how the differences in renal and bone safety parameters translate into clinical benefit over TDF. The efficacy of TAF in patients with resistance mutations associated with older nucleos(t)ide analogues is unclear.

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