Research Article

EASL JOURNAL OF HEPATOLOGY

Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection

Kosh Agarwal[1,*], Scott K. Fung[2], Tuan T. Nguyen[3], Wendy Cheng[4], Eric Sicard[5], Stephen D. Ryder[6], John F. Flaherty[7], Eileen Lawson[7], Sally Zhao[7], G. Mani Subramanian[7], John G. McHutchison[7], Edward J. Gane[8], Graham R. Foster[9]

[1]*Institute of Liver Studies, King's College Hospital, London, UK;* [2]*Toronto General Hospital, Toronto, Ontario, Canada;* [3]*T. Nguyen Research and Education, San Diego, CA, USA;* [4]*Royal Perth Hospital, Perth, Western Australia, Australia;* [5]*Algorithme Pharma, Montreal, Quebec, Canada;* [6]*Nottingham University Hospitals NHS Trust and Biomedical Research Unit, Nottingham, UK;* [7]*Gilead Sciences, Inc., Foster City, CA, USA;* [8]*Auckland Clinical Studies, Auckland, New Zealand;* [9]*Queen Mary's University of London, Barts Health, UK*

See Editorial, pages 505–507

Background & Aims: Tenofovir alafenamide, a phosphonate prodrug of tenofovir with greater plasma stability than tenofovir disoproxil fumarate, provides efficient delivery of active drug to hepatocytes at reduced systemic tenofovir exposures.

Methods: Non-cirrhotic, treatment-naïve subjects with chronic hepatitis B were randomized (1:1:1:1:1) to receive tenofovir alafenamide 8, 25, 40, or 120 mg, or tenofovir disoproxil fumarate 300 mg for 28 days and assessed for safety, antiviral response, and pharmacokinetics, followed-up by off-treatment for 4 weeks.

Results: 51 subjects were randomized and all completed study treatment. Groups were generally well matched (67% male, 57% Asian, 53% HBeAg-negative, mean HBV DNA approximately 6.0 $\log_{10}$ IU/ml) with HBV genotypes reflective of the population. No subject experienced an adverse event that was serious or severe (grade 3/4). Across the tenofovir alafenamide groups, similar mean changes in serum HBV DNA were found at Week 4 (-2.81, -2.55, -2.19, and -2.76 $\log_{10}$ IU/ml for the 8, 25, 40, and 120 mg groups, respectively) which were also comparable to the control (-2.68 $\log_{10}$ IU/ml for tenofovir disoproxil fumarate 300 mg). Kinetics of viral decline were also similar among groups. Tenofovir alafenamide pharmacokinetics were linear and proportional to the dose; doses $\leqslant$25 mg were associated with $\geqslant$92% reductions in mean tenofovir area under the curve relative to tenofovir disoproxil fumarate 300 mg.

Conclusions: Tenofovir alafenamide was safe and well tolerated; declines in HBV DNA were similar to tenofovir disoproxil fumarate at all doses evaluated. Tenofovir alafenamide 25 mg has been selected for further hepatitis B clinical development.

© 2015 Published by Elsevier B.V. on behalf of the European Association for the Study of the Liver.

Keywords: Treatment; Antiviral; Viral hepatitis; Clinical Trial.

Received 10 July 2015; received in revised form 22 October 2014; accepted 22 October 2014; available online 30 October 2014

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2014.12.003.

* Corresponding author. Address: Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK. Tel.: +44 20 7234 2730; fax: +44 20 7234 2560.

E-mail address: kosh.agarwal@nhs.net (K. Agarwal).

Abbreviations: CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TAF, tenofovir alafenamide; TFV-DP, tenofovir diphosphate; PBMC, peripheral blood mononuclear cells; eGFR, estimated glomerular filtration rate; BMD, bone mineral density; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; ALT, alanine aminotransferase; CL_{cr}, creatinine clearance; C_{max}, maximum observed plasma concentration; T_{max}, time to maximum observed plasma concentration; AUC_{0-last}, area under the concentration-time curve from time of dosing (0 h) to the last time point with measurable plasma concentration prior to next dose; AUC_{inf}, AUC from time of dosing (0 h) extrapolated to infinity; $t_{½}$, terminal elimination half-life of the drug in plasma; bsAP, bone-specific alkaline phosphatase; CKD-EPI, disease epidemiology collaboration; DAVGx, time-weighted average change in HBV DNA from baseline through Week X; AST, aspartate aminotransferase.

