

Research Article**The Pattern of Anti-retroviral therapy induced skin reactions in tertiary care teaching hospital****Ramya Rachamanti*, Chaitanya Gonugunta***Dept. of Pharmacology, Guntur Medical College & Hospital, Guntur, A.P. India*

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Abstract

Background: The most commonly prescribed Anti-retroviral medications in Human Immunodeficiency Virus(HIV) affected individuals include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). They were used as combination therapeutic regimens like ZLN (Zidovudine+ Lamivudine+ Nevirapine) / SLN (Stavudine+ Lamivudine+ Nevirapine) /ELT (Efavirenz+ Lamivudine+ Tenofovir) etc. They are associated with various adverse drug reactions(ADRs) like gastrointestinal, hematological and skin reactions. **Objective:** The main objective of our research is to know the pattern (Age group, sex, grade, causality relationship) of skin reactions caused by ZLN or ELT regimens used for HIV patients. **Materials and methods:** This study is a retrospective study. Data was collected from the pharmacovigilance center where ADRs from all the departments of tertiary care hospital were reported. We collected data of ADRs of HIV positive outpatients attending Anti-retroviral therapy unit. **Results:** Results showed that skin reactions were more common in males when compared to females and age group 21-40 years were more commonly affected. 72% of skin reactions were morbilliform rashes in the form of eruptions, 17% were pruritus or itching throughout the body with or without rashes, 10% reactions were skin Hyperpigmentation, 1% were severe reactions in the form of Steven-Johnsons syndrome. **Conclusion:** Thorough clinical monitoring with supportive and symptomatic treatment is required to avoid unnecessary ADRs. There is an utmost need for dermatologists to recognize the reactions in HIV individuals and to give appropriate rationalized therapy.

Keywords: Adverse drug reactions, Anti-retroviral medications, Pharmacovigilance center, Skin hyperpigmentation, Skin rashes, Pruritus.

Introduction

The treatment of Human Immunodeficiency Virus (HIV) positive individuals includes the combination therapy and the monotherapy. The combination therapy is more commonly prescribed as it acts by multiple mechanisms fighting HIV more effectively and improving CD₄ count to a good extent. This combination therapy is known as Highly Active Anti-Retroviral Therapy (HAART) (Breckenridge A et al. 2009, Hughes et al. 2009). Among HAART regimens, the most commonly prescribed are ZLN (Zidovudine+ Lamivudine+ Nevirapine) or SLN or ZLE or SLE or ELT (Efavirenz+ Lamivudine+ Tenofovir) at our tertiary care hospital.

The skin reactions caused by them presents as morbilliform eruptions or urticaria or pruritus with or without systemic features like fever, rigors, myalgias, and arthralgias. Severe skin reactions like Stevens-Johnson syndrome (SJS) also develop in very few patients (Wolf et al. 2005) in which lesions continue to erupt for 2 to 3 weeks (Bastuji et al., 2000). The onset of these reactions is usually 1-6 weeks after starting the regimen. If they occur after more than 3 months of starting the therapy, it is almost always due to another medication apart from HAART regimens they were using. The purpose of the present research is to know the "pattern" of skin reactions associated with ZLN or ELT combination therapy. The pattern in our study includes age group, sex factors, causative regimen affecting skin reactions, Grading of skin reactions and W.H.O. causality assessment to know the relationship of reactions with the regimens taken

Adverse cutaneous drug reactions occur more commonly in

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HIV-infected persons than in the normal population (Bigby et al., 1975) which result in the discontinuation of treatment. Thus there is an utmost need for dermatologists to recognize the reactions in HIV individuals and to give appropriate symptomatic and supportive therapy.

Materials and methods

This study is a retrospective study in which the data regarding the skin reactions was obtained from the A.D.R monitoring center or pharmacovigilance center attached to the tertiary care teaching hospital. In pharmacovigilance center, all the A.D.Rs occurring in all the departments of the tertiary hospital were collected and reported to National pharmacovigilance center. This is a cross-sectional study in which data of 200 ADRs like skin reactions of HIV positive patients were collected and analyzed using Microsoft Excel and power point of windows 10.

Inclusion criteria: Data of skin reactions occurring in HIV positive patients both males and females aged 20-60 years taking ZLN or ELT regimens who attended the ART outpatient unit was only collected. Exclusion criteria: Data of Patients who were HIV negative or patients attending departments other than ART was not collected. Data of HIV positive patients who are taking HAART regimens like SLN / ZLE/ SLE was also not included. As skin reactions were more common with ZLN and ELT regimens we included only these two regimens in our study. Usually, ZLN (300+150+200mg) is given orally twice a day and ELT (600+150+150mg) is given orally once a day. Grading was also given to all the skin reactions occurred using common terminology criteria for adverse events which is Grade 1: papules/pustules or both covering less than 10% Body surface area (BSA), Grade 2: 10% to 30 % of BSA, Grade 3 is more than 30 % (BSA) along with superinfections for which they were taking oral antibiotics, Grade 4: Extensive superinfection in which IV antibiotics given and Grade 5 is death. The relationship of adverse drug events with the regimen they were taking was assessed by WHO causality assessment scale as Certain/very likely or probable or possible or unlikely or unrelated or unclassifiable. Severity of skin reactions were assessed by Hartwig (Hartwig et al., 1992) scale as mild or moderate or severe.

