ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 4, 2022

Online - 2455-3891
Print - 0974-2441

Research Article

ADVERSE DRUG REACTION PATTERNS OF ANTI-RETROVIRAL DRUGS: A STUDY IN A TERTIARY CARE TEACHING INSTITUTE OF NORTH EAST INDIA

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Received: 19 January 2021, Revised and Accepted: 25 February 2022

ABSTRACT

Objective: The use of antiretroviral drugs is associated with significant safety concerns but there is still insufficient data about the toxicity profile of antiretroviral therapy (ART) drugs especially in developing countries. Hence, this study was done to describe the severity and pattern of different types of adverse drug reactions that occurs with ART.

Methods: A retrospective cross-sectional study was done at Pharmacovigilance center Regional Institute of Medical Sciences utilizing data from January 2016 to December 2019.

Result: A total of 190 cases reported during the study period were included in this study. Incidence was higher in females (109) as compared to males (81). The most common regimen responsible was Tenofovir/Lamivudine/Efavirenz (TLE) (69.5%) followed by Zidovudine/Lamivudine/Nevirapine (ZLN) (16.3%). Involvement of dermatological system (27.4%) was most common. The most common Adverse drug reaction (ADR) associated with TLE was skin rash (28.3%) which was less severe as compared to the most common ADR associated with ZLN, which was anemia (40.6%). On evaluation of the World Health Organization-Uppsala Monitoring Centre causality of ADRs, majority were found to be possible (78.2%).

Conclusion: TLE regimen requires special focus as it was the most common regimen causing ADR but patients on ZLN regimen need to be closely monitored as they were found to cause more serious ADRs. A more active pharmacovigilance is needed for better understanding of toxicities related to ART.

Keywords: Adverse drug reactions, Pharmacovigilance, World Health Organization-Uppsala Monitoring Centre criteria, Anti-retroviral therapy.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i4.44174. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Adverse drug reaction (ADR) is a significant contributing factor for decline in adherence to pharmacotherapy [1]. The factors which lead to ADRs vary extensively depending on patient's immune status, ethnicity, and lifestyle. ADR related death has also been attributed to be among the top five cause of death in hospitalized patients [2]. Hence, pharmacovigilance is an important tool in understanding the cause of various types of ADRs [3].

The drugs used for antiretroviral therapy (ART) have often been known to be associated with various ADRs and some other safety concerns, which contribute to many failures of therapy. Poor adherence to ART, in turn, will lead to failure of therapy and in some, may even lead to drug resistance [4]. Many studies have shown that around 25% of patients on ART discontinue treatment in the 1st year due to the adverse reactions of the drugs [5].

Acquired immunodeficiency syndrome (AIDS), in particular, is a disease which has been a global public health problem for more than three decades and yet, there is no cure or vaccine, making ART the only option available for management of the disease [6]. While the development of ART drugs contributed significantly to ease the burden of the HIV/AIDS epidemic, there are also many safety concerns related to treatment which can be either short term or long-term effects. As compared to most developed western countries, there is insufficient data about the toxicity profile of ART drugs in developing countries [7]. Among such countries, India has the third highest number of HIV cases in the world with approximately 69,000 annual AIDS related death [8].

Better understanding of the toxicity profile of ART drugs is the key to limit the incidence of ADR which can contribute to the success of management of HIV/AIDS [9]. The main objective of this study is to describe the severity and pattern of different types of ADR that occurs with ART and to assess the prevalence of ADR with respect to age and gender.

METHODS

After approval from the Institute's Research Ethics Board (Ref no: A/REB/Prop (SP) 159/134/23/2021), a retrospective cross-sectional study was conducted using the data available from the Pharmacovigilance center at department of Pharmacology, Regional Institute of Medical Sciences (RIMS), Imphal. ADRs are reported to the center from ART center RIMS using Individual Case Safety Report (ICSR) forms prescribed by Uppsala Monitoring Centre (UMC). The details of the ADRs are then entered in "Vigiflow" software provided by UMC for reporting to the National Coordinating Centre (NCC). For reporting of the ADRs the standard operating procedure of IPC.SOP no.IPC/PvPI/QA/013 is used by the Pharmacovigilance center [10].

