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A Tolerability Review of Non-Nucleoside Reverse Transcriptase Inhibitors: Focus on Laboratory Measures of Clinical Relevance

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Abstract

Background: Current antiretroviral (ARV) therapies have greatly extended the life expectancy for many living with HIV infection. Given that ARV therapies must be taken chronically, long-term tolerability associated with these agents is of great importance. Clinical trials and experience have helped clarify short and long-term adverse event data. Among non-nucleoside reverse transcriptase inhibitors (NNRTIs), common laboratory markers of toxicity and tolerability include transaminase elevations and lipid alterations. Some of these issues appear to be a class-specific effect, whereas others appear to be more agent-specific. Selection of the appropriate NNRTI to use while limiting drug-related side effects is an important clinical objective.

Objective: To review clinically relevant data regarding long-term tolerability of NNRTIs.

Methods: A PubMed search was performed using the following keywords: NNRTI, non-nucleoside reverse transcriptase inhibitor, efavirenz, nevirapine, etravirine, rilpivirine and safety, tolerability or clinical. Papers published before 2007 were excluded; papers were included if they reported clinically relevant tolerability outcomes, enrolled more than 50 patients and were conducted for ≥ 48 weeks in HIV-infected patients.

Results: Newer agents and formulations have significantly improved the tolerability issues associated with older ARVs and earlier treatment approaches.

Conclusions: Tolerability profile remains to be a distinguishing feature among the agents in this class, and is a key consideration when considering a first-line NNRTI-containing regimen that is individualized to the patient and can achieve long-term virologic suppression. This information may help guide treatment choices in clinical practice.

Keywords: Efavirenz; Nevirapine; Etravirine; Rilpivirine; Safety; Tolerability; Reverse transcriptase inhibitors

Introduction

Despite significant advances in the management of HIV infection, the burden of disease remains substantial [1]. An estimated 1.8 million people died of AIDS-related illnesses worldwide in 2009 and, with a global prevalence of 0.8%, about 33.3 million people are living with HIV/AIDS worldwide. However, the use of currently available antiretroviral (ARV) drug regimens means that the life expectancy of many individuals living with HIV infection approaches that of the general HIV-uninfected population [2]. Although current ARV therapies have become safer and better tolerated [2], concerns remain regarding tolerability and side effects from chronic use, including hepatic, cardiovascular and bone disease. Furthermore, near-term safety and efficacy data from clinical studies, rather than longer-term data, generally influence treatment guidelines and drive clinical research for developing new ARV agents. For treatment-naive patients, current guidelines (e.g, US Department of Health and Human Services [DHHS] [3] or European AIDS Clinical Society [EACS] [4]) recommend regimens consisting of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with one active drug from one of the following classes: non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs, boosted with ritonavir) or an integrase strand transfer inhibitor [3].

Class-specific, duration-dependent adverse events for ARVs are becoming better understood as clinical experience with these agents grows. For instance, NRTIs have been associated with morphologic changes in body habits (lipodystrophy), peripheral neuropathy, lactic acidemia, pancreatitis and hepatic steatosis related to mitochondrial toxicity [5-8]. The use of PIs has been associated with serum lipid alterations, glucose intolerance, lipodystrophy and increased risk of cardiovascular disease [8-10]. The NNRTIs are known to cause cutaneous reactions, neuropsychiatric symptoms, hepatotoxicity, metabolic disturbances and gastrointestinal toxicity [11]. Although there is no consensus as to the definition of "toxicity," the Division of Acquired Immunodeficiency Syndrome (DAIDS) of the US National Institute of Allergy and Infectious Diseases has defined toxicity criteria that are increasingly used in clinical trials reporting (Table 1) [12].

