No Supplement for Safety

Boaz Mendzelevski, at Cardiac Safety Consultants Ltd, continues his investigation into cardiovascular safety in drug development, focusing on drug-induced vascular thrombosis and myocardial ischemia and infarction

Cardiac safety of new drugs in development has recently gained significant momentum due to increased regulatory and public attention. However, while the focus of the new global regulatory guidance, ICH-E14, is on the early detection of potential QT prolongation and arrhythmia liability, additional major public health concerns related to other forms of cardiovascular adverse drug reactions have not yet been fully acknowledged. The new concerns regarding the potential for drug-induced cardiotoxicity have redefined the cardiac drug safety field into three major areas: cardiac repolarisation, or drug-induced QT prolongation leading to cardiac arrhythmia and sudden cardiac death; vascular thrombosis leading to myocardial ischemia, infarction and death; and direct myocardial injury leading to loss of cardiac tissue, heart failure and death. This article provides a current overview on drug-induced vascular thrombosis, myocardial ischemia and infarction and its industry, regulatory and public ramifications.

DRUG-INDUCED VASCULAR THROMBOSIS

It has long been known that drugs can induce a pathological hypercoagulable state and thrombus formation through a variety of mechanisms. Drugs such as corticosteroids, hormone replacement therapy, some non-steroidal anti-inflammatory drugs and others were implicated in venous and arterial thromboembolic complications. Thrombogenesis may result from alterations in blood flow, endothelial damage and dysfunction and the blood constituents themselves, such as coagulation factors and platelets, collectively known as the 'Virchow's triad'. However, it wasn't until very recently that the full and devastating impact of these adverse drug reactions (ADRs) on the public health had been recognised, and this is discussed in the following sections.

CYCLOOXYNASE-2 (COX-2) SELECTIVE INHIBITORS

The first generation of Cyclooxynase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), celecoxib (Celebrex, Pfizer) and rofecoxib (Vioxx, Merck), were approved by US FDA in 1998 and 1999, respectively. Within two years these drugs became blockbusters with sales exceeding $3 billion in the US alone. However, cardiovascular safety concerns were also raised as early as 2000, when a large study – Vioxx Gastrointestinal Outcomes Research (VIGOR) – showed excessive rofecoxib-related adverse cardiovascular events (1). Unfortunately, the FDA review of the issue was very slow and resulted only in a mild change to the package insert of rofecoxib, stating that "caution should be exercised when Vioxx is used in patients with a medical history of ischemic heart disease."

However, the alarm was only raised in 2004, with the premature termination of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study (2) due to increased cardiovascular risk among patients taking rofecoxib. This triggered the immediate worldwide withdrawal of rofecoxib by Merck on 30th September 2004. By this time an estimated 80 million people had already taken the drug and, following the highly publicised withdrawal of Vioxx, Merck was confronted with thousands of lawsuits.

Following the publication of two additional COX-2 trials in April 2005 – both showing increased cardiovascular risk (3,4) – the FDA requested that Pfizer remove valdecoxib (Bextra) from the market. Furthermore, the FDA issued a cautionary note against the use of coxibs and NSAIDs in general, stating that: "an increased risk of serious adverse (cardiovascular) events appears to be a class effect of NSAIDs (excluding aspirin)" (5).

A large number of possible mechanisms for the coxib thrombotic risk were discussed in the medical literature with the prevailing concept being that the selective inhibition of prostacyclin (PGI-2), which leaves the platelet thromboxane A2 generation relatively unopposed, leads to increased thrombotic risk. However, it also became apparent that not all coxibs share the same risk and some are safer than others.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS AGONISTS

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear transcription factors that modulate gene expression. Therapeutic agents that target two distinct families of PPARs (α and γ) have been introduced. The PPAR γ agonists (pioglitazone and rosiglitizone) increase insulin sensitivity when used as anti-diabetic agents. The development of dual α and γ PPAR agonists aimed at treating hyperlipidemia and insulin resistance, and ultimately reducing atherosclerosis in diabetics, became an attractive pharmaceutical target. However, four dual PPAR agonists failed during clinical development due to potentially serious toxicities, including ragaglitazar (Novo Nordisk), farglitazar (GSK), MK-767 (Merck) and TAK559 (Takeda). Unfortunately, there are no published reports available which detail the reasons that lead to the discontinuation of development of these four agents.

