

Short Communication

A randomized pilot study of triple nucleotide reverse transcriptase inhibitors therapy with tenofovir, zidovudine (AZT) plus emtricitabine in antiretroviral naïve HIV-1 infected patients – The TEAZE study

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A randomized pilot-study to evaluate the virologic efficacy of Tenofovir-DF (TDF) 300 mg/Emtricitabine (FTC) 200 mg once daily plus Zidovudine (AZT) 250 mg twice daily (armA) or 300 mg BID (armB) in naïve HIV-1 infected patients. Twenty patients with a median CD4 cell count of 288 cells/ μ l (standard deviation (SD): \pm 109) and a median viral load of 66.400 HIV RNA copies/ml (SD: \pm 70.700) were included. Three patients in armA and one in armB had a single HIV-RNA-PCR measurement of $>$ 50 copies/ml ($p = 0.58$). The combined median CD4 cells increased by 188 cells/ μ l at week 48. TDF 300 mg/FTC 200 mg once daily in combination with AZT 250 mg or 300 mg twice daily was well tolerated and no virologic failure occurred.

Key words: Class sparing, nucleoside reverse transcriptase inhibitor (NRTI), K65R, drug interaction.

INTRODUCTION

Single class treatment with triple nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) can have several advantages. For example, they can be taken concomitantly with most medications, due to their lack of clinically significant drug-drug interactions, consist of a low pill burden, and do not require refrigeration. More importantly, it could be used strategically as first line regimens, because of the lack of cross resistance to the other antiretroviral drug classes and thus preserving more treatment options for salvage therapy in the event of a virologic failure (Stürmer, 2007). Older studies with triple NRTI regimens with zidovudine (AZT), lamivudine (3TC) and abacavir (ABC) demonstrated a lower virologic efficacy when compared to two class treatment consisting of 2 NRTIs and 1 protease inhibitor (PI) or a non-nucleotide reverse transcriptase inhibitor (NNRTI), especially in patients with high baseline HIV-1 RNA PCR (Staszewski, 2001; Gulick, 2004; Vibhagool, 2004; Gallant, 2005). But more recent triple N(t)RTI combinations,

especially those including tenofovir DF (TDF) without ABC, showed promising results in non-comparative pilot studies in previously naïve patients (Masquelier, 2006; Rey, 2006; Kaleebu, 2006; Moyle, 2006). One possible explanation could be a complementary resistance profile between AZT and TDF (hypersensitization of K65R-, M184V- and/or thymidine analogue mutation (TAM)-harbouring viruses, mutual exclusion of K65R and TAMs) (Boucher, 2006; Parikh, 2006; White, 2006; Stephan, 2009).

Therefore we hypothesised that a dose-adjustment for AZT could be enough to maintain this beneficial interaction while reducing drug exposure. Our aim was to evaluate the virologic and immunologic efficacy of a fixed dose combination of TDF 300 mg /emtricitabine (FTC) 200 mg QD plus zidovudine (AZT) 250 mg BID or 300 mg BID in previously untreated HIV-1 infected patients.

MATERIALS AND METHODS

Single center, randomized, open-label phase IV pilot study. The study was conducted in an urban, university HIV outpatient clinic. All adult antiretroviral naïve HIV-1 infected patients with a CD4 cell count of $>$ 200 cells/ μ l and an HIV RNA PCR $>$ 5000 copies/ml

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Table 1. Demographics and HIV related history from the study participants. All values are shown as mean values with their standard deviation if not otherwise stated.

	Arm A AZT 250 mg BID (n = 10)	Arm B AZT 300 mg BID (n = 10)
Female (n)	1	6 *
Age (Years)	38.6 ± 8	41.5 ± 13
Bodyweight (kg)	86.5 ± 7.4	71.5 ± 25.3
CDC stage A (n)	6	6
CD4 cell nadir (cells/μl)	230 ± 91	247 ± 78
Haemoglobin (g/dl)	14.6 ± 1.2	13.8 ± 2.4
Serum lactate (mg/dl)	10.4 ± 3	9.5 ± 4.9
pre-treatment HIV RNA PCR (copies/ml)	52,300 ± 93.500	53,800 ± 39.300

* p < 0.05 comparing arm A vs B using the Fishers-Exakt test.

without other actively treated concomitant disease, were asked to participate in the study. Once written informed consent was given, patients were randomized to either receive AZT 250 mg BID (Arm A) or 300 mg BID (Arm B) plus a fixed dose combination of TDF 300mg/FTC 200 mg QD. Hematology, clinical chemistry, CD4 cell counts and HIV-1 RNA PCR were obtained at screening, day 0, and weeks 4, 8, 12, 24, 36 and 48. Virologic failure was defined as two consecutive HIV-1 RNA PCR test results > 50 copies/ml. A blip was defined as a single HIV-1 RNA PCR test results > 50 copies/ml after. Adverse events (AE) and serious adverse events (SAE) were recorded according to international GCP guidelines. Approval by the local ethics committee was given prior to the start of the study and the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. All values are shown as mean values ± their standard deviation (SD) unless otherwise stated. Numeric parameters were compared between groups using the Mann-Whitney U-test, categorical variables were compared between groups the Fisher's exact test.