Introduction

Chronic hepatitis B (CHB) affects over 350 million people worldwide, and in areas of high prevalence such as Asia and Sub-Saharan Africa, the disease burden is substantial [1,2]. Persistent viral replication is independently linked to adverse disease outcomes, including cirrhosis, hepatocellular carcinoma, and liver-related mortality [3,4]. While effective therapies exist, all have specific limitations, including emergence of drug resistance and certain safety concerns associated with long-term use [5,6]. Furthermore, lifelong antiviral treatment is necessary for most patients, as few (<10%) experience seroclearance of hepatitis B surface antigen (HBsAg) indicative of cure [5,6]. Thus, there remains a need for new antiviral therapies that are safe and effective with a high genetic barrier to resistance, and for novel immune-based strategies to enhance rates of HBV cure.

Tenofovir disoproxil fumarate (TDF, Viread®, Gilead Sciences, Inc.), a prodrug of tenofovir (TFV), is a potent nucleotide analogue inhibitor of HBV polymerase/reverse transcriptase, currently rec-

Research Article

ommended as first line treatment for CHB, including patients harbouring virus resistance to other nucleos(t)ide agents [5–8]. Long-term TDF use is associated with achievement and maintenance of viral suppression, resulting in fibrosis regression and reversal of cirrhosis in the majority of patients [9]. Furthermore, TDF resistance has not been observed through 6 years of continuous use in CHB patients [10]. While TDF is generally safe and well tolerated, clinically relevant adverse renal events and bone loss have been reported in some patients [11–14]. Patients at greatest risk include those with advanced age and/or coexisting conditions (e.g. diabetes mellitus, hypertension), and in these individuals, ongoing renal monitoring is recommended and dose modification and/or discontinuation may be required [15].

Tenofovir alafenamide (TAF, formerly GS-7340), a new phosphonate prodrug of tenofovir (TFV), has been specifically synthesized to optimize antiviral potency and clinical safety. In comparison to tenofovir disoproxil fumarate (TDF), TAF has a greater plasma stability and remains mostly intact when penetrating virally-infected cells. TAF is efficiently hydrolysed to TFV by intracellular enzymes, including carboxylesterase 1 (CES1), which is predominantly expressed within HBV-infected hepatocytes [16], and cathepsin A within HIV-infected lymphoid cells [17]. The enhanced stability of TAF enables achievement of high levels of tenofovir diphosphate (TFV-DP), the active form of TFV, within the cell when given at a substantially lower dose than TDF 300 mg, the commercially approved daily dosage. The resultant lower systemic exposures of TFV are hypothesized to translate into an improved safety margin with TAF relative to TDF.

Early proof of concept studies have shown greater viral suppression and higher concentrations of active TFV-DP in peripheral blood mononuclear cells (PBMCs) in HIV-infected patients receiving TAF monotherapy at doses of 25 mg or higher for up to 14 days compared with TDF 300 mg [18,19]. As a consequence, TAF is currently in clinical development for the treatment of HIV infection. Recent results from an ongoing phase 2 study demonstrated smaller declines in estimated glomerular filtration rate (eGFR) and in hip and spine bone mineral density (BMD) at 48 weeks in HIV-1-infected patients randomized to TAF compared with TDF, when each agent was given as a component of combination antiretroviral therapy [20].

Following oral administration in dogs, approximately 65% of the TAF dose is extracted by the liver during first pass, reflecting efficient hepatic delivery [21]. After continuous 24 h incubations in primary human hepatocytes, intracellular TFV-DP levels were 20-fold and 5-fold higher with TAF compared with TDF and TFV, respectively, indicating enhanced hepatocyte activation [16]. Further, high levels of TFV and TFV-DP were detected in liver homogenates harvested from dogs after a single dose of TAF [16]. TAF is now in clinical development for the treatment of CHB. Here, we describe the first evaluation of TAF in CHB subjects who were treated with a range of doses for 28 days in a phase 1b trial.

Patients and methods

Study design

This was a randomized, open-label, active-controlled, phase 1b study (clinicaltrials.gov identifier NCT01671787). Eligible subjects were randomized 1:1:1:1:1 to receive TAF in doses of 8, 25, 40, or 120 mg (three 40 mg tablets), or TDF 300 mg. Study medication was administered orally once daily in the morning for 28 days (4 weeks) under fasted conditions. Study drug was administered in the clinic on study days 1, 2, 5, 8, 10, 15, 19, and 22; for the non-observed dosing days, subjects were requested to take the study medication at the same time each day in the fasted state and record their time of dosing in a diary. After completing the dosing period, subjects were required to undergo two follow-up visits at Week 6 and 8 for off-treatment safety evaluations.

