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ADVERSE EVENT MONITORING OF ANTIRETROVIRAL DRUGS AT A TERTIARY CARE HOSPITAL OF NORTH INDIA

Pharma

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ABSTRACT

Background Adverse event is major problem worldwide. ADR incidence is likely to be high in India and constitute an enormous burden for society, due to malpractice by unqualified practitioners and easy availability of drugs. Pharmacovigilance reporting is still poor in India. As ART regimen is to be continued for whole life of patients, we tried to identify ADRs after long term use which are missed in clinical trials.

Material And Methods A prospective cross-sectional observational study was conducted in a tertiary care hospital in north India. Only those patients with adverse events and who gave written informed consent of any gender/ age were enrolled from all HIV infected patients on ART therapy between Jan. 2017 to Dec. 2018. The reported ADRs were assessed for causality by using WHO UMC scale.

ResultsIn this study, 245 patients experienced a total of 415 ADRs.In these 245 patients, 104 (42.44%) were men, and 141 (57.55%) were women. The most common drugs leading to Adverse Drug Reaction was combination of TLE followed by combination of ZLN, ZAT. The most common ADR noted was itching (50), dizziness (34) and Rash (33). ADR incidence was found to be 1.73 per patient. Incidence of Serious ADRs was 0.5%. Causality assessment of 80.7% ADRs were possible, 2.8% were probable and 16.4% were unlikely.

ConclusionFrom this study, we can say antiretroviral drugs are not entirely safe and there is pressing need for monitoring these drugs. Physicians should be aware of these ADRs so that these can be prevented/treated at an early stage. This will enhance the safety ofantiretroviral drugs.

KEYWORDS

Adverse Drug Reactions, Human Immune Deficiency Virus, Acquired Immunodeficiency Syndrome

INTRODUCTION

Adverse event is defined as any untoward medical occurrence that may occur due to treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with treatment.[1] When a causal relationship is established between drug and adverse event, it becomes adverse drug reaction (ADR) or adverse drug effect. Adverse event is major problem worldwide, even developed countries like US, where drugs use is monitored very cautiously, ADRs are 4th cause of death and reason for 6.7% of hospitalization.[2] In India, due to malpractice by unqualified practitioners and easy availability of drugs, ADR incidence is likely to be high and constitute an enormous burden for society[3].

ADRs result in morbidity, prolonged hospital stays, increased health expenditure and mortality, so its need of situation to prescribe drugs rationally and for constant observation of ADRs. In clinical trials, drugs are tested on a relatively small population, in highly selected patients excluding pregnant, lactating women and patients of extreme age groups, with multiple co morbid conditions and patients on multiple drug therapy for only short period (maximum 3-5 years)[4-6]. Therefore, rare adverse reactions having frequency less than 0.5 to 1%, delayed reactions and ADRs occurring due to long term use are missed in clinical trials[7,8]. After marketing of drug, it is administered to lakhs of patients with many comorbidities and patients with multiple drug therapies in all age groups.[9] Therefore, ADR monitoring must be started along with administration of drug and continued throughout life of the drug. [10]After the Thalidomide disaster in 1962, Pharmacovigilance programs were established in many countries like UK, Australia, New Zealand, Canada and Sweden for adverse event monitoring.[11]Standard Control Organization (CDSCO) has initiated a well-organized and highly participative Pharmacovigilance Programme of India (PvPI). In spite of all effort, pharmacovigilance reporting is still poor in India. India rates below 1% in pharmacovigilance as against the world rate of 5%. [12]

Infection with the human immune deficiency virus (HIV) causesAcquired Immunodeficiency Syndrome (AIDS) [13]. According to a survey conducted in 2012 by the World Health Organization, 31.4 to 35.9 million people worldwide were infected with HIV, of which about 0.8% were adults aged 15–49 years.[14] About 4.8 million people are living with HIV infection in Asia.[15]

In 1996–1997, after introduction of antiretroviral treatment (ART), approximately 50 % mortality was reduced among people living with HIV/AIDS.[16] Regardless of the efficacy of the ART regimen, there was number of ADRs due treatment, such as fat redistribution, dyslipidemia, and sexual dysfunction. These reactions were severe in some patients to cause have non-compliance or discontinuation of ART.[17,18]For example, non-nucleoside reverse transcriptase inhibitors (NNRTI's) are associated with rash and hepatotoxicity [19]. Nucleoside reverse transcriptase inhibitors (NRTI's) are associated with hypersensitivity reactions, anemia, and neutropenia. [20]Protease inhibitors are known to be associated with hyperlipidemia, hyperglycemia, and gastrointestinal symptoms [21]. Furthermore, increasingly complex drug therapies for HIV-infected patients resulted in more ADRs.[22] As ART regimen is to be continued for whole life of patients, we tried to identify ADRs after long term use which are missed in clinical trials.

To our knowledge, there has been no published data regarding ADRs associated with ART among North Indian HIV/AIDS patients. The objective of this study was to explore the occurrence of ADRs among HIV/AIDS patients receiving ART.