Inclusion criteria

Cases which were reported during January 2016 up to December 2019 were included in the study.

Exclusion criteria

Patients on treatment for other comorbidities were excluded from the study.

Evaluation of data

The World Health Organization (WHO) UMC causality assessment scale was used where the ADRs were classified into certain, probable, possible, unlikely, conditional, and un-assessable [11].

Table 1: Gender distribution

Gender	Total number	Percentage
Male	81	42.6
Female	109	57.4

Table 2: Age-wise distribution

Sl. no	Age group (years)	Number of cases	Percentage
1.	18–29 years	19	10
2.	30–39 years	38	20
3.	40–49 years	74	38.94
4.	50–59 years	44	23.15
5.	60–69 years	13	6.84
6.	>70 years	2	1

Table 3: Regimen-wise distribution

Sl. no	ART regimen	No. of cases	Percentage
1.	TLE (Tenofovir/ Lamivudine/Efavirenz)	132	69.47
2.	ZLN (Zidovudine/ Lamivudine/Nevirapine)	35	18.4
3.	ALLR (Abacavir/ Lamivudine/Lopinavir/ Ritonavir)	9	4.7
4.	ALE (Abacavir/ Lamivudine/Efavirenz)	4	2.1
5.	TLL (Tenofovir/ Lamivudine/Lopinavir)	4	2.1
6.	TLN (Tenofovir/ Lamivudine/Nevirapine)	2	1.05
7.	TLR (Tenofovir/ Lamivudine/Ritonavir)	1	0.5
8.	LNS (Lamivudine/ Nevirapine/Stavudine)	1	0.5
9.	TEE (Tenofovir/Efavirenz/ Emtricitabine)	1	0.5
10.	DRR (Darunavir/ Ritonavir/Raltegravir)	1	0.5

Table 4: System-wise distribution

Sl no.	System	No. of ADR	Percentage
1.	Dermatological system	54	27.4
2.	Gastrointestinal system	41	20.8
3.	Hepatic system	26	13.2
4.	Hematological system	25	12.7
5.	Renal system	23	11.7
6.	Central Nervous system	22	11.2
7.	Others	6	3

ADR: Adverse drug reaction

Data analysis

The data collected were entered in SPSS version 21 and the results were expressed as numbers and percentages.

RESULTS

A total of 190 patients who presented with a total of 197 ADRs were selected for this study. The patients were classified according to age, sex, and ART regimen taken. The ADRs were then classified based on the systems affected, severity, preventability, and causality.

Gender distribution

Out of the 190 ADR collected for the study, 81 (42.6%) were males and 109 (57.4%) were females (Table 1).

Age distribution

The age group was categorized under six groups from 18 years onward at a 10 years gap interval. Majority (38.9%) of the cases were observed in the 40–49 years age group (Table 2).

ART regimen wise distribution

A total of ten ART regimens contributing to ADRs were observed out of which Tenofovir/Lamivudine/Efavirenz (TLE) regimen was found to be the most common where a total of 132 cases (69.5%) were recorded. The 2nd most common ART regimen was found to be Zidovudine/ Lamivudine/Nevirapine (ZLN) where a total of 35 cases (18.4%) were recorded (Table 3).

System-wise ADR distribution

The system most commonly affected was found to be the dermatological system contributing to a total of 54 cases (27.41%). The other systems commonly involved were found to be the gastrointestinal tract, Liver, Blood, Kidney, and central nervous system (CNS). Although the total number of cases collected was 190, due to multi-system involvement in some patients, a total of 197 ADRs were recorded (Table 4).

System wise involvement of TLE and ZLN regimens

System wise involvement of the two most common ART regimens responsible for ADRs have been further elaborated in the form of bar charts. The system most affected with TLE regimen was found to be the dermatological system (Fig. 1) whereas for ZLN regimen the hematological system was most commonly affected (Fig. 2).

