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Research Article

Adverse drug reaction monitoring on antiretroviral therapy in human immunodeficiency virus patients in a tertiary care hospital

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ABSTRACT

Background: The aim of current study was to assess the pattern of adverse drug reactions (ADRs) in patients receiving antiretroviral (ARV) therapy.
Methods: A prospective, observational study was carried out for duration of 15 months. Clinical and treatment data were collected from patients, who underwent ARV therapy during the study period. CDSCO forms were used to record the ADRs. Causality, severity and preventability were assessed by suitable scales.
Result: Out of 216 patients 165 (76%) patients develop ADRs. Total of 274 ADRs were noted among 165 patients (1.66 ADR/patient). Out of them 100 (60.60%) were males and 65 (39.39%) were females. The most common ADR was gastrointestinal disorders (83, 30.29%). The most numbers of ADRs were observed in ZLN (Zidovudine + Lamivudine + Nevirapine) regimen (54%) followed by SLN (Stavudine + Lamivudine + Nevirapine) regimen (26%). According to WHO causality assessment scale most ADRs were possible (236, 86.13%). Hartwig and Siegel severity scale show 243 (88.69%) ADRs were moderate. Schumock and Thornton scale show all, ADRs were "not preventable."
Conclusion: Early detection of drug toxicity helps to treat the patient and modify the drug regimen to minimize toxic effects.

Keywords: Adverse drug reaction, Antiretroviral therapy, Human immunodeficiency virus

INTRODUCTION

Adverse drug reactions (ADRs) constitute a major clinical problem in terms of human suffering and increase healthcare cost.[1] According to the WHO an ADR is defined as "a response to a drug which is noxious and unintended, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function excluding failure to accomplish the intended purpose."[2] A study conducted in the USA revealed that adverse drug events extended the hospital stay, increased the cost of hospitalization and nearly two-fold increased risk of death.[3]

HIV disease continues to be a serious health issue for many parts of the world. Worldwide, there were about 2.5 million new cases of HIV in 2011. About 33.3 million people are living with HIV around the world. In the developed world, progression to AIDS and AIDS-related mortality has fallen dramatically since the mid-1990s, predominantly as a result of highly active antiretroviral (ARV) therapy. The effectiveness of treatment programs, particularly in low and

middle income countries could be compromised by problems related to toxicity, intolerance and drug-drug interactions. These adverse events, be they acute or chronic, mild or serious, are relatively common phenomena affecting both individual patients and public health.[4]

Pharmacovigilance of ARV drugs is significant in many ways. The treatment itself may be long (usually for the lifetime), expensive and troublesome at times due to adverse reactions. The drug toxicity may also influence the compliance and other related factors like resistance. It is, therefore, necessary that a systemic inquiry should be undertaken at various levels to elucidate the ADR profile of ART in details. This should facilitate the management of an individual patient to a greater level of satisfaction.[5]

Aims and objectives

Primary objective: To monitor ADRs due to ART and other drugs prescribed in HIV-positive patients.

Secondary objective: (1) To study the clinical presentation of various recorded ADRs, (2) to perform the WHO and NARANJO causality assessment for the observed ADRs, (3) to assess severity by modified Hartwig and Siegel scale and to asses preventability by Schmuck and Thornton scale, (4) to monitor outcome of reported ADRs.

METHODS

This study was a cohort event monitoring of ADRs to drugs prescribed for HIV positive patients. The monitoring of ADRs in this method is prospective, free of selection bias and longitudinal. A total of 216 treatment naive HIV-positive patients were enrolled for the study initially from March 2012 to May 2013. Each patient was followed up for a minimum period of 8-month from the date of enrolment in the study. The study was conducted at ART Center, Guru Gobindsingh Government Hospital, Jamnagar. The CDSCO ADR reporting form was used for collection of ADRs. ADRs were diagnosed by consulting physician and were treated accordingly. Permission from Institutional Ethics Committee was taken.

Inclusion criteria: (1) A patient who has completed the pre-ART phase and is taking ART for the first time on the date of enrolment, (2) a patient who has taken ART in the past but was lost to follow-up and is now re-registered as a fresh case at the ART center on the date of enrolment.

