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Anti-retroviral therapy induced adverse effects and its management: A brief review

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ABSTRACT

The introduction and the widespread use of Highly Active Anti-Retroviral Therapy (HAART) dramatically changed the perspective of Human Immunodeficiency Virus (HIV) which leads to substantial decrease in morbidity and mortality rates. It is now the standard care of therapy includes 15 antiretroviral drugs available in four different drug classes, adverse effects vary from drug to drug and patient to patient. Hence, choosing between many of these combinations requires the adequate knowledge about Anti-Retroviral Therapy toxicities. The basic purpose of Anti-Retroviral Therapy is to maintain the quality of life of patients, but it is difficult to continue for prolonged duration because of problem with adherence and adverse-effects. This review mainly highlights the various classes of Anti-Retroviral Therapy, associated adverse effects, possible mechanisms and their effective management in order to improve adherence and quality of life.

Key words: Highly active Anti-Retroviral Therapy, Nucleoside Reverse Transcriptase Inhibitors, Non-nucleoside Reverse Transcriptase Inhibitors, PIS, Entry and Fusion Inhibitors.

INTRODUCTION

HIV/AIDS have been significant public health concerns and the epidemic continues to challenge humanity for over twenty years [(1)]. Immune system of our body plays an important role to protect us from various kinds of infections and diseases [(2)]. India is one of the most populated countries in the world, around 2.4 million people living with HIV. In 2007, globally there were an estimated 33million [30.3million-36.1million] people are living with HIV worldwide; 10.6 million were receiving ART in 2012. [(3, 4, 5)]. The introduction of highly active antiretroviral therapy (HAART) in 1990, leads to the significant reduction in AIDS related morbidity and mortality, it contains the combination of 3 therapeutic agents which includes 2 Nucleoside Reverse Transcriptase Inhibitors (NRTI) with a protease inhibitor (PI), with a non-nucleosidal reverse transcriptase inhibitor (NNRTI) or a third NRTI constitutes the HAART regimen [(6,7)]. The goal of HAART therapy has been to achieve sustained viral suppression, increased CD4 cell count, minimize drug resistance, and simply dosage pattern [(8)]. Approximately, up to 25% of patients discontinued initial HAART therapy with in the first 8 months due to treatment failure, severe adverse drug effects, non-adherence [(9,10)]. A study conducted by Radhakrishnan rajesh *et al.,* found that anemia and hepatotoxicity were the most commonly observed ADRs. The organ system commonly affected by ADR was red blood

cell (21.4%). The ADRs were moderate in 77% of cases. Type A reactions (77%) were common. 10.8% were definitely preventable. The incidence rate of ADRs (65.9%) was highest with Zidovudine+Lamivudine+Nevirapine combination [(11)]. Identification and awareness of ART toxicity by health care professionals is necessary to facilitate patient adherence and to determine the need in change of therapy like adjustments in dose, dosing frequency and duration of therapy [(12)]. Periodic monitoring of patients undergoing treatment with ART drugs is needed to minimize drug related complications.

Nucleoside reverse transcriptase inhibitors (NRTIS)

The NRTIs are the 'back-bone' of Anti-Retroviral therapy which includes Zidovudine, Lamivudine, Didanosine, Stavudine, Abacavir and the newly released Tenofovir [(4, 9)]. NRTIs acts by inhibiting the HIV reverse transcriptase enzyme and terminate proviral DNA chain elongation. It inhibits not only viral reverse transcriptase but also cellular DNA polymerase which leads to mitochondrial toxicity and anaemia. The other common ADRs due to NRTIs include nausea, malaise, myalgia, insomnia and headache [(13, 14)].