Muraglitazar (Bristol Myers Squibb) was the first dual PPAR to be assessed by an FDA Advisory Committee in September 2005. A comprehensive safety review revealed an excess in the total number of cardiovascular deaths (due to myocardial infarction, stroke or sudden death) and cardiovascular adverse events (defined as coronary disease and stroke) in muraglitazar-treated subjects compared with pioglitazone and placebo-treated subjects (all type 2 diabetics) (6). However, the FDA safety summary concluded that, due to the small number of events, it is difficult to fully establish the cardiovascular risk associated with muraglitazar treatment from the available clinical data.

The advisory panel voted almost unanimously to approve muraglitazar as monotherapy. However, following the online publication of a paper in *JAMA* that showed a doubling of the

relative risk for every major adverse cardiovascular event in muraglitazar-treated patients, compared with pioglitazone or placebo, the FDA requested more robust safety data from longer trials (7). A few days later, on 27th October 2005, the sponsor announced that it was considering terminating further development of muraglitazar.

A recent meta-analysis published online in the *New England Journal of Medicine* found that rosiglitazone (Avandia, GSK) was associated with a borderline significant increased risk of myocardial infarction and death from cardiovascular causes (8). Several other publications also questioned the cardiac safety of rosiglitazone, due to the fact that it can cause fluid retention and lead to the development of congestive heart failure in patients with or without pre-existing left ventricular systolic or diastolic dysfunction (9). With the COX-2 experience fresh in the memory of both the public and the FDA, an FDA Advisory Committee recently voted overwhelmingly to keep Avandia on the market and to add a 'black box' warning of the risks in patients with congestive heart failure.

HERBAL SUPPLEMENTS

Ephedra, a popular herbal supplement, was recently removed from the US marketplace amid growing concerns of adverse effects. Ephedra, also called *ma huang*, is a herb that contains ephedrine, a substance regulated by the FDA as a drug when created chemically in the lab. However, ephedra has generally been marketed as an ingredient in dietary supplements, which are not bound by the same strict standards as drugs. Nevertheless, on 12th April 2004, the agency prohibited the sale of all dietary supplements containing ephedra.

The FDA said in its statement that it has long regarded ephedra-based dietary supplements as a potential health hazard. Substantial evidence of harm emerged in 2003, when a major study reported more than 16,000 adverse events – some associated with myocardial infarction or even fatalities – related to the use of dietary supplements containing ephedra (10). The underlying mechanism of myocardial infarction in patients taking ephedra is thought to be coronary vasospasm due to enhanced sympathetic activity (11). In addition, ephedra alkaloids can increase platelet reactivity, contributing to a pro-thrombotic state and possibly promoting myocardial infarction.

EFFECT ON THE REGULATORY SYSTEM

The widely-held public criticism of the US FDA's management of the COX-2 cardiovascular issues also triggered a major US Senate investigation into the practice and performance of the FDA and resulted in significant changes to the FDA structure and practice. An additional review by the US Institute of Medicine (IOM) has highlighted the need for broader drug safety surveillance and post-marketing risk management programmes; thereby extending the regulatory focus well beyond the drug approval event and introducing additional requirements to the drug approval process and the post-marketing commitments from drug manufacturers (12).

IMPACT ON DRUG DEVELOPMENT

The immediate effect of the events described was to increase public awareness and regulatory scrutiny of the drug development process in general, and cardiac safety in particular. However, while the regulatory concerns relating to cardiac repolarisation led to the development of the ICH-E14 guidance, the vascular-thrombotic cardiac safety issues have not yet achieved the same regulatory status. As long as this regulatory gap continues, the responsibility for developing and implementing an extended and rationalised cardiovascular drug safety in clinical development lies within the pharmaceutical industry. This can also be viewed as an opportunity for the industry to develop new and better strategies for drug safety and efficacy, which may potentially improve the whole drug development process.

STRATEGIES FOR THROMBOTIC-RELATED CARDIAC SAFETY ASSESSMENT

Selecting and qualifying relevant targets and biomarkers for non-clinical and clinical assays for drug-induced cardiovascular thrombotic risk should be viewed as a longitudinal and multidisciplinary effort. The full mechanistic spectrum of the thrombotic cascade, and the resulting vascular and tissue damage, should be taken into consideration. The traditional Virchow's triad may be useful for the rheological aspects, including assays for changes in blood flow, endothelial function, coagulation proteins and platelet function. The effect of the drug on known neurohumoral factors that may affect rheological properties, including prostaglandin levels, may be useful. Fortunately, well-established assays are already available, clinically and commercially, for most of the elements described.

