

Pharmacogenetics of HIV Therapy

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Summary

Professor Pirmohamed first described Highly Active Antiretroviral Therapy (HAART) and the objectives of current areas of research in applying pharmacogenetics to improve efficacy and reduce toxicity of HIV drugs. He briefly described the observed pharmacogenetic effect of a CYP2B6 polymorphism on efavirenz metabolism, and of MDR1 polymorphisms and the HIV virological response to antiretroviral treatment. Finally polymorphisms within the TNF- α promoter and MHC genes were described in the context of reducing two undesired side effects (ADRs) associated with HAART: lipodystrophy and abacavir hypersensitivity.

Since the introduction of HAART in 1995 there has been a decrease in AIDS cases, and an even larger decrease in deaths. HAART is the use of antiretroviral drugs in combination, including Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs). There are several complications associated with the use of HAART which ultimately is not a cure for HIV.

The source of inter-individual response variation to HAART treatment was summarised into three categories:

- a) HIV genomics
- b) Pharmacokinetics
- c) Pharmacodynamics

The latter two categories were described in detail.

It has been observed that patients given the same dose of different antiretroviral drugs end up with very variable blood plasma concentrations. This may be related to variations in genetic makeup between individuals. Efavirenz is a NNRTI metabolised by CYP2B6 and CYP3A4. It is associated with a neuropsychiatric ADR in some patients. CYP2B6 has numerous polymorphisms, the G516T SNP being associated with loss of function and therefore high blood concentrations of Efavirenz, which may lead to CNS adverse effects. However, differences in blood concentration between patients with different SNPs are witnessed very early in treatment (week 1) but not later on (by week 24), and therefore this observation has little clinical utility.

Protease inhibitors (PIs) are substrates for P-glycoprotein which is an efflux pump and therefore lowers the level of drug present within a cell. Increased cellular drug concentrations increase the efficacy of its action. There are many polymorphisms within the P-glycoprotein (MDR-1) gene. One studied in the context of HIV and pharmacogenetics is C3435T, located on exon 26. The TT genotype is present in 29% of the population and associated with lower expression of P-glycoprotein and subsequently increased intracellular drug concentrations. This polymorphism has been shown by some studies to affect the virological response to antiretroviral treatment causing a greater increase in CD4 count for individuals with the TT genotype when compared to the CT/CC genotype (i.e. more effective response to treatment). However, other studies contradict this evidence and therefore at present the situation is unclear and information about a patients' MDR-1 genotype cannot be used in clinical practice when prescribing anti-retroviral therapy.

Another area of interest is the tumour necrosis factor alpha (TNF- α) locus. There is a great deal of variation in TNF- α levels between individuals, some of which is due to genetic heterogeneity. TNF- α has pleiotropic effects which are consistent with ADRs to HAART including HIV lipodystrophy (metabolic effect) and abacavir hypersensitivity (immune effect).

The key features of lipodystrophy (LD) include loss of fat from the limbs, buttocks and face and fat accumulation in other regions of the body. In addition there are associated metabolic complications including diabetes, coronary artery disease and osteopenia. TNF- α levels can be potentially linked to several of these complications and therefore TNF is a good potential target gene.

Research carried out by Prof Pirmohamed's laboratory indicated that the secretion of TNF- α is altered by antiretrovirals in adipocytes. Protease inhibitors were shown to increase TNF- α secretion, although this was not a class effect. A variant at position -238 within the TNF- α promoter was found to be overrepresented in HIV patients suffering from LD compared to those not. Individuals with the genotype GA (13.1%) were found to have a faster onset LD than those with the wildtype GG genotype.

The key features of abacavir hypersensitivity include fever, skin rash and gastro-intestinal symptoms. Abacavir is a NRTI and hypersensitivity is witnessed in approximately 5% of patients. The initial reaction occurs within the first 6 weeks and rechallenge (administering the drug again) results in a more serious reaction.

Abacavir hypersensitivity is associated with several MHC genes. One of particular interest is HLA *B*5701* which strongly predicts abacavir hypersensitivity (positive predictive value 82%). A cost-effectiveness analysis has been carried out to assess the use of HLA *B*5701* genotyping in avoiding abacavir hypersensitivity. It was concluded that this would be cost-effective and is comparable to tests currently available on the NHS.

In conclusion there is a variable patient response to HAART therapy and genetic factors are responsible for some of this variation. The identification of the HLA *B*5701* genotype is clinically significant and could be used to reduce the incidence of abacavir hypersensitivity. Other promising associations have also been reported. There have been issues with replication of data in certain areas and this indicates the need for larger statistically robust studies, the use of more advanced genotyping strategies and incorporation of a greater variety of ethnically defined subject groups.