The NNRTI-based regimen recommended by current DHHS guidelines as "preferred" is efavirenz with the NRTIs tenofovir/emtricitabine (TDF/FTC) [3]. Efavirenz with abacavir/lamivudine (ABC/3TC) and rilpivirine with TDF/FTC or ABC/3TC are listed as "alternative" first-line NNRTI-based regimens [3]. All nevirapine-containing regimens have been re-classified as "acceptable" options when used in combination with two NRTIs [3]. The most recent International Antiviral Society (IAS)-USA guidelines recommend efavirenz in combination with either TDF/FTC or ABC/3TC for first-line treatment [13]. Alternatively, the EACS guidelines specify that

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Selected laboratory tests	Toxicity criteria[a]
Hepatic markers	
Alkaline phosphatase	>5×ULN
Aspartate aminotransferase	>5×ULN
Alanine aminotransferase	>5×ULN
Serum lipids	
Fasting total cholesterol	>300 mg/dl
Fasting LDL-C	≥190 mg/dl
Fasting triglycerides	>750 mg/dl
Other markers	
Amylase	>2×ULN
Creatine kinase	>10×ULN

Note: DAIDS - Division of AIDS; LDL-C- low-density lipoprotein cholesterol; ULN-upper limit of normal.
[a]Grades 3/4 by DAIDS criteria [12]

Table 1: Toxicity criteria as defined by DAIDS [12].

either efavirenz or nevirapine are recommended NNRTI agents when combined with either ABC/3TC or TDF/FTC, and used as indicated based on patient considerations such as pregnancy (not recommended for efavirenz) or CD4+ T-cell count range (nevirapine-specific CD4+ criteria) [4]. The twice-daily second-line NNRTI etravirine is indicated for use in treatment-experienced patients who have specific NNRTI resistance mutations [3,4,14].

As regimens evolve, simplification strategies to reduce pill burden and dosing frequency are increasingly being developed because they may enhance adherence and patient compliance [15-18]. The trend toward simplification has resulted in a move toward once-daily, fixed-dose combination options. Two combined formulations containing NNRTIs are available: efavirenz co-formulated with TDF/FTC (Atripla™, Bristol-Myers Squibb and Gilead Sciences, LLC) and the combination of rilpivirine with TDF/FTC (Complera®, Gilead Sciences, LLC). Also, a once-daily formulation of nevirapine (Viramune® XR, Boehringer Ingelheim Pharmaceuticals, Inc) was approved for use in the US in 2011. Simplification may be used to avoid toxicities that may develop with prolonged ARV use [3]. One common simplification strategy is changing from a PI-based to an NNRTI-based regimen.

Methods

A literature search was conducted to identify publications reporting clinical trial outcomes of the commonly used NNRTIs. Papers were identified in the PubMed database using the keywords NNRTI, non-nucleoside reverse transcriptase inhibitor, efavirenz, nevirapine, etravirine, rilpivirine and safety, tolerability or clinical. The author selected papers for inclusion in the review if they reported clinically relevant tolerability outcomes, enrolled at least 50 patients and was conducted for at least 48 weeks in patients with HIV infection. A cut-off date of 2007 was selected to capture recent clinical studies. The results from publications reporting the longest follow-up were included when multiple articles from the same study/cohort database are available.

Results

Twenty-six articles were identified for inclusion in the review, in which a total of 27,415 patients were treated with NNRTIs (Table 2). Data and clinical findings for each NNRTI are discussed according to hepatotoxicity, lipid-related abnormalities and other laboratory markers of possible clinical relevance.

Hepatotoxicity

Many medications are metabolized and/or eliminated by the liver. Hepatotoxicity is a relatively common consequence of HIV treatment and may be of greater clinical significance in patients co-infected with Hepatitis B or C. Hepatotoxicity is often detected by elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. The DAIDS criteria define elevations of 5 times the upper limit of normal (ULN) in either of these enzymes as toxicities, grade 3 or 4 (Table 1) [12].

