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A BRIEF REVIEW ON EFAVIRENZ AND IT'S ADVERSE EFFECTS

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ABSTRACT

Efavirenz is a commonly used non-nucleoside reverse transcriptase inhibitor frequently prescribed in combination with other antiretroviral regimens (e.g., protease inhibitors) for the treatment of HIV. After its admission for pharmaceutical treatment in efavirenz has become a cornerstone for highly active antiretroviral therapies (HAART). Good CNS penetration has been seen as a major strength of antiretroviral regimens, particularly efavirenz. Accumulating evidence suggests neuroprotective effects against cognitive decline such as HIV-associated dementia and other aspects of neuropsychological functioning. Recent studies have focused on the relevance of plasma concentrations and genetic predispositions as moderators of neuropsychiatric complications. Nevertheless, its proven effectiveness as a first-line treatment in suppressing plasma viral load comes along with reports of adverse central-nervous and neuropsychiatric effects which have been frequently reported after exposure to efavirenz. The use of psychophysiological measures in the assessment process enables the quantification of treatment-related side effects with high temporal solution, comparative measurements, and sensitivity toward subclinical effects, and thus provides a new source of information.

KEYWORDS: Efavirenz, Neuropsychological effects, Antiretroviral regimens.

INTRODUCTION

Efavirenz (dideoxy inosine, ddI) is an oral non-nucleoside reverse transcriptase inhibitor (NNRTI). It is a synthetic purine derivative. Efavirenz was originally The use of highly active

antiretroviral therapy (HAART) has had an important impact on the course and treatment of disease and disease-related morbidity of HIV-infected patients, increasing their lifespan and quality of life.[1]

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV) type 1.[2] Currently, the CDC recommends that Efavirenz be given as part of a three-drug regimen that includes another nucleoside reverse transcriptase inhibitor (e.g., lamivudine, stavudine, zidovudine) and a protease inhibitor or efavirenz when treating HIV infection. It works by decreasing the amount of HIV in the blood. Although efavirenz does not cure HIV, it may decrease your chance of developing acquired immunodeficiency syndrome (AIDS) and HIV-related illnesses such as serious infections or cancer.

Mechanism of Action

Efavirenz inhibits the activity of viral RNA-directed DNA polymerase (i.e., reverse transcriptase). Antiviral activity of efavirenz is dependent on intracellular conversion to the active tri phosphorylated form. The rate of efavirenz phosphorylation varies, depending on cell type. It is believed that inhibition of reverse transcriptase interferes with the generation of DNA copies of viral RNA, which, in turn, are necessary for synthesis of new virions. Intracellular enzymes subsequently eliminate the HIV particle that previously had been uncoated, and left unprotected, during entry into the host cell. Thus, reverse transcriptase inhibitors are virustatic and do not eliminate HIV from the body. Even though human DNA polymerase is less susceptible to the pharmacologic effects of tri phosphorylated efavirenz, this action may nevertheless account for some of the drug's toxicity.

Low concentrations are associated with virologic failure, while higher concentrations are associated with increased adverse effects such as sleep disorders.[3]

Efavirenz is highly protein bound to human plasma proteins, predominantly albumin. Efavirenz converts to inactive hydroxylated metabolites by the action of the CYP3A4 enzyme.[5]

Dosing & Administration

Efavirenz is available by prescription only, and it is available as an oral capsule and an oral tablet. It is also available as a component of two combination drugs: efavirenz, emtricitabine, and tenofovir disoproxil fumarate, and efavirenz, lamivudine, and tenofovir disoproxil fumarate. The capsules are available as 200 mg and 50 mg, while the tablets are available as 600 mg. The recommended adult dose is 600 mg per day, but there has been data showing that 400 mg per day yields equivalent outcomes with fewer side effects.[6]

The administration of efavirenz with food has shown to increase the serum concentrations and the incidence of side effects. For this reason, patients should not take efavirenz with food.[4] Peak concentrations are reached by 5 hours following a single oral dose, with steady-state plasma concentrations achieved in 6 to 7 days. The half-life of efavirenz is roughly 45 hours, making once-daily dosing suitable.

Efavirenz should be taken on empty stomach, as increased efavirenz serum concentrations occur when taken with food. Increased serum concentrations can lead to increased adverse effects.

CONTRAINDICATIONS

The use of efavirenz is contraindicated in patients with previously documented hypersensitivity to efavirenz and patients concurrently receiving elbasvir/grazoprevir due to a CYP3A4 interaction. Efavirenz acts as a CYP3A4 inducer, in this case, by decreasing the serum concentrations of grazoprevir. The use of efavirenz is also contraindicated in pregnant women in the first trimester due to reports of neural tube defects.[7]

ADVERSE EFFECTS

Individuals with a human immunodeficiency virus (HIV) infection are at higher risk of developing adverse drug reactions. Multiple drugs are usually prescribed to patients with HIV infection for preventing the replication of HIV and for the treatment of the associated opportunistic infections.

