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Patient Health Protection

European Medicines Agency 2013 priorities for drug safety research

DNA collection and studies on the genetic causes of adverse drug reactions: angiotensin-converting enzyme inhibitor related angioedema, and statin-induced myopathy

Studies have shown that adverse drug reactions (ADRs) are one of the most common reasons for hospitalisation in the adult population. It has also been proposed that ADRs are the fourth to sixth leading cause of death in hospitalised patients. Most ADRs are dose-dependent and pharmacologically predictable (type A reactions). Some, however, have no known pharmacological cause (type B reactions). These latter types of ADRs are non-predictable, commonly serious and lead more frequently than type A reactions to withdrawal of drugs from the market. The current knowledge about possible genetic causes of ADRs is limited. There is a need to identify genetic factors which can explain why certain patients experience ADRs. Studying the genetic basis of susceptibility to ADRs may provide possibilities for identification of susceptible individuals through genetic testing. Understanding the molecular basis of ADRs may also make it possible to design safer drugs.

One such case of type B reaction is the occurrence of angioedema following administration of angiotensin-converting enzyme inhibitors (ACEI). ACEIs and angiotensin receptor blockers (ARBs) are commonly used for the treatment of hypertension and heart failure. About 1% of patients treated with ACEIs will experience the ADR angioedema. Angioedema also occurs during ARB treatment, but less frequently. It has been estimated that ACEIs account for 30% of the angioedema patients who present to US emergency departments. Angioedema is often localised to the tongue, cheeks, lips or pharynx and can be life-threatening or lethal. The current knowledge about possible genetic causes is minimal.

Another example is stain-induced myopathy. Statins are currently the most widely used and effective drugs in the prevention of cardiovascular disease. However, there is a wide range in the efficacy of statins, and many individuals may experience side effects of statins, mainly in the form of muscle pain. Statin-associated muscle symptoms are a relatively common condition that may affect 10% - 15% of statin users. Statin myopathy includes a wide spectrum of clinical conditions, from mild myalgia to rhabdomyolysis. Certain patient and drug characteristics increase the risk of statin myopathy, including higher statin doses, statin cytochrome metabolism, and polypharmacy.

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In a recent genome-wide study SLCO1B1 variants have been shown to be strongly associated with an increased risk of statin-induced myopathy.

The purpose of the project is

1. There should be infrastructure for the collection of clinical data and DNA samples for the above mentioned drug-induced reactions. Samples from general population controls should also be collected for studies with a case-control design.
2. To identify genetic factors that explain why ACEIs and angiotensin receptor blocker (ARBs) drugs cause angioedema in certain patients.
3. To identify genetic factors that explain why statins cause myopathy in certain patients.

Genome-wide Association (GWA) studies using large numbers of markers may be used to analyse any association between genetic variants and the occurrence of the drug-induced injuries.