The assessment of drug-induced, thrombotic-related, cardiovascular risk should incorporate specific and relevant assays at the appropriate development stages. Non-clinical assays should involve both *in vivo* and *in vitro* assessments using appropriate rheological, tissue and animal models for the thrombotic mechanisms. The effects of time and concentration should also be considered, based on the body of knowledge relevant to the drugs under development.

While it may still be premature to suggest routine, systematic assessment of drug-induced thrombotic cardiovascular risk for all new drugs, it would be in the manufacturer's best interest to consider such an approach for certain drug classes associated with thrombotic complications. This may help drug companies to identify, assess and possibly mitigate any such liabilities at an early stage.

Cardiac safety in human clinical trials should take into account any non-clinical signals that potentially indicates a thrombotic risk. As discussed, the clinical development of relevant drug classes should be expanded in order to assess the potential for thrombotic complications by progressively incorporating appropriate assessments into the clinical drug development. These may include imaging, laboratory, electrocardiography (ECG) and other technologies for assessments of blood flow and velocity indices, endothelial and platelet function and systematically monitoring for cardiovascular ADRs, including ischemia and infarction, in late stage clinical trials.

CARDIOVASCULAR BIOMARKERS

Biomarkers are increasingly used in clinical and drug development process. Many biomarkers for cardiovascular events have been identified and validated through comprehensive laboratory and clinical research. As an example, atherosclerotic

arterial plaque rupture in acute coronary syndromes is associated with release of soluble CD40 ligand, placental growth factor, pregnancy-associated plasma protein A, and adhesion molecules. Superimposed thrombosis may be manifest as elevations of circulating D-dimer, plasminogen activator inhibitor-1, and von Willebrand factor. The onset of ischemia and infarction is characterised by the time-dependent release of troponins, myoglobin, creatine kinase-MB and plasma natriuretic peptide. Cardiac troponins – primarily Troponin I – became the most commonly used biomarker/s for assessing tissue damage even before any clinical evidence for ischemia/infarction.

The sophisticated use of integrated models of clinical, imaging, ECG and laboratory assays as part of an overall drug development cardiac safety strategy can be highly cost-effective – reducing the need for large and lengthy clinical trials to assess cardiovascular safety outcomes. Integrated multi-marker packages are currently under development and are becoming increasingly popular for both efficacy and safety assessments with an overall, favourable regulatory acceptance and endorsement.

POST-APPROVAL STRATEGIES

The current drug development paradigm is neither designed nor powered to detect relatively small safety signals prior to regulatory approval. Most safety signals of public interest are only discovered after large populations are exposed to the drug, as already described. It is, therefore, clear that in the current regulatory and public environment drug development programmes should continue, by design, well into the post-approval period. As recommended in the IoM report it is of the utmost importance that regulators, drug companies and healthcare providers work together in order to continuously develop more robust safety signal detection and surveillance systems, and establish well-designed risk management and risk minimisation programmes where appropriate (12).

CONCLUSION

The full implications of the potential of certain drug classes to induce thrombogenicity, and the resulting large-scale cardiovascular adverse reactions leading to severe morbidity and mortality, have only recently been recognised. Drug manufacturers can no longer ignore this risk, and regulators are likely to be vigilant in their treatment of these emerging cardiovascular adverse drug reactions.

It is, therefore, only logical that biopharmaceutical companies will now embrace new drug development practices that will include the assessment, where relevant, of the potential risk for drug-induced vascular thrombosis and cardiac safety in general. It is also important that safety monitoring programmes are extended, by design, well into the post-approval period, which may offer the first opportunity for drug developers to detect relatively small, but important, safety signals. A proactive approach from the industry may not only reduce clinical, regulatory, legal and financial liabilities, but would also improve public confidence in the drug development process and the pharmaceutical sector.

About the author

Boaz Mendzelevski, MD, is a Cardiac Safety Consultant based in London and a co-founder of Cardiac Safety Consultants Ltd. Boaz is a board certified expert in Internal Medicine and Cardiology (Jerusalem, Israel) with postgraduate training in Invasive Cardiology and Electrophysiology (London, UK). Boaz was the founder of two major core ECG labs and has authored more than 220 cardiology expert reports. He was a member of several pharmaceutical advisory boards, data safety boards and regulatory expert panels.
Email: boaz.mendzelevski@cardiacsafetyconsultants.com

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