Nervous system symptoms (including headache, dizziness, insomnia and fatigue) and dermatological effects (including maculopapular rash) appear to be the most common adverse events reported with efavirenz-containing antiretroviral regimens.[8]

❖ **Neuropsychiatric adverse effects associated with Efavirenz[9]**

Good CNS penetration has been seen as a major strength of antiretroviral regimens, particularly efavirenz. Accumulating evidence suggests neuroprotective effects against cognitive decline such as HIV-associated dementia and other aspects of neuropsychological functioning. Nevertheless, its proven effectiveness as a first-line treatment in suppressing plasma viral load comes along with reports of adverse central-nervous and neuropsychiatric effects which have been frequently reported after exposure to efavirenz.

Table 1: Neuropsychiatric effects associated with Efavirenz.

Neuropsychiatric effects associated with Efavirenz	Somnolence
	Suicidal ideation
	Impaired concentration
	Psychosis
	Depression
	Abnormal dreams
	Nervousness & Irritability
	Headache

❖ **Efavirenz-induced cutaneous reactions & skin eruptions[10]**

Efavirenz skin rashes are generally a mild-to-moderate diffuse maculopapular skin eruption or pruritic erythema.

❖ **Hemolytic anemia associated with Efavirenz[11]**

Efavirenz triggers suicidal cell death or apoptosis, an effect in part due to interference with mitochondrial potential. Causes of anemia include accelerated clearance of circulating erythrocytes. Even though lacking mitochondria, erythrocytes may enter suicidal erythrocyte death or eryptosis, which is characterized by cell shrinkage and cell membrane scrambling with phosphatidylserine translocation to the erythrocyte surface. Triggers of eryptosis include Ca2+ entry and increase of cytosolic Ca2+ activity ([Ca2+] i), oxidative stress, ceramide, as well as activation of p38 kinase, casein kinase 1α and/or cyclooxygenase.

❖ **Efavirenz induced liver injury[12]**

Efavirenz is associated with a low rate of serum enzyme elevations during therapy and is an uncommon, but well-established cause of clinically apparent acute liver injury.

❖ **Efavirenz induced gynecomastia[13]**

Gynecomastia has been recognized as an adverse event to efavirenz. It is defined as breast enlargement due to benign proliferation of glandular tissue and an association with efavirenz-based ART has been demonstrated by several studies. The exact mechanism underlying

gynecomastia remains unclear, but there are several hypotheses most of which are to do with estrogen hormone activation.

As per the review of literature, few researchers date back states as follows, According to Mukesh Dada etal, Efavirenz (EFV) is widely prescribed as part of antiretroviral therapy (ART) in South Africa, and it is most frequently prescribed in fixed-dose combination (FDC) at a dose of 600 mg.[14] Efavirenz has been linked to early (two to six weeks) transient as well as late neuropsychiatric effects, which include increased risk of suicidal ideation, encephalopathy, catatonia, psychosis and ataxia. All of these have been directly linked to EFV toxicity.[15] EFV has shown predominant effect on Neuropsychiatric effects.

Mahony etal,[16] Efavirenz induces depressive-like behavior, increased stress response and changes in the immune response in rats. Adverse central nervous system side effects such as headache, dizziness, insomnia, fatigue, severe depression and suicidal ideation are noted in patients receiving efavirenz.

Segamwenge stated that Acute Liver Failure among Patients on Efavirenz-Based Antiretroviral Therapy. Hepatotoxicity of Efavirenz is not as rare as previously described in the literature and does actually present with fatal outcomes. The frequent monitoring of liver enzymes should be done at initiation of antiretroviral therapy and should continue throughout the treatment period.

A case study has been conducted by Robert etal[17] Hemolytic anemia associated with efavirenz.

Gynecomastia in HIV-positive adult men receiving efa,virenz-based antiretroviral therapy has been reported at Newlands clinic, Harare, Zimbabwe[18] Sandra etal states, Gynecomastia is known to occur in some men taking an efavirenz-based antiretroviral therapy (ART) regimen. However, the incidence and outcomes of gynecomastia are not known in Zimbabwe. We described the characteristics and outcomes of gynecomastia among male patients on an efavirenz-based ART regimen.

Fulminant Liver Failure after Varying Periods of Exposure to Efavirenz

Throughout a 6-month amount, four patients while not different celebrated risk factors for acute liver disease bestowed with symptomatic drug-induced liver injury with variable symptoms and outcomes. The pattern of liver injury was hepatocellular for all the four cases.