Results

Data of 200 skin reactions occurring in HIV positive patients was collected between January 2015 to January 2016 and analyzed. Results were represented graphically.

Figure 1 shows the distribution of various types of skin reactions reported. Among them, most common were found to be morbilliform skin rashes.

Figure 2 shows the relationship of gender with type of skin reactions.

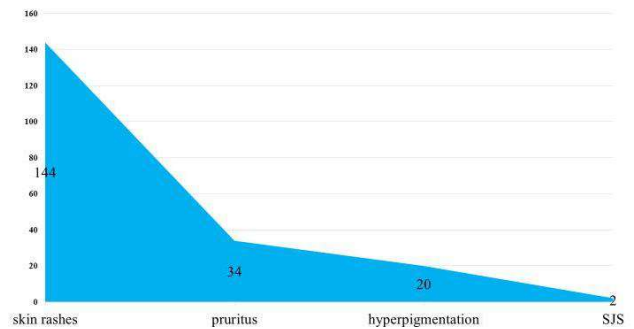


Figure 1. Distribution of various types of skin reactions

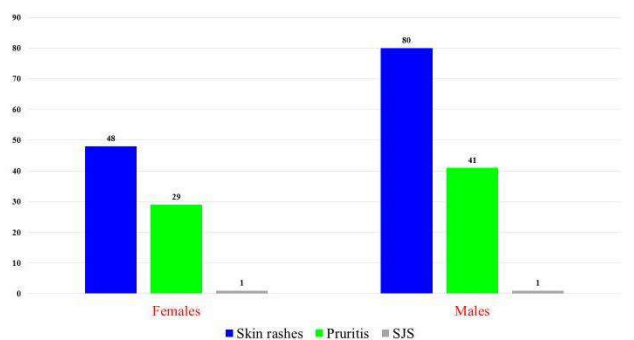


Figure 2. Distribution of Skin reactions among males and females

Overall skin reactions were found to be more common in males. Among them morbilliform rashes were common in males when compared to females and pruritus is found common in females than males while SJS is seen only in 1% cases where both males and females were equally affected.

Figure 3 depicted skin reactions in relation to age group which showed that 20-30yrs age group patients who were using ZLN regimen had more skin reactions when compared to 30-60yrs age group. 30-40yrs age group patients who were using ELT regimen had more reactions. Finally skin reactions were found to be more common in patients using ZLN regimen when compared to ELT regimen.