Eligible subjects were randomized using an interactive response technology system (via telephone or the internet) and randomization was accomplished in accordance with a central randomization schedule, provided by the study sponsor (Gilead Sciences, Inc., Foster City, CA, USA).

The study was conducted at 12 sites in Australia, Canada, New Zealand, the United Kingdom, and the United States. The study protocol and informed consent form were in conformance with the principles embodied in the Declaration of Helsinki, and were approved by an independent ethics committee or institutional review board at each participating site. All subjects provided written informed consent prior to undertaking any study-related procedures.

Subjects

Adult (18–65 years) male and non-pregnant, non-lactating female subjects with chronic HBV infection (e.g. hepatitis B surface antigen [HBsAg] positive for $\geqslant$6 months) who were hepatitis B e antigen positive ($HBeAg^+$) or negative ($HBeAg^-$), and treatment-naïve were eligible to participate. Subjects were required to have screening serum HBV DNA $\geqslant 2 \times 10^3$ IU/ml, serum alanine amino transferase (ALT) $\leqslant$10 times upper limit of normal, and adequate renal function based on the estimated creatinine clearance (CL_{cr}) $\geqslant$70 ml/min by the Cockcroft-Gault method [22]. Subjects with a history of interferon use were allowed to participate, provided it was not used within 6 months prior to the screening visit. Subjects with cirrhosis as determined by recent invasive or non-invasive (e.g. FibroTest™) means and those co-infected with HIV, HCV, or HDV were excluded.

Assessments

Serum samples were analysed for HBV DNA by the COBAS TaqMan HBV test for use with the High Pure System (Roche Molecular Systems, Inc., Pleasanton, CA) at screening (within 45 days of study start), pre-dose, 4 and 8 h post-dose on day 1 (first day of dosing), pre-dose on days 2, 5, 8, 10, 15, 19, 22, and 29, and at both follow-up visits. Blood samples for pharmacokinetic analyses were collected pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h post-dose on day 1, and pre-dose on days 2, 5, 8, 10, 15, 19, 22, and 29. Samples were analysed using a validated high-performance liquid chromatography-tandem mass spectrometry method to determine concentrations of TAF and TFV in plasma at QPS laboratories (Newark, DE, USA). Plasma pharmacokinetic parameters, including maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), area under the concentration-time curve from time of dosing (0 h) to the last time point with measurable plasma concentration (AUC_{0-last}) prior to the next dose, AUC from time of dosing (0 h) extrapolated to infinity (AUC_{inf}), and terminal elimination half-life of the drug in plasma ($t_{½}$) were estimated based on the observed concentration-time data by the non-compartmental pharmacokinetic approach using WinNonlin version 6.3 (Pharsight Corporation, Mountain View, CA).

Safety assessments, including evaluation for adverse events, and assessments of clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), physical examination, and concomitant medications were performed at baseline and regularly throughout the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 16, MedDRA MSSO, McLean, VA). The severity of adverse events and laboratory abnormalities were graded according to protocol defined toxicity criteria based on the 2009 DAIDS Therapeutic Research Program's ''Table for Grading Severity of Adult Adverse Experiences''. The effect of treatment on bone-specific alkaline phosphatase (bsAP) levels, an exploratory biomarker of bone formation, was assessed at baseline, and days 15, 29 and at the last follow-up visit. Effects of treatment on renal function, as assessed by the estimated glomerular filtration rate (eGFR) were explored at baseline, and during the treatment and off-treatment periods by creatinine clearance (CL_{cr}) using the Cockcroft-Gault method, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [23].

The primary antiviral end point was the log change from baseline (day 1) to day 29 in serum HBV DNA. Other efficacy end points included time-weighted change in HBV DNA through Week 4, ($DAVG_4$) the details of which have been previously described [24], and by estimation of the slope of viral decay from baseline to Week 4. Other measures of efficacy included change in ALT and change in quantitative HBsAg levels from baseline to day 29. The comparative intensive plasma pharmacokinetics of TAF and TFV were assessed following the initial (day 1) dose of TAF or TDF.

Download English Version:

https://daneshyari.com/en/article/6102020

Download Persian Version:

https://daneshyari.com/article/6102020

Daneshyari.com