Liver biopsies were in deep trouble all the four cases and also the results showed a significant mixed inflammatory cell infiltrate with eosinophils. for 3 patients withdrawal of Efavirenz from their antiretroviral program was enough to revive aminopherase levels to traditional and crystal rectifier to improvement of clinical symptoms. For one patient his clinical course was characterised by sudden liver failure and unsteady episodes of internal organ neurological disease that ultimately resulted in his death.[19]

Neuropsychiatric Adverse Events

Depression, suicidal ideation, aggressive/impulsive behavior, paranoid reactions, manic reactions and (largely anecdotal reports of) psychosis-like behavior, suicide, and severe delusions are among the most frequently reported psychiatric symptoms associated with efavirenz treatment. Dizziness, insomnia, impaired concentration, irritability, nervousness, somnolence, abnormal dreams, and hallucinations are usually classified as CNS symptoms. The differentiation between CNS-related and psychiatric symptoms is rather arbitrary and has not been consistent; in general, psychiatric symptoms include some sort of behavioral or conscious component. This differentiation aims to reflect differences at the symptom level but does not necessarily imply distinct causal mechanisms.Recent studies have focused on the relevance of plasma concentrations and genetic predispositions as moderators of neuropsychiatric complications.[20]

Efavirenz-Induced Hypersensitivity

Efavirenz hypersensitivity reactions generally embrace cutaneal reactions that ar ascertained within the 1st two weeks of treatment, ar usually delicate to moderate while not general manifestation, and improve with continuing medical care. Previously, triple-crown decrease protocols are delineate in patients receiving efavirenz United Nations agency developed rash while not general symptoms, however these protocols were dole out over seven or fourteen days.[21]

Efavirenz-Associated Gynecomastia

Gynecomastia has been recognized as associate adverse event to efavirenz. it's outlined as breast enlargement thanks to benign proliferation of organ tissue associated an association with efavirenz-based ART has been incontestible by many studies. the precise mechanism underlying abnormal condition remains unclear, however there ar many hypotheses most of that ar to try to to with internal secretion|steroid|sex hormone} hormone activation [22].Besides efavirenz, alternative medication have additionally been related to abnormal

condition. though benign, abnormal condition will cause vital psychological morbidity with potential negative implications on adherence to ART. Lipomastia (pseudogynecomastia), a breast enlargement thanks to central fat, could occur as a part of a fat distribution syndrome that has been related to highly active antiretroviral therapy regimens and several other unhealthful mechanisms are advocated in its development. Here we tend to report associate empiric longitudinal study of 5 patients diagnosed of abnormal condition related to efavirenz-based highly active antiretroviral therapy regimens[23].All cases reached triple-crown immunological and virologic responses to highly active antiretroviral therapy. The delay of look of abnormal condition from the start of highly active antiretroviral therapy ranged between four to fifteen months. altogether 5 cases, abnormal condition regressed when efavirenz withdrawal (mean amount of five months). In summary, we predict that highly active antiretroviral therapy induced abnormal condition ought to be suspected in HIV patients receiving efavirenz-containing regimens. Though pathological process is unclear, this study and a review of nation literature implicates 2 potential mechanisms: (a) immune restoration processes and (b) efavirenz mediate estradiol-like effects.[24]

Haemolytic Anaemia Related To Efavirenz

The polymerase matter efavirenz used for the treatment of human immunological disorder virus (HIV)-1 infection, triggers self-destructive necrobiosis or caspase-mediated cell death, a sway partly thanks to interference with mitochondrial potential. aspect effects of efavirenz embrace anemia.[25] Causes of anemia embrace accelerated clearance of current erythrocytes. albeit lacking mitochondria, blood cells could enter self-destructive erythrocyte death or eryptosis, that is characterised by cell shrinkage and semipermeable membrane scrambling with phosphatidylserine translocation to the blood cell surface. Triggers of eryptosis embrace Ca2+ entry and increase of cytosolic Ca2+ activity ([Ca2+]i), aerobic stress, ceramide, furthermore as activation of p38 enzyme, casein enzyme enzyme and/or enzyme.[26]

