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Original Article

Internal Medicine Section

The Immunological Response after the Initiation of the Second Line Anti-Retroviral Therapy (ART) in HIV Patients

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ABSTRACT

Introduction: The treatment with the second line ART is initiated when the first line therapy fails. There is less experience with the immunologic response for the second-line ART for adults. Hence, this study was done to find out the immunological response after the initiation of the second line ART by doing an analysis of the CD4 counts.

Methods: This retrospective study is conducted in a tertiary level hospital which was attached to a medical college that caters to a large number of HIV positive patients. The study population for this analysis included all the HIV positive individuals who were undergoing the second line ART treatment. The data was collected by using a semi-structured, pre-tested proforma which was obtained from the hospital records of the HIV positive individuals. The immunological response after the initiation of the second line ART was analyzed by using the CD4 cell counts which were taken at intervals of 3 months and 6 months after the initiation of the treatment.

Results: Of the 32 patients who were studied, 27(84.4%) were males and only 5(15.6%) were females. The mean age of the patients was 40.56±6.78 years. The mean CD4 value at the initiation of the treatment was 152.35±142.89 cells/μL, which significantly increased to 324.43 ±163.65cells /μL within 3 months after the initiation (p value=.000) and to 348.21±253.57cells /μL by 6 months after the initiation. Around 91.3% of the patients had a baseline CD4 T cell count of <350 cells L^{-6}. After 3 months of therapy, 65.2% of the patients and after 6 months, 46.2% of the patients had a baseline CD4 T cell count of <350 cells /μL. The mean weight at the initiation of the treatment was 50.548±11.37 kg, which very significantly increased to 53.30±11.1 kg within 3 months of therapy (p=.001, table 1) and to 54.63±10.29kg at the end of 6 months.

Conclusion: The CD4 counts increased very significantly within the first 3 months of the initiation of the second line therapy. The rise in the CD4 count between 3 months and 6 months is not as statistically significant as the earlier one. Also, there is significant gain in weight within 6 months of the initiation of the second line therapy.

Key Words: CD4 count, HIV, Immunological response, Antiretroviral therapy

INTRODUCTION

Around 40 million people worldwide are infected with HIV [1]. The antiretroviral treatment (ART) has led to significant reductions in the morbidity and the mortality which are associated with the HIV infection. The treatment options have been consolidated into 2 sequential ART regimens- the First Line and the Second Line. Protease inhibitors are reserved for the second-line therapy. The goal of the second-line therapy is to re-establish a virological suppression. Protease inhibitors have had a dramatic impact on the management and the natural history of the HIV disease [2]. In a study which was done by Kaufmann et al., even the patients who experienced a virological failure had a sustainable CD4 count after the therapy [3-5].

Typically, the HIV viral load decreases and the peripheral CD4 T cells increase following the initiation of the ART [6]. The CD4 T cell counts have been shown to increase for 3-7 years after starting with ART [7]. One of the largest observational HIV cohort studies, EuroSIDA, recently reported an ongoing immune recovery of up to six years after starting with ART in patients with maximal viral suppression, across all the baseline CD4 T cell count strata. The ongoing immune recovery was also reported in a small study which was done on patients with a sustained viral suppression, following 6 years of a lopinavir-ritonavir based treatment regimen [8]. There have been other reports, however, of a plateau in the immune recovery after three or more years of ART, despite having a viral suppression [9]. In addition, approximately one third of the patients with a viral suppression in the Swiss Cohort Study did not achieve CD4 T cell counts above the lower limit of the normal (500 cells/μL) after 5 years of taking ART [10].

The treatment with the second line ART is initiated when the first line therapy has failed (a drop in the CD4 count below the pre-ART level or more than a 50% decrease from the peak CD4 count while on ART, a viral load of more than 1000copies/ml or a change in the WHO clinical stage setting). There is less experience with and a demand for the second-line ART for adults. Therefore, it is important to find out the immunological response of the patients after initiating the second line ART [1]. Hence, we planned this study to find out the immunological response after the initiation of the second line ART by doing an analysis of the CD4 counts and to find out the rate of weight gain after the second line initiation.

METHODS

This retrospective study was conducted in a tertiary level hospital which was attached to a medical college that caters to a large

number of HIV positive patients. The study was approved by the institutional ethics committee. The study population for this analysis included all the HIV positive individuals who were undergoing the second line ART treatment. The patients were eligible for inclusion in this analysis if they: 1) started on the second line ART regimen (the regimen includes PIs) during the years from 2005 to 2009. 2) remained on the second line ART regimen for at least 6 months; and if they 3) had a CD4 cell count measured within the six month period, prior to starting with the second line ART regimen (baseline) and a CD4 T cell count, 3-6 months after starting with the same regimen. All those patients who were on the first line ART regimen and the patients whose CD4 counts were unavailable, were excluded from the study. The data was collected by using a semi-structured, pre-tested proforma which was obtained from the hospital records of the HIV positive individuals. The immunological response after the initiation of the second line ART was analyzed by using the CD4 cell counts which were taken at intervals of 3 months and 6 months after the initiation. The demographic details of the patients were also collected from the patient records.

Statistical analysis: The data which was collected was analyzed by using SPSS ver.11.5. The Student's't' test was used to analyze the categorical data.