Efavirenz: Hepatotoxicity resulting from the use of efavirenz-based ARV therapy has been reported in a number of studies. The STARTMRK trial is the phase 3 study with the longest follow-up to date; 156-week results have recently been published [19]. In this trial, 282 patients were treated with an efavirenz-based regimen. After 3 years, elevations >5 times the ULN in both ALT and AST were reported in approximately 3% of patients.

In the AIDS Clinical Trials Group (ACTG) 5202 trial, efavirenz in combination with ABC/3TC or TDF/FTC was studied [20]. Data were reported on 923 patients with a median follow-up of 138 weeks. Overall, grade 3 or 4 elevations in ALT were reported in only 14 patients (2%), whereas grade 3 or 4 elevations in AST were reported in only 12 patients (1%). The differences between the two efavirenz-based regimens were not statistically different. Another trial of efavirenz in combination with zidovudine (ZDV)/3TC in 361 patients for 96 weeks (Maraviroc versus Efavirenz Regimens as Initial Therapy) reported grade 3 elevations in ALT of 3.1% at 48 weeks and 3.4% at 96 weeks [21]. For AST, the following numbers were comparable: 3.1% at 48 weeks and 3.4% at 96 weeks, respectively. Also, grade 4 elevations of ALT and AST occurred in only 0.6% of all patients at both time points.

Shorter-term outcomes have also been published from phase 3 studies with efavirenz. Both the ECHO and THRIVE studies enrolled similar numbers of patients treated with efavirenz (N=344 and 338) and have reported 48-week results [22,23]. In the ECHO trial, efavirenz was combined with TDF/FTC and 4% of patients had grade 3 or 4 elevations in ALT or AST [22]. In the THRIVE study, efavirenz was given with two NRTIs (TDF/FTC in the majority of patients), grade 3 or 4 elevations in ALT were reported in 3% of patients and grade 3 or 4 elevations in AST were reported in only 2% of patients [23]. Similar results were described by Pozniak et al. [24] in the phase 2b study of rilpivirine, in which 89 patients were treated with efavirenz and two NRTIs. Grade 3 or 4 elevations in both ALT and AST were reported in fewer than 4% of these patients. The study with the longest follow-up overall in which a group of patients received efavirenz-based therapy and in which safety outcomes have been reported is the FIRST study. Over a median time of 5 years, 6% of 111 patients had grade 4 elevations in ALT or AST levels [25].

Nevirapine: In general, higher rates of hepatotoxicity have been described in patients treated with nevirapine-based regimens than those treated with efavirenz. However, most of these were conducted before the development of the baseline CD4+T-cell count guidelines for the initiation of nevirapine treatment, or the introduction of the extended-release (XR) formulation of nevirapine. Two recent 48-week randomized studies compared the efficacy and safety of the once-daily, XR formulation of nevirapine [26,27]. The larger of these was the VERxVE trial (n=1011), which reported higher rates of grade 3 or 4 ALT elevations (7.1% *vs.* 4.8%) and symptomatic hepatic events (4.3% *vs.* 2.8%) with the twice-daily (immediate-release) formulation as compared with the nevirapine XR group [26]. Worth noting is that the rates for hepatic toxicities for the XR group were in keeping with rates normally associated for efavirenz, and that for both treatment groups, the laboratory test abnormalities primarily occurred during