MATERIALS AND METHODS

A prospective cross-sectional observational study was conducted at antiretroviral center of a tertiary care hospital in north India. This study was conducted as a part of spontaneous monitoring of adverse events for reporting to PvPI. All HIV infected patients on antiretroviral therapy with adverse events between Jan. 2017 to Dec. 2018 of any gender/ age were included in the study after taking written informed consent. Patients not giving consent were excluded from study. Patient' records were thoroughly reviewed and relevant data was noted on a validated data collection form. Demographic and clinical characteristics of patients that were susceptible to ADRs were recorded and observed during the study period. The reported ADRs were assessed for causality by using WHO UMC scale. Categorical data was reported numerically as numbers and percentages of the total, while continuous data was reported using mean and standard deviations.

RESULTS

A total of 51,234 patients diagnosed with HIV infection visited ART center between Jan. 2017 and Dec. 2018 in tertiary care hospital in north India. Out of 50,000, only 245 patients fulfilled our inclusion criteria. In these 245 patients, 104 (42.44%) were men, and 141 (57.55%) were women. Overall, 245 patients experienced a total of 415 ADRs. A statistically significant relationship was observed between patient sex and the occurrence of ADR ($P < 0.005$).

The most common drugs leading to Adverse Drug Reaction was

combination of Tenofovir, Lamivudine and Efavirenz followed by combination of Zidovudine, Nevirapine and Lamivudine, Zidovudine, abacavirand Tenofovir as shown in Table 1. The most common ADR noted was itching (50), dizziness (34) and Rash (33). Patients suffering from ADRs due to Tenofovir, Lamivudine and Efavirenz shown in figure 1. Patients suffering from ADRs due to Zidovudine, Nevirapine and Lamivudine are shown in figure 2. ADR incidence was found to be 1.73 per patient. The average number of drugs prescribed was 1.64 per patient. Incidence of Serious ADRs was 0.5%. A difference in adverse drug reactions according to age was also seen. Mean age of patients was 41.65 ± 13.48 years. Maximum patients having adverse events due to antiretroviral treatment were from adolescent age group and very less patients from extremes of age were having ADRs.

Table 1

Drugs	Patients suffering from ADRs
Tenofovir, Lamivudine and Efavirenz	336
Zidovudine, Nevirapine and Lamivudine	57
Zidovudine	12
Abacavir	5
Tenofovir	5
Total	415

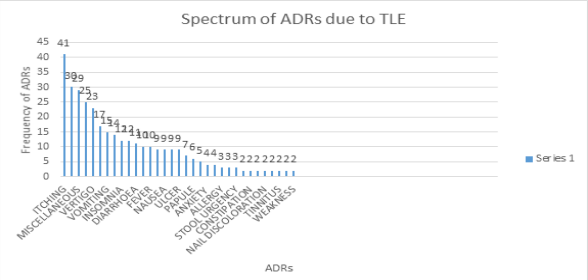

Fig.1

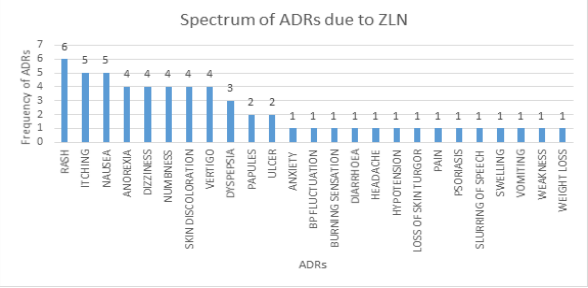

Fig 2

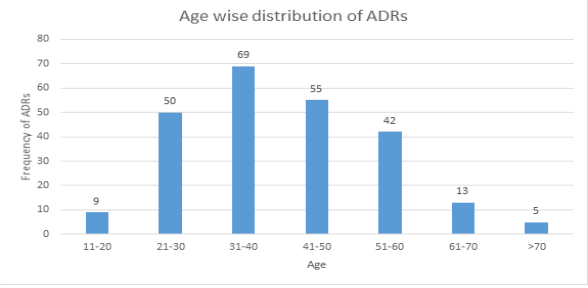

Fig.3

Causality Assessment:

A causal relationship between the drug and the reaction was established on the basis of lag period between the start of the drug and appearance of the reaction, response to dechallenge, laboratory tests and the data available regarding the drug using the WHO UMC causality assessment scale. Dechallenge (discontinuation of the suspected drug) was done in 22 % cases, whereas in 78 % of the cases initial drug therapy was continued. Causality assessment was done according to WHO UMC causality assessment in figure 4. Causality assessment of 80.7% ADRs were possible, 2.8% were probable and 16.4% were unlikely. All data of ADRs due to antiretroviral drugs was reported to PvPI in Vigibase through vigiflow software in regional ADR monitoring center.