RESULTS

Twenty previously naïve HIV-1 infected patients (7 female) with a median CD4 cell count of 279 ± 109 cells/μl and a median viral load of 52300 ± 144.000 HIV RNA copies/ml were included in the study. Median age was 41 ± 8.5 years. None of the patients had a medical history of an AIDS defining event according to the Center for Disease Control (CDC) classification from 1993. There were more female patients randomised to Arm B (p < 0.05), but no other significant differences between the two arms was observed for CD4 cell count, HIV RNA PCR, age or bodyweight between the two groups at baseline (Table 1).

Two patients were randomized but not enrolled in the study, one due to a protocol violation and the other had active pulmonary tuberculosis. Four patients, two from each arm, had to quit the regimen prior to week 16, three due to nausea (Arm A = 2, Arm B = 1) and one in Arm B due to anaemia. None of the patients developed virologic failure, clinical disease progression, or an SAE during the 48 week study period. After week 12, three patients in Arm A had a single HIV-1 RNA PCR measurement of

>50 copies/ml which was not confirmed by a second measurement, compared with one patient in Arm B (p = ns). In the on treatment analysis (OTT) 71% in Arm A vs 100% in Arm B of the patients had a HIV RNA PCR < 50 c/ml at week 48 (p = ns). In the intent-to-treat analysis, including all patients who started the study drugs, 70% of the patients in each arm had a HIV RNA PCR of < 50 c/ml. By week 48 the median CD4 cell count has increased by 172 ± 116 cells/μl in Arm A and by 289 ± 158 cells/μl in Arm B, respectively (p=ns). The median bodyweight in both groups combined, increased by 4.3 kg, haemoglobin by 0.85 g/dl, and serum lactate by 4.1 mg/dl at week 48 without a significant difference between the two arms.

DISCUSSION

The combination of TDF 300 mg / FTC 200 mg QD with AZT 250 mg or 300 mg BID was overall well tolerated and efficacious in this pilot study. No virologic failure occurred, but blips, transient increases of the HIV RNA PCR, were more frequently observed with AZT 250 mg BID compared with AZT 300 mg BID. So far, three published investigations have used a similar combination with AZT 300 mg /3TC 150 mg BID and TDF 300 mg QD and found the following results: The rate of patients with a HIV RNA PCR of < 50 copies/ml at week 48 in the OTT analysis was: 88% of 24 patients (Masquelier, 2006), 78% of 51 patients (Rey, 2006) and 61% of 300 patients (Kaleebu, 2006). The last and largest investigation (conducted by the DART Trial Team in Uganda and Zimbabwe) included naïve patients with a baseline CD4 cell count of <2 00 cells/μl. In this study higher CD4 cell count at baseline but not the HIV RNA PCR was a predictor for virologic response (Kaleebu, 2006). The second largest investigation by Rey et al. (2006) also found the baseline HIV RNA PCR to be independent of virologic response. These findings are in contrast to older triple NRTI studies, mainly with AZT/3TC and ABC, in

which an HIV RNA PCR of $> 10^5$ copies/ml was a negative predictor for a sustained virologic response (Gulick, 2004; Gallant, 2005).

The major limitation of our study is the small sample size which makes a definitive statistical analysis underpowered and the results have to remain descriptive. Previous triple NRTI treatment with AZT, 3TC, and ABC or the combination of ABC and TDF are less potent than standard two class regimens and are therefore no longer recommended for first line therapy (Hammer, 2008). But for class sparing N(t)RTI therapies remain a strategically and clinically important for the initial HIV therapy, due to the lack of significant drug-drug interactions, low pill burden and the lack of cross resistance with other antiretroviral drug classes and therefore preserve future treatment options. Recently, licensed antiretroviral drugs such as raltegravir are also lacking a clinical significant drug-drug interaction and showed excellent virology response rates, but might not be available for patients in countries with limited resources and are far more expensive compared to all other antiretroviral agents in resource rich countries. Especially for HIV-1 infected patients who need simple regimens with a low pill burden or with concomitant medication such as tuberculostatic or anticonvulsive treatment triple N(t)RTI treatment remains important.

Therefore several trials have continued to evaluate the efficacy and tolerability of triple N(t)RTI treatment. Up till now, no trials compared newer triple N(t)RTI treatment, especially with TDF and AZT, to standard HIV treatment. Moreover, comparative randomized trials are warranted to further confirm the results of this and other pilot studies. Our small pilot study suggests that both 300 as well as 250 mg AZT twice daily could be explored in larger trials.

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