Reference	Design	N	Duration (weeks)	Study name/Comment
Arribas et al. [40]	Randomized, open-label, non-inferiority	511	96-144	—
Calmy et al. [32]	Retrospective	5,636	218 (4.2 years)	ATHENA, SHCS, HOMER cohorts
Cohen et al. [23]	Phase 3, randomized, double-blind, double-dummy, non-inferiority	338	48	THRIVE
Daar et al. [20]	Randomized, equivalence	922	138	ACTG 5202
DeJesus et al. [42]	Randomized, controlled, open-label	203	48	—
DeJesus et al. [44]	Phase 4, randomized	76	48	NEWART
Fätkenheuer et al. [39]	Randomized, double-blind, non-inferiority	157	48	SENSE
Gathe et al. [26]	Randomized, double-blind, double-dummy, parallel group	1168	48	VERxVE
Hodder et al. [36]	Phase 3b, open-label	207	48	GRACE
Katlama et al. [35]	Phase 3, randomized, double-blind	599	96	DUET-1 and -2
Labarga et al. [33]	Retrospective	178	64 (16 months)	—
Lockman et al. [51]	Prospective, open-label	500	48 weeks	ACTG A5208/OCTANE
Molina et al. [22]	Phase 3, randomized, double-blind, double-dummy, active-controlled	344	48	ECHO
Mugavero et al. [52]	Meta-analysis of completed trials ART-CC cohort vs ACTG 5095 and 5142 trials	ACTG 5095 + ART-CC (n=5,363) ACTG 5142 and ART-CC (n=8,710)	24 and 48 weeks	ACTG 5095 ACTG 5142 ART-CC chort
Podzamczer et al. [28]	Randomized, open-label	289	48	—
Post et al. [41]	Randomized, open-label	385	48	ASSERT
Pozniak et al. [24]	Phase 2b, randomized	89	96	—
Reliquet et al. [30]	Retrospective	592	624 (12 years)	—
Riddler et al. [53]	Prospective, open-label study	757	112 weeks median follow-up	
Rockstroh et al. [19]	Phase 3, randomized, double-blind, non-inferiority	282	156	STARTMRK
Rodriguez-Arrondo et al. [31]	Retrospective	229	312 (6 years)	—
Sierra-Madero et al. [21]	Double-blind, double-dummy, non-inferiority	361	96	MERIT
Soriano et al. [27]	Randomized, open-label, non-inferiority	383	48	ARTEN
Vallecillo et al. [34]	Retrospective	123	48	—
van den Berg-Wolf et al. [25]	Randomized, strategy	111	260 (5 years)	FIRST
Weberschock et al. [29]	Prospective, non-randomized	70	72	TENOR
Wilkin et al. [43]	Phase 2b, randomized	89	192	—

Table 2: Overview of studies included.

the first 4 weeks of treatment [26]. The ArTEN study was a non-inferiority endpoint trial comparing nevirapine with the protease inhibitor atazanavir (ritonavir-boosted), each given with TDF/FTC. In the nevirapine arm (n=383), patients received 2×200 mg/day of the immediate-release formulation of this drug, on a once or twice daily schedule. Of these patients, 4% developed grade 3 and 4 ALT elevations. Regarding AST, grade 3 elevations were reported in 4% of patients and grade 4 in only 2% [27].

In a smaller study from Spain (NODy), patients taking twice-daily nevirapine for at least 12 weeks and who had ALT levels < 2.5 times the ULN were switched to once-daily nevirapine [28]. The primary endpoint was the number of patients with ALT/AST ≥ grade 3. Only 4 patients (3 in the once-daily and 1 in the twice-daily arms) developed nevirapine-related grade 3 or 4 ALT/AST elevations and 2 in the once-daily group experienced transaminase declines with continuation of therapy [28].

In the first study mentioned previously, another group of patients received nevirapine (n=117) as part of their regimen [25]. Over the course of 5 years, 8.5% of the patients in this group experienced grade 4 elevated ALT/AST [25]. In a prospective, but not randomized study (TEN OR), 70 patients were treated with nevirapine in combination with TDF/FTC for 72 weeks, resulting in 5 patients (7%) discontinuing treatment due to hepatotoxicity [29]. A number of retrospective analyses have evaluated the safety of nevirapine in large numbers of patients. Follow-up of 592 patients for 12 years revealed a discontinuation rate of only 4% due to hepatotoxicity (22 patients), with hepatic cytolysis at least grade 2 in fewer than 3% of patients [30].

