Short Communication

Safety profile of antiretroviral therapy: An urgent need for monitoring

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ABSTRACT

The diminution of CD4 lymphocytes is the diagnostic characteristic of human immunodeficiency virus (HIV) infection. Since the discovery of the disease 35 years ago, the infection has become one of the greatest menaces for the modern civilization. There are many individual drug toxicities and a number of class-specific or therapy-related toxicities of anti-HIV agents. Hepatotoxicity is a well-recognized side effect developing asymptomatic mild elevation of transaminases. It is known that the incidence of adverse reactions is high in long-term reactions such as lipodystrophy, paresthesia, and neuromotor disorders. Antiretroviral (ARV) therapy is not only effective but also complex. There are many adverse effects of the therapy, which affect varieties of the organ system. To optimize the treatment, health professionals should focus on preventing the adverse effect of ARV agents.

INTRODUCTION

The diminution of CD4 lymphocytes is the diagnostic characteristic of human immunodeficiency virus (HIV) infection. Since the discovery of the disease 35 years ago, the infection has become one of the greatest menaces for the modern civilization.[1] For the near future, HIV is like to be one of the most common chronic infectious diseases on the planet.[2] The estimated number of persons living with HIV worldwide in 2013 was 35 million. In the year 2013, 2.1 million people were newly infected with HIV and about 1.5 million people died from acquired immune deficiency syndrome (AIDS), mostly because of inadequate access to HIV prevention and treatment services. In 2013, an estimated 4.8 million people in Asia and the Pacific were living with HIV including the 350,000 people newly infected. Approximately, 250,000 people died from AIDS-related illnesses. There were almost 6% declined in new HIV infections from 2005 to 2013.[3] In Nepal, the estimated number of people living with HIV is about 39,000 while the prevalence rate in adults aged 15–49 is 0.2%. The HIV prevalence among the adults has not changed much over the last 5 years and has remained within the range of 0.2–0.3%. The mortality due to HIV in the year 2014 was around 2500, and the projected death in 2020 is 1266, due to an expected rise in antiretroviral therapy (ART).[4]

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With the discovery of effective antiretroviral (ARV) agents, agent-specific toxicity pattern has emerged that require prudent ARV selection to minimize treatment-related morbidity and mortality. There are many individual drug toxicities and a number of class-specific or therapy-related toxicities, which warrant further discussion. Nucleoside reverse transcriptase inhibitors (NRTIs) have infrequently been associated with lactic acidosis, peripheral neuropathy, myopathy, and pancreatitis. Rashes and hepatitis are both recognized side effects of the non-NRTIs (NNRTIs) class although the incidence and severity of these complications appear greatest with nevirapine.[5-7] All ARV drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from class to drug class, and from patient to patient. A better understanding of the adverse effect of ARV agents is of interest not only for HIV specialist as they try to optimize therapy but also for other physician who care for HIV-positive patients.

Many drugs that are used in the management of HIV-related disease are unlicensed or are prescribed for an unlicensed indication. Comprehensive data, for example, on drug interactions or side effect, is therefore lacking. Hence, in this review, we aimed to highlight the adverse effects of ART and ways of monitoring these effects.

PREDISPOSING FACTORS AND TYPES OF ADVERSE DRUG REACTIONS DUE TO ANTIRETROVIRAL DRUGS

The predisposing factors for adverse drug reactions (ADRs) are age,[8,9] compliance,[10-12] type of drug used,[8,13-17] CD4 count,[3,14,18] pregnancy,[19] sex,[8,19-21] race,[21-23] osteonecrosis,[24,25] coinfections.[26-29] The different type of ADRs associated are hyperglycemic and diabetogenic,[30-32] adipogenic,[33-35] hyperlipidemia,[19,36,37] dyslipidemia,[38] spontaneous bleeding episodes,[39,40] dermatologic and sensitive reaction,[41-44] hepatic effect,[28,29,45-47] lactic acidosis and steatosis,[48-51] gastrointestinal symptoms,[6,15,19] teratogenic effect,[52] nervous system effect,[18,53-56] peripheral neuropathy,[56-58] hematologic effect,[59] immune reconstitution syndrome,[60,61] cardiovascular effect,[62] sulfonamide sensitivity,[63] renal and genitourinary effect,[44,64] respiratory effect,[65] and pancreatitis.[6]

INCIDENCE OF ADVERSE DRUG REACTIONS OF ANTIRETROVIRAL THERAPY

It is known that the incidence of adverse reactions is high in the initial ART and tends to decrease in later stages when long-term reactions such as lipodystrophy, paresthesia, and neuromotor disorders may occur.[66] Prevalence of attributed adverse event was highest in three-class-ARV treatment than the single protease inhibitor (PI)-ARV treatment of PI-sparing.[66] Hepatotoxicity is a well-recognized side effect of PI therapy with over 50% of patients develop asymptomatic mild elevation of transaminases. In some series up to 10–20% developed severe hepatotoxicity with liver enzymes rising above five times the upper limit of normal.[28] The hepatotoxicity of this drug class varies with the specific drug, 30% of patient who are treatment with ritonavir show toxicity, but only 6–7% of those are initiated therapy with saquinavir, nelfinavir, or indinavir experienced severe hepatotoxicity.[28] The NNRTIs are also associated with transaminitis and hepatotoxicity. The rate was hepatotoxicity is 8.9% and 10.8%, respectively, in a patient receiving nevirapine and efavirenz.[38] Rash is a common adverse effect of the NNRTIs, particularly nevirapine. Approximately, 16% of patients taking this agent experience a mild to moderate maculopapular rash with or without pruritus on the trunk, face, and extremities within the first 6 weeks on therapy.[38]