Zidovudine induced anaemia

Anaemia is a condition in which the number of red blood cells count is low. Anaemia and Neutropenia are the major toxicities associated with Zidovudine containing regimen of which anaemia has been reported in 5.4- 34.5 % of patients [(15)]. The exact mechanism of ZDV-induced anaemia is still unknown. It is mainly attributable to inhibition of proliferation of blood cell progenitor cells in a time and dose-dependent fashion. Anaemia is clearly presented after 4 weeks of Zidovudine therapy and the high prevalence starts from 4-24 weeks, which is related to impaired erythrocyte maturation results in macrocytosis in patients with lower baseline CD4 lymphocyte count, haemoglobin concentration and granulocyte count. ZDV induced anaemia can be effectively managed with Iron supplements, folic acid (Vit B12), or Blood transfusions. Based on its severity and Hb level should be monitored for the first few months of ART regimen initiated with ZDV and then checked for every 6 months[(15,16,17)].

Stavudine induced lactic acidosis

Lactic acidosis is a form of metabolic acidosis due to inadequate clearance of lactic acid from the blood. Compared to all NRTIs, Stavudine appears to cause lactic acidemia more frequently [(18, 19, 20)]. Stavudine induced lactic acidosis has been reported in 1.5-2.5% of patients taking NRTIs. Other side effects include peripheral neuropathy, headache, diarrhoea and allergic manifestations which are reported less frequently [(21, 22).] The mechanism involved in Stavudine induced lactic acidosis is due to the inhibition of mitochondrial DNA poly merase-γ, leading to depletion of mtDNA and diminished capacity of oxidative phoshorylation system [(23)]. Patients on long-term Stavudine therapy often complaints as loss of appetite, fatigue, nausea, weight loss, must be tested for levels of venous lactate to detect the early stage of symptomatic hyperlactatemia to avoid fatal complications such as lactic acidosis by prompt with drawl of drug and timely management. Administering Riboflavin (vitamin B2), Ubiquinone (coenzyme Q10) and Thiamine at an earlier stage shows significant clinical benefit in HIV infected patients with lactic acidemia [(24)].

Non-nucleoside reverse transcriptase inhibitors (NNRTIS)

Currently US Food and Drug administration approved five NNRTIs (Nevirapine, Delavirdine, Etravirine, Rilpivirine) of which Nevirapine and Efavirenz has been used as first-line antiretroviral therapy since 2002 [(25)]. They acts by reducing HIV-1 replication by inhibiting the viral reverse transcriptase enzyme by binding to hydrophobic pocket located close to the enzymes catalystic site and inducing conformational changes that effect the catalytic activities of the enzymes [(26)]. The common side effects includes increased transaminase levels, headache, diarrhoea, nausea and skin rashes, Steven Johnson syndrome and hepatotoxicity were more observed in treatment with Nevirapine [(11,27)] .

Nevirapine induced hepatotoxicity

Hepatotoxicity can be defined as an injury to the liver usually associated with impaired liver function due to

any drug exposure or non-infectious agent. Incidence of Nevirapine induced hepatotoxicity was reported to be 16% [28] which is more common among women than men and in patients with higher CD4 T-cell counts. NNRTIs can cause hepatotoxicity in the first 2-3 months of therapy [29]. Mechanism of hepatic injury with Nevirapine is believed to be immunoallergic, since nevirapine has extensive hepatic metabolism and it acts as a substrate for CYP 2B6 and 3A4 and a potent inducer of these enzymes as well, results in liver injury [30]. Management includes early detection and removal of the offending agent along with adequate support care [31].

Nevirapine induced steven-johnson syndrome (hypersensitivity reactions)

Steven Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN) is an immune complex hypersensitivity reaction which is variant of Erythema multiforme caused by many factors such as infections, drugs and malignancies. SJS is usually characterized by an extensive detachment of epidermis and erosions of mucous membranes [32, 33]. It has been reported that 0.3% of patients affected with SJS is due to Nevirapine [29]. The mechanism of this reaction is mostly unclear and postulated to involve drug specific cytotoxic lymphocytes and secretes IFN-gamma against the drug leads to drug induced rashes and also it has been observed that CD4+T cells depletion reduces as well as delays the severity of Nevirapine induced skin rashes [27]. Early diagnosis and withdrawal of offending agent is the initial step to be followed in treating Nevirapine induced SJS. Although the use of 2-week lead-in-dose of 200mg/day followed by 200mg twice a day may reduce the overall risk of rash, Corticosteroids and topical emollients can be used as a mainstay therapy for SJS. So, physicians should consider this fact before prescribing HAART while treating HIV patients [34, 35].