Another study reported no significant changes in liver function tests for 6 years in 229 patients given nevirapine as part of therapy [31]. In a larger study that included 5,636 participants from three large cohorts (Dutch AIDS Therapy Evaluation in the Netherlands, Swiss HIV Cohort Study and Canadian HAART Observational Medical Evaluation and Research) with a mean follow-up of 4.2 years, discontinuations due to hepatotoxicity were reported in only 1% of patients, with differences in rate being comparable irrespective of once or twice-daily nevirapine [32]. Also, in two short-term studies from Spain (both retrospective in design), nevirapine was given with TDF/FTC for 16 months and 12 months [33,34]. The trials found that only 2/178 (1%) and 3/123 (2%) patients had notable hepatotoxicity.

Rilpivirine: In two similar 48-week phase 3 studies in which

rilpivirine was compared with efavirenz (ECHO and THRIVE studies), 346 and 340 patients, respectively, received rilpivirine primarily in combination with TDF and FTC [22,23]. In both of these studies, grade 3 or 4 elevations in ALT and AST were reported at rates of only 1% or 2%. In a similar phase 2b randomized study by Pozniak et al. [24] rilpivirine (n=279) or efavirenz (n=89) was combined with two NRTIs. Grade 3 or 4 elevations in ALT were reported in 6% of patients, and 3% of patients had grade 3 or 4 AST elevations.

Etravirine: Hepatotoxicity with the second-line NNRTI etravirine appears to occur infrequently, but clinical trial data with this agent are limited. The DUET study investigators reported outcomes on the use of etravirine in 599 treatment-experienced patients, with a follow-up of 96 weeks [35]. Grade 3 or 4 elevations in ALT and AST were reported in 4% of patients in the pooled DUET-1 and -2studies. Also, the Gender, Race And Clinical Experience (GRACE) study included 207 female patients treated with etravirine in addition to darunavir/ritonavir for 48 weeks [36]. Grade 3 or 4 elevations in ALT and AST were reported in 3% and 4% of these patients, respectively.

Lipid-related abnormalities

Lipid-related changes in HIV-infected patients are important because of their strong association with increased cardiovascular risk [37]. Clinically relevant lipid-related abnormalities (Table 1) include increases in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) [12]. These metabolic parameters have been consistently included in most clinical trials of antiretroviral medications as important secondary outcomes. The measurement of high-density lipoprotein cholesterol (HDL-C) also has cardiovascular implications; however, elevations of HDL-C have been associated with a decreased cardiovascular risk [38].

Efavirenz: In the STARTMRK study, DAIDS-defined fasting lipid abnormalities were reported at rates of 5.2% for elevated TC, 8.8% for elevated LDL-C and 2.2% for elevated TGs [19]. In ACTG 5202 (efavirenz with ABC/3TC *vs.* TDF/FTC), grade 3/4 elevations in fasting TC (5.2%), fasting LDL-C (8.8%) and fasting TGs (2.2%) were reported in 282 patients in the efavirenz group (n=282) at 156 weeks [20]. Of note, more patients had lipid-related abnormalities, specifically increased TC and LDL-C, in the group treated with efavirenz plus ABC/3TC than with efavirenz plus TDF/FTC.

Similar degrees of fasting lipid elevations were reported in the ECHO and THRIVE studies [22,23]. In the ECHO trial, increases in TC, LDL-C and TGs were noted in only 2% of patients receiving efavirenz [22]. In the THRIVE trial, clinically relevant (grade 3-4) elevations in TC and TGs were reported in 3% of patients taking efavirenz. The incidence of elevated LDL-C with efavirenz was 6%.

