e-ISSN: 2248-9126
Vol 6 | Issue 2 | 2016 |56-61. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

EFFECTIVENESS AND SAFETY OF ZIDOVUDINE/ LAMIVUDINE/ NEVIRAPINE IN HIV-1 INFECTED PATIENTS IN WESTERN INDIA

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ABSTRACT

The safety and efficacy of triple combination of antiretroviral therapy for Human Immunodeficiency Virus-1 infection in Indian population are lacking. The current study was aimed to assess the immunological efficacy and safety of combination of 2 Nucleoside Reverse Transcriptase Inhibitor and 1 Non-nucleoside Reverse Transcriptase Inhibitors in Indian population. This was an open-label, non-randomized, multicentrestudy. The study comprised of fixed dose combination of Zidovudine 300 mg and Lamivudine 150 mg + Nevirapine 200 mg twice a day. Each subject was followed up for 24 weeks. The immunological efficacy was assessed by change in CD4 cells count and CD8 cells count from baseline. Safety was assessed by recording of adverse events, laboratory data, vital signs, clinical and physical examination. The paired t-test was used to analyze the data to measure the efficacy in terms of change from baseline to endpoint. A total of 100 subjects were enrolled. The statistically significant (<0.001) increase in CD4 and CD8 cells count was reported with mean increase from 212.39 cells/mm^3 to 339.42 cell/mm^3 and 758.50 cells/mm^3 to 1058.40 cells/mm^3, respectively. There was no new safety signal reported in the study. The combination of Zidovudine 300 mg and Lamivudine 150 mg + Nevirapine 200 mg proves the immunological efficacy and safety and tolerability and hence, promotes the use in the patients with HIV-1 infection of India.

Keywords: Zidovudine, Lamivudine, Nevirapine, HIV-1 infection.

INTRODUCTION

Human Immunodeficiency Virus (HIV) attacks the body's immune system, specifically the CD4 cells (T cells). If left untreated, HIV reduces the number of CD4 cells in the body, resulting in opportunistic infections or cancers because of a very weak immune system and signal that the person has Acquired Immunodeficiency Syndrome (AIDS), the last state of HIV infection. Unlike some other viruses, the human body can't get rid of HIV completely, so stays life long.

India has the third largest HIV epidemic in the world. In 2013, HIV prevalence in India was an estimated 0.3%, equates to 2.1 million people living with HIV. An estimated 130,000 people died from AIDS-related illnesses in same year [1].Treatment for HIV typically involves highly active antiretroviral therapy (HAART), which is a customized combination of different classes of medications. The mortality in-patients on antiretroviral treatment (ART) remains high, especially in first year of treatment initiation, partly may be most patients start ART when their CD4 count is very low [2-4].In the near future, large programmes should promote earlier HIV diagnosis and optimize a linkage between HIV testing and access to care so that a larger percentage of patients can start treatment as soon as their CD4 count reaches 350 cells/mm^3[5-8].The published outcomes also raised numerous issues which need to be addressed to further improve ARV treatment protocols. Important considerations include: the selection of optimal regimens, especially with regards to tolerability and efficacy; the determination of the optimal time for initiation; the optimal means to promote and sustain ARV medication adherence;

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and the issue of drug resistance among persons infected [9-11].

Combination antiretroviral therapy (cART) has led to declining morbidity and mortality in resource-poor settings, [12-13] and scale-up at the end of 2012 had reached 9.7 million HIV-infected individuals worldwide [14].Several triple nucleoside reverse transcriptase inhibitor (NRTI) combinations have shown good efficacy and tolerance[7, 15].Although less effective than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based or protease inhibitor (PI)-based regimens in patients with high pre-ART plasma HIV RNA levels, 3-NRTI regimens have been considered acceptable first-line ART regimens for other patients [5-8]. The 3-NRTI regimens could be especially attractive in patients who start ART early and who cannot receive NNRTIs. In settings where genotype testing is almost never available and where the number of drugs is limited, keeping PIs for potent second line treatment is crucial [5-8].

To increase the effectiveness of HIV-1 treatment through optimizing antiretroviral regimens for simplification and reduced toxicity is a priority in the recent UNAIDS Treatment 2.0 initiative [16, 17].World Health Organization (WHO) guidelines recommend initiation of antiretroviral therapy with two NRTI and NNRTI [18]. Randomized clinical trials conducted in developed countries provide evidence that these regimens are safe and effective [7, 19, 20].However, most existing knowledge of antiretroviral safety and efficacy comes from clinical trials in high-income countries with study populations not representative of the global diversity of people infected with HIV-1. Prospective comparisons of antiretroviral efficacy and safety in diverse multinational settings are needed to better inform the choice of antiretroviral drugs for initial HIV-1 treatment. Because data on 3-NRTIs are limited, especially data comparing 3-NRTIs to other regimens, WHO experts called for more efficacy and tolerance data to support their use [5-8].Although a regimen of Zidovudine, Lamivudine and Nevirapine meets criteria outlined in Treatment 2.0 including low toxicity and simplified once-daily dosing, the comparative safety and efficacy of this regimen in low-resource settings is unknown.