Exclusion criteria: (1) A patient who is although registered at the ART center but is still in the pre-ART phase, (2) a patient registered at the ART center but has already been receiving the ART from any other center or private clinic before the beginning of the study.

Evaluation of data: Reported ADRs were analyzed with respect to patient's demographics, nature of the reactions, characteristics of the drugs involved and causality, severity and preventability assessment of the ADRs were done.

Causality assessment was done by using Naranjo and WHO causality scale[6] whereby the ADRs were classified into certain, probable, possible to be drug induced depending on the level of association.

Preventability assessment: ADRs were categorized into preventable or not preventable using the criteria of Schumock and Thornton.[7]

Severity assessment: ADRs were classified into mild, moderate and severe reactions using modified Hartwig Siegel scale.[8]

RESULTS

In our study, out of total 216 patient 165 (76%) patients developed at least one ADR. In this study, most of the patient developed two ADRs (85/165, 51%) followed by one (68/165, 41%) and three (12/165, 8%) ADRs. Total 274 ADRs were observed among 165 patients. Among 165 patients who developed ADRs 100 (60.60%) patients were male and 65 (39.39%) patients were female.

In our study, most of the patients were between age group of 31-45 years (108/216, 50%) followed by 16-30 years (60/216, 27.77%) and above 60 years (21/216, 9.72%) (Figure 1). Most of the ADRs were developed between 1 and 6 months of initiation of therapy (163/274, 59.48%) followed by above 6 months of initiation of therapy (41/274, 14.36%) and 1 week to 1 month of initiation of therapy (37/274, 13.5%).

Most of the ADRs were of gastrointestinal (83, 30.29%) followed by cutaneous (71, 25.91%) and neurological ADRs (49, 17.88%) (Figure 2). Other ADRs observed were anemia (21. 7.66%), fever (16, 5.84%), cough (8, 2.91%), immune reconstitution inflammatory syndrome (IRIS) (9, 3.28%), hepatitis (2, 0.73%), lactic acidosis (1, 0.37%), and other ADRs (19, 5.13%), which include body ache, insomnia, vertigo, delirium and myositis.

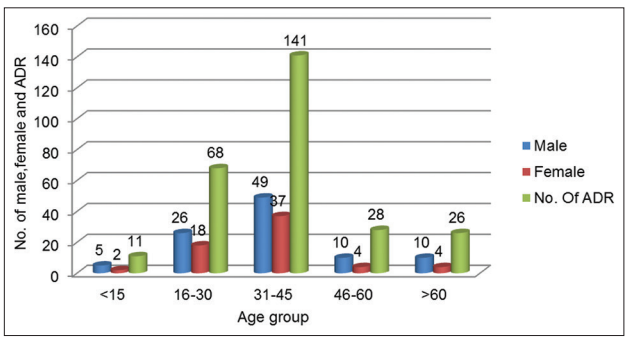

Figure 1: Age and sex distribution of adverse drug reactions.

Among gastrointestinal ADRs most common ADR was nausea (23/83, 27.71%) followed by vomiting (21, 25.30%), diarrhea (15, 18.07%), abdominal pain (14, 16.86%) and constipation (10, 12.04%). Among the cutaneous ADRs papule was the most common ADR (31/71, 43.66%) followed by pruritus (26, 36.61%), skin rash (8, 11.26%), blackening of nail and skin (2, 2.81%), fixed drug reaction (2, 2.81%) acne (1, 1.41%), and hyper pigmentation (1, 1.41%).

Most numbers of ADRs were observed in ZLN regimen (Zidovudine + Lamivudine + Nevirapine) (148/274, 54%) followed by SLN regimen (Stavudine + Lamivudine + Nevirapine) (26%), ZLE regimen (Zidovudine + Lamivudine + Efavirenz) (9%), SLE regimen (Stavudine + Lamivudine + Efavirenz) (7%) and TLN regimen (Tenofovir + Lamivudine + Nevirapine) (4%) (Figure 3).