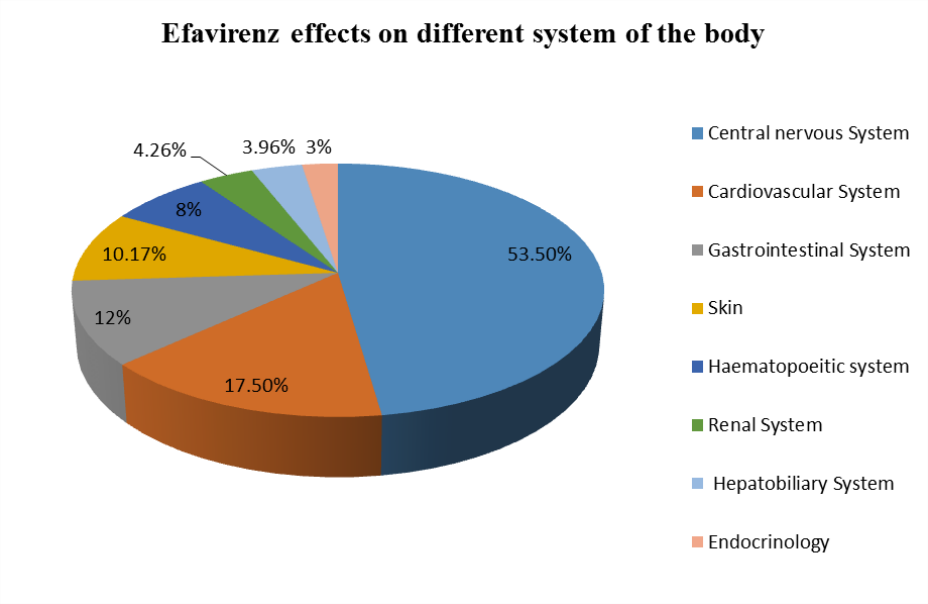

Figure 1: Efavirenz effects on various organ systems in our body.

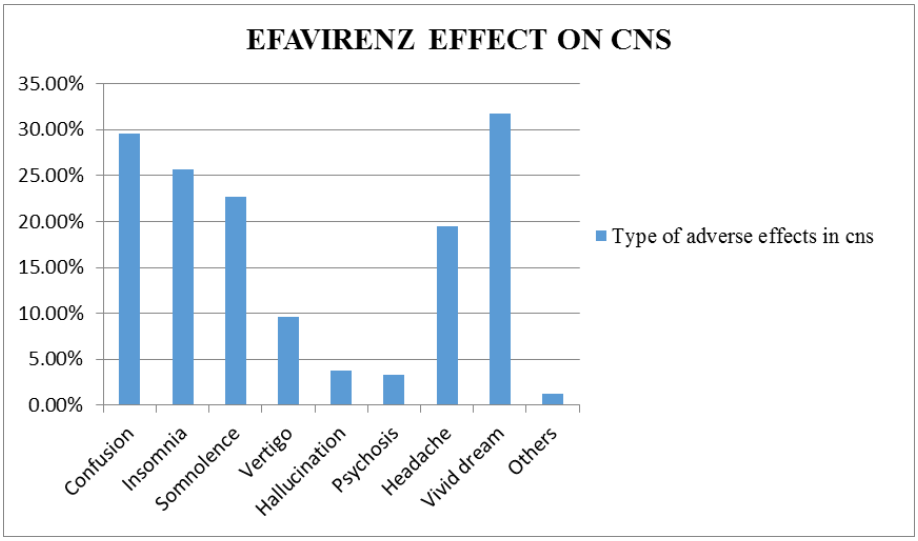

Figure 2: EFAVIRENZ EFFECTS ON CNS.

DISCUSSION

Hepatotoxicity of antiretroviral drugs is one of the more serious and life-threatening complications of antiretroviral drugs. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are the drugs most commonly implicated in hepatotoxicity yet these drugs are frequently used as part of the triple combination first-line ART regimen.[27] The greatest risk of NNRTI-associated severe hepatotoxicity are observed in patients taking Nevirapine, those with hepatitis B or C coinfection, and those co-administered protease inhibitors.[28] Severe hepatotoxicity is relatively uncommon among non-hepatitis C infected individuals and those not receiving protease inhibitor therapy.[29] Studies looking at grade 3-4[30] hepatotoxicity of

ART reported that most patients were asymptomatic and no deaths were due to liver-related events.[29,30,31] Fulminant hepatic failure due to Efavirenz leading to death is rare. Only one death due to fulminant liver failure after starting Efavirenz-based ART has been reported in the literature and two case reports of Efavirenz induced liver failure which required liver transplantation with good outcomes have been reported.[32,33,34] Hepatotoxicity due to Efavirenz has been described to occur between 100 days and 168 days (14 to 24 weeks).[28,35] It is possible that both immune mediated mechanisms and intrinsic toxic effects of the Efavirenz all had a role in the hepatotoxicity in patients.

CONCLUSION

Hepatotoxicity of Efavirenz is not as rare as previously described in the literature and does actually present with fatal outcomes. The greatest risk of Neuropsychiatric effects associated with Efavirenz. Fulminant hepatic failure due to Efavirenz leading to death is rare. The key message to note is that frequent monitoring of liver enzymes should be done at initiation of antiretroviral therapy and should continue throughout the treatment period. The use of psychophysiological measures in the assessment process enables the quantification of treatment-related side effects with high temporal solution, comparative measurements, and sensitivity toward subclinical effects, and thus provides a new source of information.

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