A degree of insulin resistance is also present and this lead to the development of Type 2 diabetes in about 7% of cases with a further 16% having impaired glucose tolerance.[67] The overall prevalence at least one physical abnormality related to lipodystrophy has been estimated about 50% after more than a year of ART. The prevalence of lipodystrophy increases progressively with duration of use so that 50% of the subjects are recognizable affected after 10 months use of agent.[33] The incidence of NRTI-associated lactic acidosis is 1.3/ 1000 person-year.[68] The risk of liver enzyme elevation among patients with chronic hepatitis B or C was, respectively, 2.77- or 2.47-fold greater after initiation of PI-containing regimen than among patients without evidence of viral hepatitis.[38,69] New-onset diabetes mellitus, clinically similar to Type II diabetes, affects a small proportion (1–6%) of infected patient treated with PI-based ARV regimens.[30,38] Osteonecrosis occurs only rarely in HIV patient. For example in one series, six cases occurred among 508 HIV patients.[70] The nucleoside analog abacavir causes a hypersensitivity syndrome in 3–5% of patients.[71,72]

NEED FOR MONITORING PROGRAM

The clinical trials of drug therapy, particularly those conducted before drug licensing are typically

designed to gather detailed adverse event data. They are typically conducted in relatively well-controlled settings in regard to concomitant drug therapy and other medical management, with sample sizes usually in the hundreds. The population may also be relatively homogeneous typically with a large proportion men, nonminority/ethnic group, and noninjecting drug users. This makes it more difficult to assess comparative rates of adverse events by demographic characteristics of the patients.[14] Most of the studies on adverse effect have been conducted in developed countries where disease prevalence, access to medicine, drug use patterns, and drug management systems differ markedly from those of developing countries.[73] People have been using the oldest anti-HIV drug for more than a decade, but it is still not clear what effect may develop when people take highly active ART (HAART) over the course of most of the patient's lifetimes. Because many of the anti-HIV drugs were given rapid Food and Drug Administration approval, they have not benefited from years-long clinical trials to reveal uncommon or long-term side effects. Adverse reactions have been recorded anecdotally and in randomized clinical trial.[74]

HOW CAN MONITORING BE PERFORMED?

In general, there are three major methods of monitoring.

Cohort event monitoring

It is often referred to as prescription event monitoring, but this terminology is inappropriate where individual prescriptions with subsequent dispensing are not part of the process. The cohort needs to be as complete and as representative as possible. Decisions will be required on how to select patients. Two options are available. The first is to enroll all patients in selected, representative regions until the number of patients in the cohort reaches the target figure. The second is a method of systematically sampling patients from the whole country. Cohort event monitoring is more labor intensive and more costly, and it is new to health professionals and pharmacovigilance centers.

Spontaneous reporting

It is an unsolicited communication by health-care professionals or consumers that describe one or more ADRs in a patient who was given one or more medical products, and that does not derive from a study or any organized data collection scheme. Spontaneous reports play a major role in the identification of safety signals, once a medicine is marketed. It can also provide important information on at-risk groups, risk factors (to a limited degree), and clinical features of known serious ADRs. Spontaneous reporting is dependent on encouraging clinicians and other health professionals to report details of suspected adverse reactions in patients on ARV treatment. Underreporting is a serious problem with this method, but reporting can be intensified in selected units such as hospitals.

Special phase IV studies

Discussion to date has indicated the need to establish pregnancy registers, monitor for specific toxicities, and monitor special populations such as children. These cannot be accomplished as an integral part of a spontaneous reporting program, and special studies would therefore be needed. However, adequate data in these important areas should be recorded in the normal course of events when using cohort event monitoring and special studies should be unnecessary. If special studies are to be undertaken, then the same principles will apply as outlined for cohort monitoring. Special forms would need to be designed to provide the information needed, and advice and training given on what is required and the appropriate data flow.

EXPECTED OUTCOMES

The monitoring program will help to:

- Identify signals of previously unidentified adverse reactions to medicines
- Quickly identify events that are likely to affect adherence to treatment; determine their rates and the risk factors that make these events more likely. Self-reported adverse effects can act as major determinants of ART adherence.[75] A more holistic approach to treatment regimen and adapting it to patient daily routines might improve better adherence[76]
- Estimate rates of events so that risk can be measured and the safety of medicines can be compared to make informed choices and to clearly identify risk factors to clearly identify risk factors
- Determine safety in pregnancy
- Determine safety in children
- Monitor for specific toxicities to establish rates, risk factors and to characterize the reactions.

CONCLUSIONS

There are numerous options and recommendations[77-79] to formulate the HAART regimens. However, the pioneer consideration is to ensure selection of ARV agents to which the virus is susceptible. Then, adherence and minimizing drug toxicity should be considered. The cardiovascular risk profiles should be assessed

for each patient and specific comorbidities should be taken into consideration. Thus, ART is becoming not only increasing effective but also increasing complex. There are many adverse effects of the therapy may cause symptoms affecting a variety of organ system. To optimize the treatment health professionals should focus on preventing adverse effect of ARV agents.

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Conflicts of interest

There are no conflicts of interest.

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