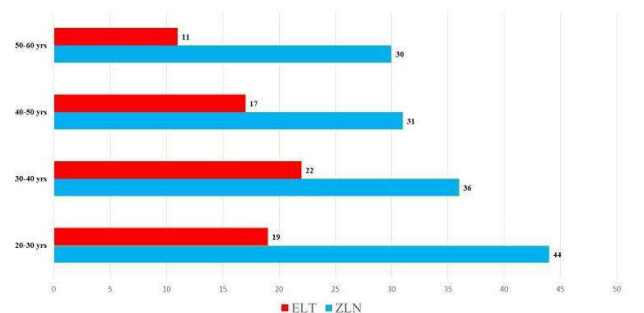


Figure 3. No of Skin reactions among various age groups in ZLN and ELT regimens

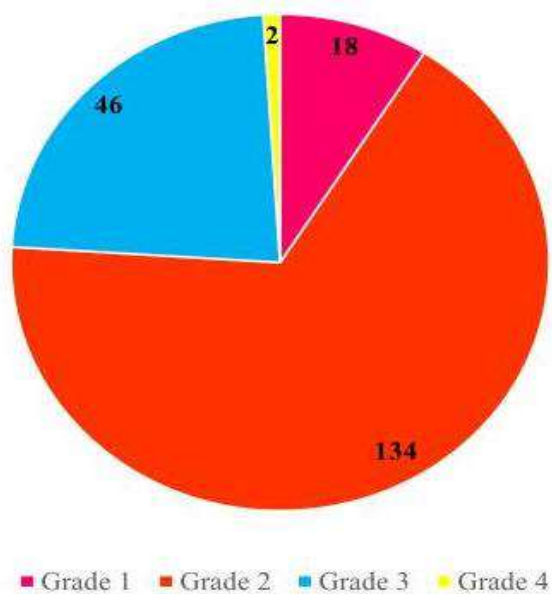


Figure 4. Grading of skin reactions

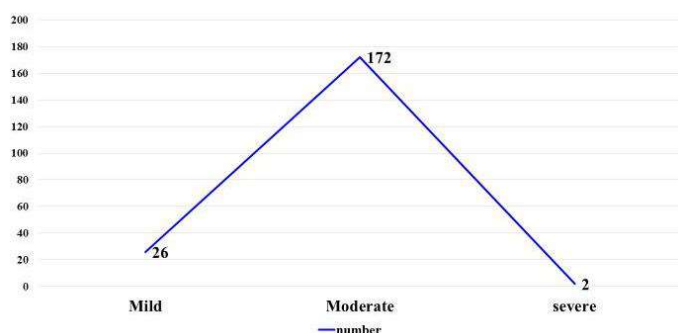


Figure 5. severity of skin reactions as per Hartwig scale

Figure 4 showed grading of skin reactions in which 134 reactions belong to grade 2 involving 10-30 % of body surface area and 46 belong to grade 3 reactions in which patients are taking oral antibiotics apart from HAART regimens for their superinfections. Severity of skin reactions was showed in Figure 5. 86 % of these skin reactions were moderate for which treatment was given symptomatically with oral anti-histaminic drugs (level 3 and level 4) and 13% were mild reactions for which no treatment was given and they resolved spontaneously. 1% were severe reactions in the form of SJS which required hospitalization with intensive medical care (level 5).

Under W.H.O causality assessment scale all the reactions were considered "possible" as HIV patients will receive multiple drug therapies to prevent secondary infections, to maintain the vitamin and mineral deficiencies etc.

Discussion

This is a retrospective study done on skin reactions in HIV-positive patients taking HAART regimens. In our study, the

majority of the skin reactions were observed in the age group 20 to 40 years. This may be due to a large number of new HIV-positive cases getting treated with HAART regimens at our tertiary care hospital. In our study, it was proved that the incidence of skin reactions was high with ZLN regimen when compared to other regimens like ELT. This finding is similar to findings of the study conducted by (Radhakrishnan et al., 2011) and (Srikanth et al., 2012).

Most of the skin reactions were moderate in severity which needed just symptomatic treatment and they were found to be more common in males than females in our study. Patients taking ZLN combination had higher rates of ADRs compared to patients on ELT. These findings as same as results obtained in the previous studies conducted by (Spaulding et al., 2010) and (Webster et al., 2010). The Study done by (Mehta et al., 2008) concluded that almost all Anti retro viral-related ADRs are often inevitable and unpredictable, which makes treatment of these ADRs problematic. This creates extra economic burden on most of the public health systems that are related to important health problems. Better understanding, timely and active pharmacovigilance surveillance with proper reporting, especially the ADRs of problematic regimens of ART is advisable.

Limitations of this study: several factors may predispose patients to adverse reactions of antiretroviral medications like co-administered medication, alcoholism and viral hepatitis, tuberculosis co-infection were also not explored (Este, 2010; Mallal et al., 2008). Further studies using large and more complete data from various settings would be needed to solidify the findings in this study.

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References

- Srikanth A, Babu SC, 2012. Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy. *Journal of Advanced Pharmaceutical Technology and Research*, 3(1): 62–67.
- Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. 2000. A severity-of-illness score for toxic epidermal necrolysis. *Journal of Investigative Dermatology*, 115:149–53.
- Bigby M, Jick S, Jick H, Arndt K 1986. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients. *Journal of American Medical*

- Association, 256:3358-3363.
- Breckenridge A. 2009. Pharmacology of drugs for HIV. *Medicine*, 37:374–7.
- Este JA, Cihlar T. 2010. Current status and challenges of antiretroviral research and therapy. *Antiviral Research Journal*, 85:25–33.
- Hartwig SC, Siegel J, Schneider PJ. 1992. Preventability and severity assessment in reporting adverse drug reactions. *American Journal of Hospital Pharmacy*, 49:2229–32.
- Hughes CA, Robinson L, Tseng A, MacArthur RD. 2009. New antiretroviral drugs: a review of the efficacy, safety, pharmacokinetics, and resistance profile of tipranavir, darunavir, etravirine, rilpivirine, maraviroc, and raltegravir. *Expert Opinion on Pharmacotherapy*, 10:2445–66.
- Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A. 2008. HLA-B*5701 Screening for Hypersensitivity to Abacavir. *New England Journal of Medicine*, 358:568–79.
- Mehta U, Durrheim DN, Blockman M, Kredo T, Gounden R, Barnes KI. 2008. Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. *British Journal of Clinical Pharmacology*, 65:396–406. 15.
- Radhakrishnan R, Vidyasagar S, Nandakumar K. 2011. Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients. *Pharmacy Practice (Granada)*, 9(1): 48–55.
- Spaulding A, Rutherford GW, Siegfried N. 2010. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals. *The Cochrane Database Systematic Review*, (8): CD008651.
- Wester WC, Thomas AM, Bussmann H, Moyo S, Makhema JM, Gaolathe T, Novitsky V, Essex M, deGruttola V, Marlink RG. 2010. Non-Nucleoside Reverse Transcriptase Inhibitor Outcomes Among ART-Treated Adults in Botswana. *AIDS*, 24(Supplement 1):S27–36.
- Wolf R, Orion E, Marcos B, Matz H. 2005. Life-threatening acute adverse cutaneous drug reactions. *Clinical Dermatology*, 23:171–81.