Causality assessment based on WHO-UMC causality assessment scale

Among the 197 ADRs observed, 43 were classified as probable and 154 were classified as possible(Fig. 3).

DISCUSSION

The focus of this study was mainly on the incidence and pattern of ADRs that occur in various regimens used in the ART center of a tertiary care teaching hospital. A total of 190 patients who developed ADR while on ART were selected for this study. Majority of ADRs were observed in females (57.4%) as compared to males (42.6%) which was similar to the study done by Reddy *et al.* [1] and Bansal *et al.* [3]. However, male or female predominance differs in many studies as evident from the findings of Singh *et al.* [4] and Chauhan *et al.* [12] where the no of cases was higher in males. Although there is yet to be any conclusive evidence, the difference in gender prevalence could be due to body mass index, fat composition, hormonal effects, or genetics [13]. The maximum number of cases was seen in the age group of 40–49 years (38.9% of all cases) which was similar to the findings of Chauhan *et al.* [12] where majority of the cases belonged to 38–48 years of age. Some studies have also reported that ADR occurred more frequently in younger age group as seen in the findings of Patil *et al.* [14] where the highest no of ADRs were found in the age group of 26–35 years and also in the findings of Rukmangathen *et al.* [13] where the highest no of ADRs were found in the age group of 21–30 years. Many other studies have found ADRs to be more common in younger age group possibly due to the fact that they may be more sexually active hence more no of patients may be susceptible to HIV infections. However, other studies like Eluwa *et al.* [15] have also argued that age and gender may not be an important factor in determining the incidence of ADRs.

The incidence of ADRs of all the different types of ART regimens was included in this study. TLE regimen was observed to be the regimen which contributed to majority of the ADRs (69.5%), and this finding was similar to the study done by Bansal *et al.* [3] and Chauhan *et al.* [12]. In contrast, other studies like Patil *et al.* [14] noted ZLN to be the regimen responsible for majority of the ADRs, while SLN regimen was the most common in the study done by Oumar *et al.* [5]. TLE is the preferred regimen for initiation of ART especially among doctors in India, which could be one of the reasons for the high incidence in this study. The most common system affected was found to be the dermatological

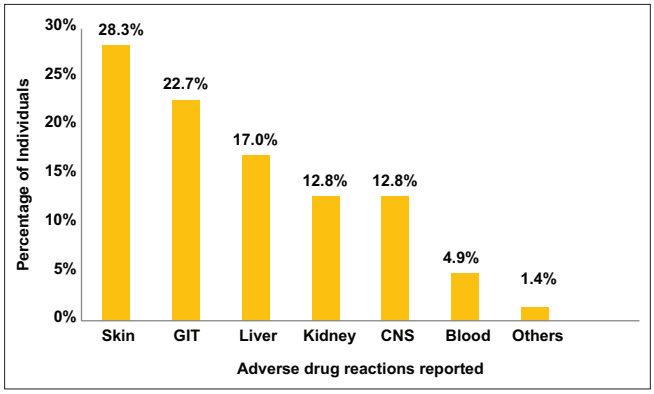

Fig. 1: System wise adverse drug reaction related to Tenofovir/ Lamivudine/Efavirenz regimen

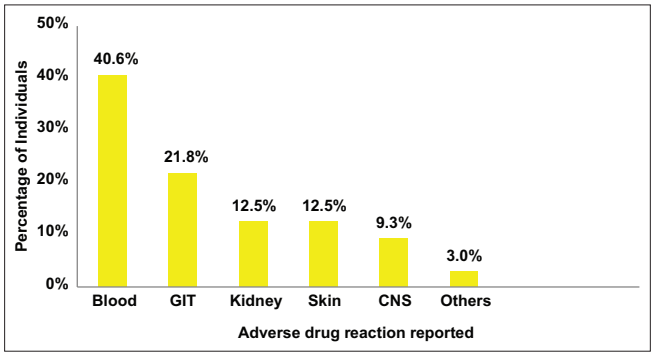

Fig. 2: System wise adverse drug reaction related to Zidovudine/ Lamivudine/Nevirapine regimen

