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Review

Pharmacogenetics of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in resource-limited settings: Influence on antiretroviral therapy response and concomitant anti-tubercular, antimalarial and contraceptive treatments

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ABSTRACT

The burden of human immunodeficiency virus (HIV) is mainly concentrated to resources-limited countries where the response to available antiretroviral therapy is often limited by the occurrence of toxicity or by the emergence of HIV drug resistance. Efavirenz and nevirapine are the antiretroviral drugs most prescribed in resources-limited countries as part of antiretroviral combination therapy. Their metabolism and conjugation are largely influenced by enzymatic genetic polymorphisms. The genetic variability of their metabolism could be associated to different metabolic phenotypes causing reduced patients' adherence because of toxicity or drug–drug interactions with concomitant therapies. The purpose of this review is to summarize published evidence on pharmacogenetic and pharmacokinetic aspects related to efavirenz and nevirapine, the influence of concomitant anti-tubercular, anti-malarial or contraceptive treatments, and the impact of human genetic variation and drug–drug interaction on the virologic and immunologic response to antiretroviral therapy in resources-limited countries.

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1. Introduction

The burden of the human immunodeficiency virus (HIV) infection is mainly concentrated to resource-limited countries (RLCs) (UNAIDS, 2013) as defined according to the human development index ranking (UNDP, 2014) in this review. Thus, most of HIV-infected people on antiretroviral therapy (ART) live in RLCs and the vast majority of them receive as first-line ART a combination therapy based on non-nucleoside reverse transcriptase inhibitors (NNRTI) (WHO, 2013). Considering that efavirenz (EFV) and nevirapine (NVP) are the only NNRTIs presently available in RLCs, both drugs are the main prescribed antiretroviral (ARV) drugs globally (WHO, 2013). EFV and NVP are metabolised by cytochrome P450 (CYP) (phase I) and also UDP-glucuronosyl-transferase (UGT) enzymes (conjugation phase). Both drugs are characterized by a pharmacokinetic variability highly influenced by genetic factors that may impact on efficacy and toxicity. Moreover, it is known that hepatic CYP450 enzyme activity changes with age and thereby the impact of CYP450 polymorphism may differ between children and adults (Croom et al., 2009).

Response to ART is often limited by the occurrence of toxicity or by the emergence of HIV drug resistance (WHO, 2012). Viral, human host and environmental factors may all play a role in the appearance and transmission of mutations associated with resistance to ARV drugs (Ribaudo et al., 2006; Bertagnolio et al., 2012; Tang and Shafer, 2012). Because of high variability among viral populations, genetic barriers for resistance can vary for different ARV drugs (Tang and Shafer, 2012). Moreover, inter-individual variability of the pharmacokinetics of ARV drugs, driven by genetic, environmental and polytherapy factors can play a role in treatment failure or toxicity. This can either be directly, because of sub-therapeutic drug levels that can increase the risk of a poor virologic response, or indirectly, when high drug levels produce significant toxicity leading to poor adherence. Both situations are associated with increased risk of developing viral resistance mutations (Ribaudo et al., 2006; Rosenbloom et al., 2012). This phenomenon, together with the significant proportion of patients on ART that are lost to follow-up, represents a serious risk in a public health point of view for HIV programme efficacy in RLCs. Moreover, genetic variation in drug metabolising enzymes has potentially higher impact in African populations where most of the human genetic variability is present (Campbell and Tishkoff, 2008).

Commonly pharmacogenetics refers to how variation in a single gene influences an individual's response to a single drug, while pharmagenomics refers to how all of the genes in the genome can collectively influence responses to drugs (Aceti et al., 2015). In recent years, an increasing number of studies have addressed the pharmacogenetics of ART. However, considering the genetic variability observed among different groups and/or ethnicities, as well as the breadth of the human genetics, a pharmacogenomics view of ART remains a long-term objective of bio-molecular sciences not yet fully defined.

The purpose of this critical review is to summarize published evidences related to pharmacogenetic and pharmacokinetic aspects of NNRTIs (EFV and NVP) and the impact on immunological and virologic response to ART, mainly focused in the context of RLCs. This review also considers the effect of the exposure to hormonal contraceptive, antitubercular and anti-malarial drugs in combination with NNRTI-based ART.

2. Overview of pharmacokinetics and pharmacogenetics of NNRTI

Three main factors influence plasma concentrations of ARV drugs: compliance, drug-drug interactions, and differences in ADME (absorption, distribution, metabolism and excretion). Among subjects who have almost complete adherence to their medications and who are not taking other drugs, most variability in plasma concentrations of a given ARV agent is the result of differences in host factors, genetics being one of the main determinants.

All NNRTIs act by binding directly to viral reverse transcriptase causing inhibition of viral RNA- and DNA-dependent DNA polymerase activities by disrupting the catalytic site. NNRTIs are metabolized by the liver, with NVP and EFV sharing most of their metabolic pathway through CYP450 enzymes.

2.1. Efavirenz metabolism

2.1.1. General aspects

The first-step of EFV biotransformation leads to the formation of two hydroxylated metabolites, 8- and 7-hydroxy-EFV, which account for ~92% and <8% of the total, respectively (Desta et al., 2007) (Fig. 1). The hydroxylation involves primarily CYP2B6, with secondary contribution from CYP2A6, and a negligible participation of CYP1A2, CYP3A4/5 (Desta et al., 2007; di Iulio et al., 2009). The hydroxylated metabolites, that do not show antiviral activity, undergo urinary and biliary excretion after conjugation by UGT pathway (Kwara et al., 2009). EFV also undergoes direct conjugation by UGT2B7 to form N-glucuronide in vitro, but its contribution to the clearance of the drug seems minimal (Bélanger et al., 2009) (Fig. 1). EFV mid-dosing interval plasma concentration <1 μg/ml has been associated with treatment failure (and potential selection of viral drug resistance mutations), while plasma concentration >4 μg/ml increases the risk of adverse neuropsychiatric effects (Haas et al., 2004; Rodriguez-Novoa et al., 2005). The influence of gender and weight of patients on EFV metabolism remains controversial. Moreover, it is known that hepatic enzyme activity changes with age, increasing to adult level from birth to 1-year of age, then exceeding adult level in 1–4 year-old children, and then returning back to adult levels after puberty. Thus, the impact of CYP450 polymorphism may differ between children and adults (Saitoh et al., 2007a).