Protease inhibitors (PIS)

Currently approved PIs by FDA include Areamprenavir, Etazanavir, Darunavir, Fosampreavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir and Tipranavir [36]. They act as competitive inhibitors which directly bind to HIV protease enzyme, prevents subsequent cleavage of polypeptides [37]. Generally Lopinavir/Retonavir containing ART regimens is well tolerated. Common adverse effects include gastrointestinal effects, Lipohypertrophy, glucose intolerance [12].

Protease inhibitors induced lipodystrophy

Lipodystrophy is characterized by abnormal or degenerative conditions of the body's adipose tissue, associated with metabolic changes including impaired glucose tolerance present in 15 -20% of patients with HIV infection and hyperlipidemia. It is more commonly seen in longstanding use of older PIs like Indinavir, Saquinavir and Lopinavir [16]. PIs induced Peripheral Lipodystrophy results from impaired CRABP1-mediated cis-9-retinoic acid stimulation of retinoid X receptor [38]. Effective management of protease inhibitor induced peripheral lipodystrophy includes withdrawal of the drug and switching to ART agents less likely to cause lipodystrophy. Darunavir and Atazanavir are the best choices if baseline hyperlipidemia is significant. All medications for diabetes such as insulin-sensitizing agents, Metformin and thiazolidinediones are recommended without dosage adjustment. Should encourage a healthy diet and regular exercise to reduce the fat accumulation and improve glucose and lipid abnormalities [12, 16].

HIV-1 entry inhibitors (fusion and ccr5 antagonist)

Recent advances in the development of antiviral drugs include fusion inhibitors, which acts extracellularly to prevent the fusion of HIV to the CD4 or other target cell [37, 38, 39]. Enfuvirtide is a fusion inhibitor primarily used in patients with limited therapeutic options. However, it is not commonly used since it is a painful subcutaneous injection. Thus a second generation fusion inhibitor, Tifuvirtide has been developed which is more potent against HIV than Enfuvirtide. Common adverse effects include neutropenia and increased risk of pneumonia but have not been reported in any patients till date [12, 40].

CCR5 antagonist

Maraviroc, an entry inhibitor, currently being used to treat patients with resistance to multiple HIV drugs that has been recently approved for the first-line HIV treatment regimens [41].Maraviroc is better tolerated as well as effective as Efavirenz when combined with

Lamivudine/Zidovudine. It acts by preventing the entry of HIV into host cells by blocking the CCR5 co-receptor. Incidence of pruritis and vascular hypertensive disorders has been reported in 3.8% of the patients and Upper respiratory tract infections where also more common in Maraviroc recipients in the clinical trials [12, 42, 43].

Integrase inhibitors

Raltegravir and Elvitegravir were the drugs comes under the class of HIV-1 integrase inhibitors and sometimes referred as INSTI (Integrase Strand Transfer Inhibitor). Integrase inhibitors acts by blocking an HIV enzyme called integrase which prevents HIV from multiplying and can reduce the amount of HIV in the body. The possible adverse effects caused by raltegravir are diaphoresis (4%) and pruritis in (2.3% to 6.7% of patients) whereas myopathy, rhabdomyolysis and muscle problems with muscle damage has been incidentally reported [43, 44, 45, 46, 47].

CONCLUSION

Antiretroviral therapy is becoming increasingly effective but also increasingly complex. Effective pharmaceutical care is required to manage the ADR'S which results from ART. Thus treating physicians and clinical pharmacists must remain aware of new and developing syndromes associated with Anti-retroviral therapy and clinical follow-up is required to manage the ADR associated with ART/HAART.

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