title

Pharmacogenetics in HIV Clinical Practice

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summary

The best choosing of antiretroviral therapy for an individual patient is one that physicians have always tried to practice, making use of whatever knowledge or tools are available to guide treatment decisions. Individual genetic variations provide scope for a wide range of host-drug interactions that will differentiate therapeutic outcomes within an otherwise homogenous population. Pharmacogenetics looks set to become an increasingly important field to refine the medical tools to personalize antiretroviral treatment. The integration of pharmacogenetic tests into routine patient management has a great challenge for HIV – guidelines and for clinical care. Pharmacogenetics will increasingly impact on medical disciplines. The use of genetic tests in clinical practice improve drug prescribing holds great promise to improve the lives of individuals affected by HIV.

key words

genetic screening, HLA allels, genetic factors in HIV, hypersensitivity reaction

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INTRODUCTION

The term of "pharmacogenetics" was implemented by Friedrich Vogel in 1959 to denote the effects of polymorphism within a particular human gene on the disposition and action of drug [1]. It has long been recognized that individuals vary in their susceptibility to diseases and their response to drugs, but in the last years that progress has been made in elucidating the genetic basis of this phenomenon.

It is known numerous examples of polymorphisms in genes encoding drug-metabolising enzymes, drug transporters and drug targets (enzymes, receptors, etc.). Recent years have seen the mile stone in translating the pharmacogenetics into clinical practice through the use of molecular diagnostics (genotyping) to identify patients at risk of toxicity and drug reaction [2]. Pharmacogentetic tests to identify variations (polymorphism) in human genes can reliably predict the treatment efficacy and toxicity of clinically important medications. This is important area of intense research that is particularly relevant to HIV, given the need for chronic administration of multiple drugs to treat HIV infrction and the frequent need to discontinue or change regimens for the reason of safety and efficacy treatment. However, while multidrug of antiretroviral regimens provide considerable opportunity for host – drug interaction that may be affected by genetic variants, it is a challenge to elucidate the contribution of human genetic variability for each individual drug in the context of multidrug regimens.

Technological advances allowing the application of genome – wide approaches to identify the multiple genetic polymorphism that affect a drug response hold out promise for the identification of disease – susceptibility genes and genetic markers for drug efficacy, thereby opening the way for personalized drug therapy.

GENETIC POLYMORPHISM

An important of HIV research is the immune response and how HIV circumvents it to create a successful and chronic infection. Various studies have provided not only a basic understanding of " how HIV invade", but also clues for the development of vaccines to fight against AIDS. Although HIV initially evokes an immune system response, it later escapes and evades the immune system for a successful viral infection. Methods of escape from the immune response include rapid mutations altering the organization of cell surface receptors, alterations in the expression profile of human leucocyte antigen (HLA) and destruction of immune efector cells.

HIV infection of viral particles are counterattacked by CTL – mediated immune responses (CTL: cytotoxic T cells). Though the cellular immune response fails to control HIV infection completely in most infected individuals, its occurrence is evident in regulating viral load during chronic infection. The initial CTL response may be directed against a few epitopes, which subsequently broadens during prolonged antigen stimulation [3]. When CTL recognize self – HLA molecules loaded with foreign peptide, they activate *Fas* and secrete perforins and granzymes, which lyse target cell [4]. The CTL produces cytokines, such as interferon-α (IFN α) and tumor necrosis factor (TNF), that affect viral replication. HIV-1 – specific CTL also produce the CC chemokines macrophage inflammatory protein 1-α and 1-β and "rantes" which suppress HIV-1 replication [5]. Even with these various effector functions, CTL cannot completely check viral intrusion in the immune system.

During HIV infection, selective pressure imposed by CTL leads to the generation of various escape mutations and these variants may constitute the majority of the total viral pool. The role of CTL is selection pressure for occurrence and than for maintenance of these mutations. Later on, evidence of escape mutations in HLA – B8 restricted epitope in *Nef*, HLA-B44 restricted epitope in *Env* and HLA – B27 restricted *Gag* epitope [6]. After CTL response, HIV inhibits surface expression of the host major histocompatibility complex (MHC) class I.

THE ROLE OF HLA IN HIV INFECTION

Through various genetic factors have been associated with susceptibility to HIV. Table No.1 has shown the genetic factors in HIV infection susceptibility (tab. 1).

Table 1. Genetic factors in HIV susceptibility

Gene	allele	Impact on disease
CCR 5	Del 32	Prevent infection
CCR 5	P 1	Progression of disease
CCR 2	V 641	Delayed disease progression
CCL 5	In 1. 1C	Accelerate disease progression
CXCL 12	CXCL 12 3'A	Delayed disease progression
HLA-A, B, C	Homozygous	Disease progression
HLA-B	B*27	Delayed disease progression
	B*57	Delayed disease progression
	B*35	Rapid disease progression
HLA-G	G*0105N	Decreased risk of infection
HLA-E	HLA-EG	Decreased risk of infection

The role of HLA antigens has concentrated on three areas: zygosity of HLA loci, HLA-sharing alleles and specific HLA-allelic/halotyping association with the outcome of disease progression. It has been shown that homozygosity at the class I – loci is associated with relatively rapid progression to AIDS, compared with heterozygotes [7].

Another genetic component that predisposes to the progression to AIDS is HLA-sharing. If the MHC class I is common to the donor and recipient, the basis of successful transplantation, it would lead to increased susceptibility to viral infection. One natural model of viral transmission between HLA-sharing donor and recipient is mother-to-child transmission, which further supports increased transmission of HIV in these circumstances [8]. Significant increase in susceptibility to HIV has been shown to be associated with concordance at the HLA-B locus but not at HLA-A or HLA-C.

Various studies have confirmed the contribution of specific class I alleles and more particularly HLA-B alleles in the outcome of disease. This remarkable contribution of HLA-B may be because this group has the highest diversity among the class I antigens: approximately 661 alleles com-