Lipid profiles have also been reported from the Study of Efavirenz Neuropsychiatric Events versus Etravirine (SENSE) trial (n=157) that specifically compared lipid profiles in patients randomized (1:1) to receive etravirine or efavirenz with two NRTIs (ABC/3TC, ZDV/3TC or TDF/FTC) for 48 weeks [39]. Patients treated with efavirenz had significantly greater mean increases in HDL-C, LDL-C, TC and TGs compared with those who took etravirine. Grade 3 or 4 elevations in TC were reported in 8% of patients, LDL-C elevations in 10% and TG elevations in 3% of those who took efavirenz [39]. Increases in HDL-C occurred in <1% of all patients in this study, and the mean ratio of TC to HDL remained stable for 48 weeks in both arms.

The lipid-related effects of efavirenz have also been reported in a number of open-label, randomized studies. The GS-934 study by Arribas et al. [40] included 511 patients who received efavirenz as part of therapy with either TDF/FTC or ZDV/3TC with data collected through 144 weeks. Significant increases from baseline in mean fasting TC, (+30mg/dl), LDL-C (+13 mg/dl) and HDL-C (+10 mg/dl) occurred in both study arms. Fasting levels of TGs were elevated in 5% of patients receiving efavirenz plus ZDV/3TC and in 3% taking efavirenz plus TDF/FTC.

In the 48-week ASSERT study, 385 patients were randomized to either efavirenz with ABC/3TC or TDF/FTC [41]. Although both groups experienced increases in fasting lipid measures, the authors reported greater fasting lipid increases among patients receiving efavirenz plus ABC/3TC compared with those taking efavirenz plus TDF/FTC, including TC (1.36 mg/dl *vs.* 0.66 mg/dl), LDL-C (0.81 mg/dl *vs.* 0.39 mg/dl) and TGs (0.23 mg/dl *vs.* 0.05 mg/dl).

A 48-week study (n=203) by DeJesus et al. evaluated virologically suppressed patients (HIV-RNA <50 copies/ml) who were on a variety of ARV regimens and switched to a fixed-dose combination of efavirenz plus TDF/FTC [42]. The mean changes from baseline in fasting HDL-C and TGs showed some modest but significant improvement, whereas other changes in lipid parameters (+1.0 mg/dl for TC and −4.0 mg/dl for LDL-C) were not significantly changed.

Two early phase 2b studies with efavirenz (both n=89) have also shown lipid-related changes. Wilkin et al. [43] found that increases in TC, LDL-C, HDL-C and TGs were significantly higher with efavirenz than with rilpivirine over 192 weeks. In the study cited earlier by Pozniak et al. [24] 5% of patients had grade 3/4 elevations in TC and LDL-C over 96 weeks [24].

Nevirapine: Studies with nevirapine have shown changes in lipid parameters, although most have reported changes from baseline rather than incidence of events. In the ARTEN trial, <1% of patients (n=383) who received either once or twice daily nevirapine experienced drug-related elevations in TGs [27]. In a randomized, phase 4 study (NEWART; n=152) that was designed to support and confirm ARTEN, patients also received either nevirapine or ritonavir-boosted at azanavir with TDF/FTC. At 48 weeks, increases in TC (18.2 mg/dl) and LDL-C (8.7 mg/dl) from baseline were reported among patients in the nevirapine group. However, mean plasma HDL-C increased by 9.6 mg/dl and TG levels declined by 4.7 mg/dl [44].

Nevirapine-related lipid changes have also been reported in several long-term observational studies. In an article by Reliquet et al. [30] 592 patients who received nevirapine from 1996 to 2008 were included. After 12 years, 361 patients (61%) were still taking nevirapine with undetectable viral loads. Noted were increases in TC and LDL-C of 1.2 mg/dl and 12.4 mg/dl, respectively, and decreases in TGs of 48 mg/dl. Mean increase in HDL-C was 8.1 mg/dl. Worth noting was that 6% of patients had dyslipidemia (LDL-C>190 mg/dl) before starting nevirapine and only 5% during treatment.