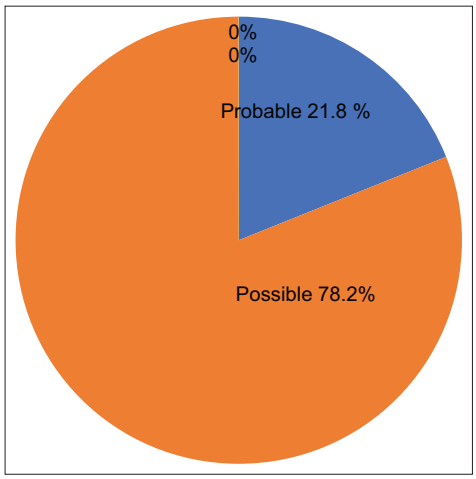

Fig. 3: The World Health Organization causality assessment

system (27.4%) which is similar to the findings of Chauhan *et al.* [12]. Contrary to this CNS was the system most commonly affected in the study done by Reddy *et al.* [1] and in case of Singh *et al.* [4] it was the hematological system.

Focusing on the two most common regimens in this study which are TLE (69.5%) and ZLN (18.4%), the system most commonly affected due to TLE was found to be the dermatological system, and for ZLN regimen it was the hematological system. Similar findings were observed in the study by Badii *et al.* [16] where two thirds of cutaneous ADRs were due TLE regimen but in the study by Chauhan *et al.* [12] the CNS was the most common. Singh *et al.* [4] reported the hematological system to be the most commonly affected with ZLN regimen which is similar to this study, but contrary to this Hemasri *et al.* [17] observed that dermatological system was most commonly affected with ZLN regimen. Efavirenz and tenofovir are known to reach higher concentrations in the CSF which increases the risk of neurotoxicity. Increased incidence of cutaneous ADRs with TLE regimen has also been attributed to the synergistic reaction of tenofovir and efavirenz [10]. Animal studies have shown that nevirapine is prone to cause cutaneous ADRs due to its metabolite 12-OH-nevirapine which is a contributing factor for increased incidence of skin related ADRs with ZLN regimen. The high incidence of hematological system related to ZLN regimen is because Zidovudine is known to cause bone marrow suppression subsequently leading to anemia and thrombocytopenia [18].

WHO-UMC causality assessment showed that 78.2% of the ADRs were possible while 21.8% were probable. Similar findings were observed by Reddy *et al.* [1] and Rukmangathen *et al.* [13] while Bansal *et al.* [3] found that majority of the ADRs were probable.

LIMITATIONS OF THE STUDY

1. The study was done using data collected from a single center, hence may not be entirely representative of the region.
2. Since data analyzed were only those which were spontaneously reported, some ADRs could have been missed.

CONCLUSION

Antiretroviral drugs have helped achieve great milestone for HIV/AIDS treatment even though there may be undesirable related toxicities. Special focus may be initiated for patients receiving TLE regimen as it was found to be the most common ART drug regimen responsible for ADRs. However, patients on ZLN regimen also need to be closely monitored as they were more prone to serious adverse reactions. A more active pharmacovigilance is needed for better understanding of toxicities related to ART especially in developing countries like India. Furthermore, a good portion of the ADRs were found to be preventable which further establishes the need for close monitoring of people on ART with efficient pharmacovigilance and ADR reporting system.

ACKNOWLEDGMENTS

The authors would like to thank ART center, RIMS, Imphal, Manipur, for regular reporting of ADRs to the pharmacovigilance center. Special gratitude is also expressed to the Pharmacovigilance Program of India (PvPI) and Indian Pharmacopoeia Commission (IPC).

AUTHOR'S CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

FUNDING

No funding received for this study.

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