Among ZLN regimen most of the ADRs were cutaneous (35%) followed by gastrointestinal (34%), anemia (12%), fever (6%), IRIS (4%), cough (4%), neurological (4%), and lactic acidosis. Among SLN based regimen most of the ADRs were neuropathy (46%) followed by cutaneous (21%), gastrointestinal tract (GIT) (20%), fever (7%), IRIS (3%), and hepatitis. Among ZLE based regimen most of the ADRs were of gastrointestinal (36%) followed by anemia (16%), cough (8%), fever (4%), IRIS (4%) and others (8%) which includes insomnia, vertigo, dyspnea, leg pain. Among SLE based regimen most of the ADRs were

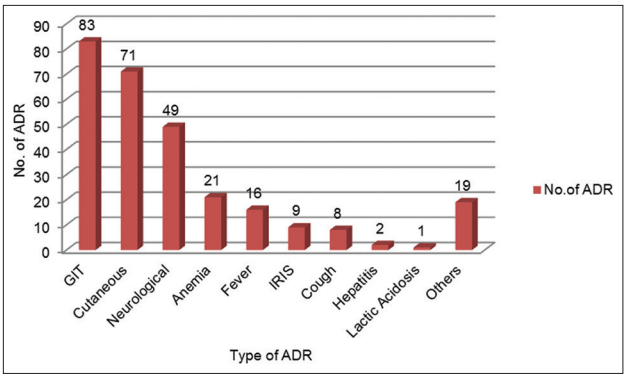

Figure 2: Clinical presentation of adverse drug reactions.

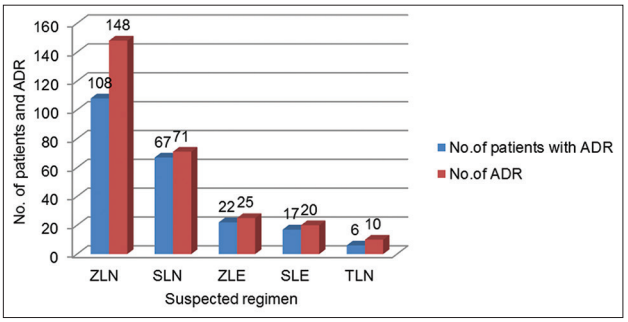

Figure 3: Suspected drug regimen and adverse drug reactions.

neurological (55%) followed by GIT (25%) and skin (20%). 10 ADRs were observed due to cotrimoxazole.

Among 274 ADRs, most were not serious (210, 76.64%), followed by 43 (15.69%) which required intervention to prevent permanent damage, 18 (6.56%) required hospitalization and 3 (1.09%) were life threatening.

According to WHO causality assessment scale 236 (86.13%) ADRs were possible and 38 (13.86%) were probable. According to Naranjo's causality assessment most common ADRs were possible (143, 52.18%) and rest were probable (131, 47.82%).

In our study, most of the ADRs were moderate (243, 88.69%) followed by mild (23, 8.39%) and severe (8, 2.92%) according to modified Hartwig and Siegel scale. In our study, all ADRs were not preventable according to Schumock and Thornton scale. In this study, dechallenge was done in total 55 patients who developed serious ADR. Most common ADR responsible for dechallenge was anemia (38%) followed by neuropathy (20%), cutaneous (18%), IRIS (11%), gastrointestinal (7%), hepatitis (4%), and lactic acidosis (2%).

DISCUSSION

Out of total 216 patients on ART 165 patients (76%) developed at least one ADR. This finding is in agreement with another study conducted at a tertiary care center in Baroda which reported ADRs in 71% of the patients.[9] Furthermore, study conducted in Chhattisgarh revealed 86% of patients developed at least one ADR.[10] The study conducted in Delhi[11] shows 90.66% patient developed ADRs. This is in sharp contrast to a study conducted at tertiary care ART center Surat where incidence of ADR was only 26.75% of the patients.[12] This may be due to short duration of their study conducted for 6 months.