The current study was aimed to assess the immunological efficacy and safety of combination of Zidovudine, Lamivudine and Nevirapine. Zidovudine and Lamivudine are nucleoside analogues, are indicated in combination with other antiretrovirals for the treatment of HIV-1 infection. These get phosphorylated to their active metabolites and inhibit reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue. Zidovudine is widely prescribed in resource-limited settings [21-23]. However, Zidovudine is threatened by its bone marrow suppression effects [24]. Nevirapine is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

MATERIAL AND METHODS

This was an open-label, non-randomized multicentre trial to assess the immunological efficacy and safety of a combination of ART recommended by WHO in patients with HIV-1 infection. The trial included the subjects with age 18 years or older, with AIDS defining illness with any CD4 cell counts. Subjects who were being treated with nephrotoxic drugs or any investigational product, having known allergy/sensitivity or any hypersensitivity to components of any study drug, or have any drug or alcohol dependence or subjects having any serious medical or psychiatric illness that would interfere with the ability to adhere to study requirements were excluded from the trial. Additionally, patients with any safety, behavioural, clinical, or administrative reasons that, in the investigator's judgment, would potentially compromise study compliance or the ability to evaluate safety/efficacy were excluded.

Once enrolled, subject was treated with combination of ART. The study comprised of combination of ART containing fixed dose combination (FDC) of Zidovudine300 mg +Lamivudine 150 mg and Nevirapine 200 mg twice a day. Each subject was followed up for 24 weeks after initiation of therapy.

The immunological efficacy was assessed by CD4 cell count and CD8 cells count at baseline and at the end of 24 weeks. The change from baseline to end of 24 weeks in CD4 cell count and CD8 cell count were recorded. The safety was assessed by recording of adverse events, clinical laboratory data evaluation, vital signs, clinical and physical examination data at baseline, 1 month, 3 months and 6 months from the initiation of the therapy.

Efficacy data were summarized by treatment arm and by visit time point. Both means and medians (and associated measures of variation) were calculated for CD4 and CD8 analyses.Thepaired t-test was used to analyze the data to measure the efficacy in terms of change from baseline to endpoint.For safety analysis, all available data were included, and variables were summarized descriptively by treatment arm. A total of 100 subjects were planned to enrol in the study.

This study was conducted at two private tertiaryreferral HIV care centers in Ahmedabad, Western India. Patients paid for their own drugs and laboratory investigations. The study was approved by institutional ethics committee for each site. The study was conducted in compliance with the principles originating or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines and local regulatory requirements.

RESULTS

A total of 100 subjects were enrolled and treated with the study medication in the study as per plan. All subjects treated with FDC of Zidovudine 300 mg + Lamivudine 150 mg and Nevirapine 200 mg in twice a day

dose. Nevirapine was added to therapy after 14 days in tolerant subjects with Zidovudine and Lamivudine.

Baseline demographic and anthropometric characteristics of study population were provided in Table 1. The mean (± SD) age of all treated subjects were 39.11 (± 11.70) years (Range: 20-72 years), 66% and 34% were male and female, respectively with mean (± SD) weight was 49.67 (± 10.51) kg (Range: 30-81 kg). The 82% of the subjects were married, 14% were unmarried and 4% were divorcee. Among married, 27 subjects' spouse were also positive while 26 subjects' spouse were negative with HIV-1 infection. The spouse of 5 subjects was died and 24 subjects' spouse was reported as unknown in terms of HIV-1 infection. Only 23% and 16% of subjects were active on alcohol and smoking, respectively while 35% of subjects were taking tobacco at the time of enrolment. There were no subject on IV drug treatment at the time of enrolment. The major (>25%) baseline disease characteristics included fever (48%), weight loss (40%), weakness (32%), anorexia (29%), while 4% of subjects were asymptomatic. The temperature and pulse rate were slightly higher than the normal value while respiratory rate was within the normal range. All the patients were negative to HBsAg.

The increase in CD4 cells and CD8 cells were noted at 24 weeks after the treatment. The mean (± SD) CD4 cell count and % at baseline was 212.39 (± 81.20) cell/mm^3 and 18.45%. At end of treatment at 24 weeks mean (± SD) CD4 cell count and % at were 339.42 (± 101.87) cells/mm^3 and 19.29%. This change in CD4 cell count from baseline to endpoint was statistically significant ($p<0.001$). The mean (± SD) CD8 cell count and % at baseline were 758.50(±385.51) cell/mm^3 and 63.53%, respectively. At the end of treatment at 24 weeks mean (± SD) CD8 cell count and % at were 1058.40 (± 440.84) cells/mm^3 and 74.43%, respectively with statistically significant ($p<0.001$) change from baseline. The ratio of CD4 cells count to CD8 cells count was increased from 0.30 at baseline to 0.35 at the end of 24 weeks of the treatment.