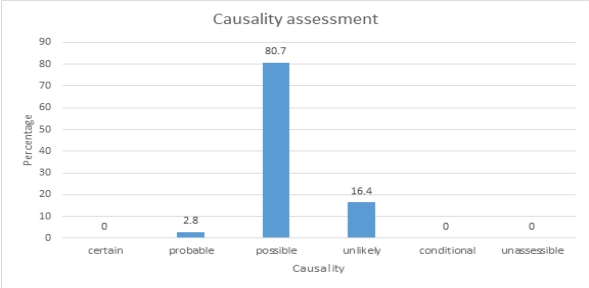

Fig4

DISCUSSION

A wide range of adverse drug reactions are caused by anti-retroviral drugs. This study was conducted in patients attending the Attending antiretroviral center of a Medical College and Hospital of North India. The ADRs reported with anti-retroviral drugs were recorded over a period of two years. The frequency and distribution of adverse drug reactions and antiretroviral drugs implicated in these reactions were studied.

The most common drug leading to Serious Adverse Drug Reaction was Tenofovir, Lamivudine and Efavirenz followed by Zidovudine, Nevirapine and Lamivudine. In a prospective study conducted by Sharma et. al. from 2004-06 in Department of Skin and V.D Medical College and SSG Hospital, Vadodara concluded the maximal frequency of ADRs was seen with zidovudine (AZT) (50%) followed by stavudine (d4T) (47.9%), efavirenz (EFV) (45.4%) and finally, Nevirapine (NVP) (18.4%). [23]

The most common ADR in ours study, was itching (50), dizziness (34) and Rash (33). In an observational retrospective study by khan et al on patients on HAART therapy diagnosed with HIV infection conducted at Hospital Pulau Pinang, Malaysia from Jan 2007 to Dec 2012 was Lipodystrophy was recorded 151 (35.5%) followed by Skin rashes 80 (18.8%), Anaemia, 74 (17.4%) and Peripheral Neuropathy 27 (6.3%).[24]

In this study 245 patients were enrolled, in which preponderance of ADRs was more than women. In a prospective observational study conducted by Modayil et al. has found high prevalence of ADRs in females, when compared to males. The reason for differences in prevalence of ADRs among gender might be due to difference in body mass index and fat composition or hormonal effects on drug metabolism.[25]

A difference in adverse drug reactions according to age was also seen. Mean age of patients was 41.65± 13.48 years. Maximum patients having adverse events due to antiretroviral treatment were from adolescent age group and very less patients from extremes of age were having ADRs. In observational retrospective study by khan et al on patients on HAART therapy, most of the patients were belonged to the age group of 31-40 years and 41-50 years i.e.257(34.5%) and 254(34.1%) respectively ; therefore we might have detected majority of ADRs from this group of patients. An ADRs observed in adults was similar to Mehta et al.,however, Melmon KL has reported large percentages of ADRs in geriatric and pediatric populations. [26,27]

Dechallenge (discontinuation of the suspected drug) was done in 22 % cases, whereas in 78 % of the cases initial drug therapy was continued. In a prospective observational study conducted by Rajesh et al from August 2009 to May 2012 to characterize the pattern of ADRs to cART at Kasturba Hospital, Manipal in South India elaborated 63.5% of the reports after “dechallenge” of the suspected antiretroviral medication, definite improvement was documented. In 94% of the reports “No rechallenge” was instituted. After “rechallenge of the suspected antiretroviral medication” recurrence of symptoms positive was observed in 1.3% of the reports and no occurrence of symptoms negative with “rechallenge of the suspected antiretroviral medication” was seen in 1.7%.[28]

In our study, Causality assessment of 80.7% ADRs was possible, 2.8% was probable and 16.4% was unlikely. In a prospective

observational study conducted by Rajesh et al from August 2009 to May 2012 to characterize the pattern of ADRs to cART at Kasturba Hospital, Manipal in South India elaborated Out of 230 suspected ADRs, WHO causality assessment was Probable in 132 (57.4%) of ADRs. In 181 (78.7%) of the reports, the suspected drug was predictable. [28]

CONCLUSION

In conclusion, the current study was an attempt to detect the most commonly reported ART-induced ADRs during ART Therapy in a tertiary care hospital in northIndia. Drugs. From this study, we can say antiretroviral drugs are not entirely safe and there is pressing need for monitoring these drugs. This can be done by post marketing surveillance at large number of centers over a long period of time. However, these results should be verified in multi-centric studies as sample size for some of them was small and hence cannot be extrapolated to large population. Since all the adverse effects of the drugs cannot be prevented, it is necessary to assess pattern of adverse reactions and the common drugs causing these reactions. Physicians should be aware of these ADRs so that these can be prevented/treated at an early stage. This will enhance the safety ofantiretroviral drugs.

Conflict Of Interest: Nil

Abbreviations:

ADR: adverse drug reactions, HIV: human immune deficiency virus, AIDS-Acquired Immunodeficiency Syndrome, TLE: Tenofovir, Lamivudine and Efavirenz, ZLN: Zidovudine, Nevirapine and Lamivudine, ZAT: Zidovudine, abacavir and Tenofovir

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