In the study by Rodriguez-Arrondo et al., lipid profiles on treatment were compared with baseline among patients who were taking nevirapine for up to 6 years [31]. During follow-up, both LDL-C and TG levels decreased (135 mg/dl to 109 mg/dl and 216 mg/dl to 153 mg/dl, respectively). Also, HDL-C increased from 48 mg/dl at baseline to 62 mg/dl, as seen in several other studies. Offering insights into the possible mechanisms behind HDL-C increases, the Nevirapine Intensive Lipid Evaluation (NILE) study [45] found that nevirapine increased the level of HDL-C by 16 mg/dl (6%) by increasing levels of the enzyme Apo A1. Although this was a small kinetics-based study of just 12 patients, these changes were observed after 24 weeks of nevirapine therapy.

Rilpivirine: The ECHO and THRIVE studies reported lower increases in lipid parameters with rilpivirine than with efavirenz [22,23]. Lipid-related abnormalities at grade 3 or 4 were reported in ≤ 1% of patients in the rilpivirine arms in both studies. Similarly, the safety of rilpivirine compared with efavirenz with regards to lipid changes is supported by phase 2b studies with this drug. Mean changes in key parameters including TC, LDL and TG were lower with rilpivirine through 192 weeks of follow-up in the studies by Wilkin et al. [43] as well as Pozniak et al. [24].

Etravirine: The DUET-1 and -2 studies by Katalama et al. [35] reported lipid-related changes in patients receiving etravirine-based regimens. For 96 weeks, grade 3 or 4 elevations in TC, LDL-C and TGs were reported in 9%, 9% and 11% of patients, respectively. These changes did not differ significantly from the placebo arm. Lipid abnormalities were also reported in the GRACE study, in which 7% of patients experienced grade 3 or 4 elevations in TC and 5% experienced grade 3 or 4 elevations in TGs [36]. In the SENSE study, patients in the etravirine arm, regardless of which NRTI combination they were taking (ABC/3TC, ZDV/3TC or TDF/FTC), had few changes in lipid profiles from baseline. Only 2 patients had grade 3 or 4 elevations in TC, 1 patient with elevation in LDL-C and none with major changes in TGs [39].

Other laboratory markers of clinical relevance

In addition to the hepatic and lipid-related charges associated with NNRTI-based therapy discussed previously, other grade 3 or 4 laboratory changes have been reported from clinical trials that may be of clinical relevance. In particular, elevations in pancreatic amylase, which may indicate acute pancreatitis, and creatine phosphokinase (CK), as a marker of rhabdomyolysis or myocardial infarction, are important. Drug-induced changes in serum phosphate levels also may indicate renal dysfunction.

Efavirenz: In the ECHO and THRIVE studies, amylase elevations were reported in 3% and 5% of patients, respectively [22,23]. In the phase 2b trial by Pozniak et al. [24] 4% of patients also had grade 3 or 4 elevated amylase with no elevations in lipase noted. Comparable incidences of hyperamylasemia were reported in the GS-934 study of efavirenzin combination with TDF/FTC (8%) or ZDV/3TC (4%), with follow-up ranging from 96-144 weeks. Regarding other potential markers of drug toxicity, 1% of patients in the GS-934 study had grade 3 or 4 hypophosphatemia [40].

Nevirapine: In the VERxVE study, levels of CK and phosphate were elevated in the once-daily and twice-daily groups [26]. Comparable grade 3 and 4 CK elevations were reported in approximately 3% of patients in both groups. Serum phosphate abnormalities (grade 3 and 4) were 5.5% and 0% of the nevirapine XR arm, respectively. For the nevirapine twice-daily group, these numbers were 4.9% and 0.2%, respectively [26]. A low incidence of elevated CK was reported in the TENOR study of nevirapine plus TDF/FTC, with only 1 patient discontinuing therapy as a result of this toxicity at week 2 [29].