In our study, 274 ADRs developed among 165 patients. So, average 1.66 ADRs per patient were developed. This finding is accordance with the study conducted in Chhattisgarh which revealed 1.76 ADRs per patient.[10] The study conducted in Delhi[11] shows 2.9 ADRs per patient. While in Mysore[13] study show 1.16 ADR was developed per patient and study conducted in Nigeria[14] shows 1.5 ADR was developed per patient.

Maximum ADRs (209/274, 76.27%) were seen in the reproductive age group (16-45 years) because they comprised the major part (168/216, 77.77%) of the study population. This result is consonance with study conducted at tertiary care ART center Surat which revealed incidence of ADR was high in <40 years of age group.[12] In our study, females were reported to have higher incidence of ADRs (1.80 ADR per patient, 117/65) than males (1.57 ADR per patient, 157/100). This finding is in agreement to study conducted in Surat[12] which found that the ADR rate for female subjects was higher

than males. Possible explanation for this gender difference in ADR incidence could be a gender specific difference in drug susceptibility, metabolism and elimination, although the same has not been proved conclusively.[15]

Most of the ADRs (85%) in our study were observed within 6 months of starting the therapy. High percentage of ADRs in the initial few months increases the overall pill burden of the patient. Consequently, the adherence to the therapy can be seriously jeopardized and resistance may develop. Accordingly it has been reported that poor adherence was more common in patients (26.1% of patients) during the initial 3 months of therapy than a year after starting the treatment (19% of patients).[16] Initial few months of therapy are critical in terms of maintaining adherence to the ART.

Gastrointestinal (83/274, 30.29%), cutaneous (71/274, 25.91%), neurological (49/274, 17.88%), and hematological (25/274, 9.12%) ADRs were most common reported in our study. In another pharmacovigilance study in Surat revealed gastrointestinal, hematological and cutaneous ADRs were most common.[12] They noticed less peripheral neuropathy because of short duration of study as peripheral neuropathy develops only after 6 months of treatment.[12] Study conducted in Chhattisgarh show peripheral neuropathy as most common ADR followed by cutaneous, metabolic and hematological ADRs.[10] Peripheral neuropathy was most common ADR in Chhattisgarh study because 63% of their patients were prescribed SLN regime and stavudine is responsible for peripheral neuropathy. Metabolic ADRs were common in Baroda[9] studies due to the fact that they included both treatment naive as well as experienced patients and the follow-up period of Baroda study was also longer (2 years). In our study, incidence of ADR was higher in ZLN regimen (148/138, 1.07) as compared to SLN based regimen (75/71, 0.95). So, incidence in both treatment groups is comparable to each other. This finding is also comparable with study conducted in Surat.[12] While study conducted in Mangalore revealed incidence of ADR was higher in SLN based regimen (142/66, 2.15) as compared to ZLN based regimen (64/31, 2.06).[17]

In our study, most of ADRs were mild to moderate (266/274, 97.08%) and only 2.92% ADRs were severe according to modified Hartwig and Siegel scale. Study conducted in Mysore[13] revealed 64.92% ADR were moderate. While study conducted in Chhattisgarh revealed most common ADRs were mild to moderate (47/68, 69.11%) and rest were severe (21/68, 30.88%).[10] They found more severe ADRs which may be explained by more common SLN based regimen (63%) and stavudine is responsible for severe neurological and metabolic ADRs.

In our study, the WHO causality shows most common ADRs were possible (236, 86.13%) and rest were probable (38, 13.86%). This finding is agreement with study conducted in Surat in which possible ADRs were more than probable.[12] Thus, studies are needed to judge the exact nature of the problem. However, ADRs such as anemia, IRIS, neuropathy, and lactic acidosis were life threatening, lead to hospitalization or required intervention to prevent permanent damage in many patients. Suspicion of the disease itself being an alternative cause for most of the ADR. Polypharmacy, use of fixed dose combinations and simultaneous intake of more than one drug at a time make it to be a very difficult proposition.

CONCLUSION

The incidence of ADRs (76%) with ART is higher in our study. ADRs can be minimized by early detection of drug toxicity and the drug regimen implicating adverse effect. This study provides baseline characteristic of ADRs due to ART in our institute. Studies covering more patients from different regions are needed to rectify the findings of this study.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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