RESULTS

On the analysis of the hospital records, it was found that there were only 32 patients on the second line anti-retroviral therapy. Of the 32 patients who were studied, 27(84.4%) were males and only 5(15.6%) were females. The mean age of the patients was 40.56±6.78 years. Out of the 32 patients, 8 (25%) were started on the first line therapy in 2002 and 4 (12.5%) were started on in 2001, 2003 and 2005. 3(9.4%) were started on the first line therapy in 2004 and 2009, and 1(3.1%) each were started on in 1999, 2000 and 2006. For 3 patients (9.4%) the data regarding the initiation of the first line ART was not available. Of the 32 patients, 14(43.8%) were started on the second line therapy in 2009, 6(18.8%) were started on in 2008, 4(12.5%) were started on in 2010, 3(9.4%) were started on in 2005 and 2007, and 2(6.3%) were started on in 2006. A majority of the patients received lamivudine, stavudine, indinavir and ritonavir as their second line regimen. For 23 (71.9%) patients, the data on their occupations was not available. Three (9.4%) were businessmen, 1(3.1%) was a policeman, 1(3.1%) was working as a servant, 1(3.1%) had a private job and 3(9.4%) were housewives.

The mean CD4 value at the initiation of the therapy was 152.35±142.89cells /µL, which significantly increased to 324.43 ±163.65cells /µL within 3 months after the initiation (p value=0 .0001) and to 348.21± 253.57cells/µL within 6 months after the initiation (p value=0 .004, [Table/Fig-1]).

Visits	CD4 count (cells /µL)	Body weight (kg)
Baseline	152.35 ± 142.89	50.55 ± 11.37
3 months after second line ART	324.43 ± 163.65*	53.30 ± 11.1*
6 months after second line ART	348.21 ± 253.57*	54.63 ± 10.29*

[Table/Fig-1]: Comparison of CD4 count and bodyweight between different visits.
All values are expressed as Mean± S.D.
The Student's't' test*= very highly significant

The mean weight at the initiation was 50.548± 11.37 kg, which very significantly increased to 53.30± 11.1 kg within 3 months of the therapy (p =0 .001, [Table/Fig-1]) and to 54.63 ± 10.29kg at the end of 6 months (p = 0.001, [Table/Fig-1]).

Around 91.3% of the patients had a baseline CD4 T cell count of <350 cells /µL. After 3 months of the therapy, 65.2% of the patients and after 6 months, 46.2% of the patients had a baseline CD4 T cell count of <350 cells/µL.

DISCUSSION

The results of our study showed a highly significant increase in the CD4 counts after the initiation of the second line anti-retroviral therapy (p value= .001). The mean rise within the first 3 months was 172.09±141.16cells/µL. This was in accordance with the results of the studies which were conducted by Kaufmann *et al.,* and Deeks *et al*. [1]. The rise in the CD4 counts between 3 months and 6 months was not as statistically significant as that between the initiation and 3 months. This can be due to the fact that 2of the patients did not respond to the second line therapy. The percentage of the patients who had an immunological recovery also progressively increased from the baseline to 6 months after the initiation of the second line ART. The weight gain within 6 months after the second line initiation was also found to be significant, thus indicating an improvement in the general health of the patients as well.

Protease inhibitors have had a dramatic impact on the management and the natural history of the HIV disease [1]. Whether there is an association between the type of the anti-retroviral treatment and the immune recovery in the patients with viral suppression is controversial, because of the conflicting evidences which were obtained from different studies. No association was found between the immune recovery, 5-6 years after starting with the ART and the individual antiretroviral drugs [10] or the drug classes [9] which were contained in the first ART regimen in some studies, while the zidovudine/lamivudine based treatment regimens [11] and the combination of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the same regimen [12] were associated with the short term immune responses in other studies. There are few reports on the immunological response to the second-line regimens, and few clinical trials which are available for comparison.

In a study which was done by Kaufmann et al., even the patients who experienced a virological failure were found to have a sustainable CD4 count after the therapy [1,3]. In a study which was done by Deeks et al, those patients who had an initial virological response and later bounced back towards the baseline, were found to maintain a stable increase in the CD4 count up to 1 year of the follow up. Immunological failures were rare in the study group, even though virological failures were common [1].

In a non-randomized study which was done on 1522 subjects by Wood et al, the patients who were initially prescribed NNRTI-based ART had more rapid CD4 cell count responses than those who were prescribed PI-based ART. Their data did not support the view that the PI- based therapy was associated with a greater CD4 cell count [13,15]. A study which was done by Manosuthi et al, revealed that ritonavir-boosted lopinavir showed a greater immunological response after 48 weeks of therapy [14,16]. Another study showed that a regimen of ritonavir-boosted lopinavir with 2 NNRTI's had a greater CD4 cell count response when it was compared with efavirenz and 2NRTI's [15].

Older age, duration of the infection, injecting drug use, a baseline viral load and a poor adherence to the therapy, have previously

been associated with an incomplete or slower rates of immune recovery in patients with viral suppression. Whether the patients with an advanced immunodeficiency at the time of initiating the ART have the potential to achieve a better immune recovery, remains controversial, because of the conflicting findings which have been seen in short to medium term studies which had been published till date [16].

Our study had some limitations. The sample size was relatively small, to draw valid conclusions. The data regarding the viral load were also not available in our study, as the viral load testing is very expensive and our patients could not afford the test. Our analysis were also limited by a relatively short follow up in the data which was available to us. Our findings need to be confirmed by doing studies with a larger sample size and with a longer follow up data.

To conclude, the CD4 counts increase very significantly within the first 3 months of the initiation of the second line therapy. The rise in the CD4 count between 3 months and 6 months is not as statistically significant as the earlier one. Also, there is a significant gain in weight within 6 months of the initiation of the second line therapy.

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