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Monitoring liver safety in drug development: The GSK experience

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Abstract

To promptly identify and evaluate liver safety events, an evidence-based liver safety system was created for global Phase I–III clinical trials. The goals of this system included improving clinical trial subject safety, expanding information on liver safety events, and improving data quality across studies by establishing and communicating:

- Liver chemistry subject stopping criteria.
- Hepatitis B and C screening and exclusion criteria.
- Close monitoring and follow-up of subjects to determine the etiology of the liver event.

Two different algorithms for liver stopping criteria were developed. The most stringent criteria were selected for healthy volunteers in Phase I studies, where no treatment benefit is anticipated and clinical safety data are limited. With an interest in assessing potential liver "tolerance" or adaptation with accruing safety information, slightly higher liver chemistry thresholds were set for Phase II–III studies. This paper will describe the importance of liver safety in drug development, laboratory tests used to monitor liver safety, the rationale for selected liver chemistry subject stopping criteria, and implementation of this safety system.

Keywords: Liver safety; Safety systems; Liver chemistries; Hepatitis B screening; Hepatitis C screening; Hy's Law; Transaminase elevation

1. Introduction

Drug-induced liver injury is the most frequent cause of acute liver failure resulting in liver transplantation in the U.S. (Lee, 2003). Despite considerable research efforts into mechanisms of drug-induced liver injury, it remains challenging to predict which compounds will result in clinically important idiosyncratic liver injury in drug development. This is due to limited information on mechanisms of drug-induced injury, imperfect preclinical models (Olson et al., 2000), the low frequency of clinically important events and lack of understanding of what makes some persons more susceptible to drug-induced injury. For example, although troglitazone was linked to acute liver failure in 89 patients (Graham et al., 2003), approximately one in 1000 troglitazone-treated patients (or less) progressed to acute liver failure (Graham et al., 2003; Kaplowitz, 2005; Temple, 2006). As most drug development programs administer study drug to fewer than 2000 subjects, rare events of severe liver injury may not arise

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during drug development. Hence, improved measures are needed to quantify signals of hepatotoxicity throughout the development process.

Liver safety issues are the single leading cause of drug withdrawals from the market (Temple, 2006). FDA and other global regulatory authorities have been proactive in providing information on clinically worrisome hepatotoxicity, coining the term, ''Hy's Law'' to describe serious events of probable drug-induced hepatocellular injury in which at least threefold transaminase elevations are associated with twofold bilirubin elevations or jaundice (FDA Draft Concept Paper, 2007; Temple, 2006; Senior, 2006). The occurrence of a ''Hy's Law'' event during drug development immediately signals potential liver safety issues, as demonstrated for troglitazone, trovafloxacin and bromfenac (Kaplowitz, 2005). However, these events are seldom seen during Phase I–III drug development, even in compounds later demonstrated to be hepatotoxic (Pauls, 2004).

Diverse liver chemistry thresholds have been recommended as stopping criteria for subjects receiving novel therapeutic agents (FDA Draft Concept Paper, 2007; Kaplowitz, 2005; CDER-PHRMA-AASLD Conference, 2000; Kaplowitz, 2006). Prompt cessation of the suspect drug in events of acute drug-induced liver injury is recommended to decrease risk of progression from acute liver injury to acute liver failure or chronic liver injury (Zimmerman, 1999; Andrade et al., 2006; Aithal and Day, 1999). Affirming earlier results (Aithal and Day, 1999), follow-up of a large Spanish case series of acute drug-induced liver injury revealed that while only 5.7% progress to chronic liver injury, 60% of subjects progressing to chronic liver injury had continued the suspect drug after symptoms appeared (Andrade et al., 2005).

Development of a standard safety system provides a consistent view across therapeutic programs, facilitating liver safety comparisons. Medical errors decrease when standardized safety systems are in place (Longo et al., 2005). Therefore, an evidence-based liver safety system was developed at GlaxoSmithKline (GSK) for use in Phase I–III studies to enhance subject safety, expand information on liver safety events, and facilitate comparisons across studies.

2. Background—liver chemistries

2.1. Transaminases

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are enzymes which are released into the blood, generally in proportion to liver damage. While ALT measurements can exhibit a 1.1% laboratory intra-assay coefficient of variation (Prati et al., 2002), current ALT measurement performance goals allow for a 20% total error (Dufour et al., 2000). The serum half-life of ALT is approximately 2 days (Price and Alberti, 1979). ALT is more liver-specific than AST, as ALT is found in highest concentration in the cytosol of hepatocytes in the liver, while AST is also present in blood, skeletal muscle, and heart (Green and Flamm, 2002). Therefore, ALT is generally a better predictor of liver injury. AST serves an important supporting role in the interpretation of liver chemistry elevations, with the ratio of AST to ALT useful in developing a differential diagnosis of the liver diseases (Green and Flamm, 2002). For example, elevated AST:ALT ratios of >3:1 generally indicate muscle injury or necrosis when accompanied by parallel elevations in CPK and LDH (Nathwani et al., 2005), ratios >2:1 are seen with alcoholic liver injury (Green and Flamm, 2002), and a ratio of 1:1 in nonalcoholic fatty liver disease without fibrosis (Angulo, 2002).

Mild ALT elevations are common, and have been observed in healthy volunteer subjects receiving placebo in Phase I studies (Rosenzweig et al., 1999). In over 15,000 U.S. adults participating in the Third National Health and Nutrition Examination Survey (NHANES), elevated aminotransferases were detected in 7.9% (Clark et al., 2003); the majority (69%) had unexplained elevations which were significantly associated with indices of adiposity or metabolic syndrome, while a minority (31%) had associated high alcohol consumption, hepatitis B or C infection or high transferrin saturation. Transaminase elevations were more common in men, Mexican Americans, and African Americans (Clark et al., 2003). In NHANES, ALT equal to or exceeding 3 times upper limit of normal (ULN) was uncommon, detected in only 0.4% of the total population and 0.7% of those with Type 2 diabetes (Erbey et al., 2000). Background rates of ALT equal to or exceeding 3 times ULN typically range from 0.2% to 1.0% in clinical trial populations receiving placebo (Kaplowitz, 2005). Within a convenience sample (from studies using common laboratory and data standards) of GSK Phase II–III clinical studies of low risk populations ($n = 18{,}530$), ALT equal to or exceeding 3 times upper limits normal (ULN) was observed at baseline in only 0.1% (or 1/1000) of the population (unpublished results). Of note, in clinical studies of subjects receiving an idiosyncratic hepatotoxin, the incidence of ALT exceeding 3 times ULN is twofold higher in the treated population, relative to those receiving placebo or comparator (Kaplowitz, 2005). In summary, ALT levels greater than 3 times ULN may suggest mild liver injury, hence this threshold is sensitive, but not specific, for liver toxicity (Kaplowitz, 2005).

2.2. Bilirubin

With drug-induced liver injury, elevations in total bilirubin are comprised of an increased proportion of conjugated bilirubin (or direct bilirubin), which can be detected through fractionation of total bilirubin in the serum, or in urine as bilirubinuria. Elevations in total bilirubin and predominantly indirect bilirubin are most commonly due to the innocuous Gilbert's Syndrome (Green and Flamm, 2002), resulting from decreased activity of the UGT1A1 enzyme responsible for bilirubin glucuronidation. Elevations in total bilirubin and predominantly indirect bilirubin also result from select drugs inhibiting unconjugated