The safety in the study was assessed by reporting of AE, vital signs, clinical laboratory tests, clinical and physical examination. The most common AE reported in the study was anaemia (18%) and rash (12%). The other major (>2%) adverse event reported in the study were hypophosphatemia (8%), nausea (8%), diarrhoea (6%), fatigue (6%), vomiting (6%), peripheral neuropathy (6%), bone suppression (6%), hyperbillirubinemia (5%), eosinophilia (4%), SGPT increased (4%), aches (3%). All these AEs whose incidence is more than 2% in the study which were related to study medications. There were no deaths reported in the study, also no serious AE was reported in the study. All the AE reported were mild to moderate in severity.

Table 1. Baseline Demographic and anthropometric Characteristics of Subject Population

Parameters	Values
N	**100**
Age	
Mean	39.11
SD	11.70
Median	37
Range (Min-Max)	20-72
Sex	
Male	66
Female	34
Weight	
Mean	49.67
SD	10.51
Median	50
Range (Min-Max)	30-81
Marital Status	
Married	82
Unmarried	14
Divorcee	4
Spouse status	
Positive	27
negative	26
unknown	24
Died	5
NA	14

Alcohol	
Yes	23
No	77
Smoking	
Yes	16
No	84
Tobacco	
Yes	35
No	65
IV Drug	
Yes	0
No	100
Temperature	
Mean	99.12
SD	1.00
Median	98.6
Range (Min-Max)	98.0-103.6
Pulse	
Mean	92.16
SD	15.93
Median	88
Range (Min-Max)	68-138
Respiratory rate	
Mean	16.34
SD	1.42
Median	16
Range (Min-Max)	16 - 26
SBP	
Mean	114.49
SD	17.12
Median	110
Range (Min-Max)	80 - 160
DBP	
Mean	75.52
SD	8.09
Median	72
Range (Min-Max)	60 - 100

Key: DBP: Diastolic blood pressure IV: Intravenous; NA: Not applicable; SBP: Systolic blood pressure; SD: Standard deviation;

Table 2. Result of CD4 cells count and CD8 cells count – change from baseline

	Baseline	**Percentage**	**24 weeks**	**Percentage**
CD4 cells count				
Mean	212.39	18.45	339.42	19.29
SD	81.20	6.72	101.87	7.71
Median	214	15	337	19
Range (Min-Max)	45-400	4-28	104-730	4-49
P value			<0.001	
CD8 cells count				
Mean	758.5	63.53	1058.40	74.43
SD	385.51	15.86	440.84	17.85
Median	691	67	1009	74
Range (Min-Max)	93-2184	28-94	310-2209	32-98
P value			<0.001	

Key: SD: Standard deviation

DISCUSSION

The results of this study demonstrated immunological efficacy of combination of FDC of Zidovudine 300 mg + Lamivudine 150 mg and Nevirapine 200mg in twice a day dose. There was a significant increase in CD4 cells count from baseline to endpoint. The mean increase of 127.03 cells/mm^3 in CD4 cells was reported at the end of 24 weeks of treatment. The CD8 cells were also improved statistically significantly at 24 weeks endpoint. The mean increase of 299.90 cells/mm^3 in CD8 cells was reported at the end of 24 weeks.

The results showed that triple-drug therapy with Zidovudine, Lamivudine and Nevirapine in twice a day dose can have a significant and immunologic benefit in HIV-1-infected individuals. The results of immunological efficacy for this combination were encouraging. The immunologic benefit of the triple-drug regimen shouldbe noted, with increases in CD4 T cell counts similar tothose observed in similar type of setting.

The AE reported in the study were low and these combinations of study drug were safe and well tolerated among the subjects in the study. There were few adverse events which requires monitoring of subjects initially with the start of the treatment like anaemia with Zidovudine and rash with Nevirapine. But overall, this combination reported acceptable safety profile and promote the use of study medication for the patients with HIV-1 infection in Indian patients.

In this study, the effect of this combinational drug was not assessed on viral load of the patients. But literature support the result of efficacy of this combination drugs on the viral load of the patient [24]. Also, a randomized trail can also be beneficial for HIV-1 infection patients to assess the efficacy of this combination of 2 NRTI + 1 NNRTI on viral load in Indian population.

As multiple choices for antiviral therapy are available, it is particularly instructive to determine whether any differences inefficacy need to be considered as part of the design of an appropriate regimen for a given patient [25].On the basis of the comparison of results of the this study and published worldwide data available, this seems to be the case when considering regimens that consist of 2 nucleoside analogues and an NNRTI, at least for initial therapy.

The immunologic efficacy of the nevirapine-containing regimen appears to be somewhat superior [26]. However, the combination of NRTI with protease inhibitor has also proved efficacy in few worldwide randomized trails. Hence, a randomized clinical trial to compare the addition of either protease inhibitor or NNRTI with two NRTI will be beneficial to initiate the therapy for HIV-1 infection in India.

CONCLUSION

In conclusion, this combination of 2 NRTI and 1 NNRTI i.e. FDC of Zidovudine300 mg + Lamivudine 150 mg and Nevirapine 200 mg proves the immunological efficacy and safety and tolerability and hence, promotes the use in the patients with HIV-1 infection of India.

ACKNOWLEDGMENTS

We would like to thank the investigator, and study participants of this study.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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