Rilpivirine: Grade 3 or 4 elevations in serum amylase were observed in 3% of patients over 48 weeks from the ECHO and THRIVE trials [22,23]. In the study reported by Pozniak et al. [24] increase in pancreatic amylase was noted collectively in about 4% of all patients receiving rilpivirine at three different doses, whereas elevation in lipase was noted in 2.5%. Hypophosphatemia of grade 3 or 4 was reported in 2% of patients in the ECHO study [22] and no patients from the THRIVE study [23].

Etravirine: A relatively high rate (62/599; 10%) of grade 3 or 4 elevations in pancreatic amylase was reported in the DUET-1 and -2 studies at 96 weeks [35]. However, the same percentage also was noted in the placebo arm of the study. In the GRACE study, approximately 3% of patients were reported to have grade 3 or 4 amylase elevations [36].

Discussion

This review of several major clinical trials of NNRTIs is consistent with other publications that also confirm the overall safety of the NNRTIs as a class. It supports the use of these agents as a part of standard three-drug treatment regimens as recommended by current DHHS, IAS-USA, EACS and World Health Organization treatment guidelines [3,4,46,47]. Of the newer NNRTIs, the limited data on rilpivirine purport a favorable safety profile, with low incidences of hepatic and lipid-related abnormalities. This review also highlights the variety of studies that have reported tolerability outcomes for the NNRTIs. However, with several of the trials reporting data at 48 weeks, one could argue that study durations are consistently not long enough to draw long-term safety conclusions.

Hepatotoxicity, mainly elevations in AST and ALT, is often observed in patients receiving NNRTIs. However, this infrequently necessitates stopping the NNRTI therapy even in patients co-infected with hepatitis B or C virus. Nonetheless, use of these agents warrants regular lab monitoring of patients for any evidence of drug-induced hepatitis or liver toxicity in general.

In particular, an increased risk of hepatotoxicity with nevirapine has been noted at treatment initiation in women with CD4+ lymphocyte counts >250 cells/mm^3 and men with CD4+ counts >400 cells/mm^3. Therefore, in accordance with treatment recommendations noted in the prescribing label, nevirapine should not be given to patients with CD4+ counts greater than these thresholds [48]. An increased risk of hepatotoxicity has been observed in many studies with nevirapine. Although effectively used for many years in patients with HIV disease, nevirapine should not be given to those with moderate or severe hepatic impairment (i.e. Child-Pugh Class B or C). Nevirapine should only be used with caution in patients with baseline liver disease if the benefits outweigh the risks.

Lipid abnormalities are consistently seen across clinical studies with all antiretroviral agents. However, with the exception of ritonavir-boosted protease inhibitors (lopinavir and indinavir) and some of the older NRTIs (thymidine analogues), these are infrequent and of questionable clinical significance, particularly if looking at cardiovascular outcomes as a consequence. To date, the NNRTIs as a class have not been associated with an increased risk of cardiovascular disease or myocardial infarction [49]. Moreover, in some studies, it may be the use of NRTIs or effects of HIV infection itself that is responsible for hyperlipidemia.

Based on the studies discussed previously, efavirenz seems to be the NNRTI most likely to cause elevation in total and LDL-C values. Conversely, in the case of nevirapine, there are data from several studies showing elevations in HDL-C, which is known to be cardioprotective. Current guidelines recommend a fasting lipid profile on all HIV-infected patients at baseline, 3-6 months after initiation of antiretroviral therapy and thereafter on a yearly basis [50-53]. Management of hyperlipidemia in HIV-infected adults is generally based on current guidelines of the National Cholesterol Education Program Adult Treatment Panel III [38].

Overall, the NNRTI class remains clinically useful as an option for long-term therapy for persons with HIV infection. Moreover, co-formulation with NRTIs helps overcome some of the adherence issues that have been associated with HIV treatment. These agents will likely remain an important component of antiretroviral regimens in the US and throughout the world for the next several years. As older agents within this class are coming off patent, additional generic versions will likely become available with the potential for continued use associated with some cost savings as well.

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