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Qualified kidney biomarkers and their potential significance in drug safety evaluation and prediction☆

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ABSTRACT

The kidney is one of the major organs drug toxicity may target. Some renal safety biomarkers have been proposed to measure kidney injury and function accordingly. Despite the widespread use for diagnosis and monitoring of renal injury and function for decades, serum creatinine and blood urea nitrogen are nonspecific biomarkers with insensitive and delayed response in the clinical setting. There is an urgent need to identify and qualify novel kidney safety biomarkers that would be used to detect and predict drug-induced nephrotoxicity in preclinical toxicological studies, clinical trials and patient care in sequence. To do that, eight novel renal safety biomarkers have been well characterized and qualified for preclinical drug safety screening, and their clinical bridging validation is underway as well. Of them, some are used to detect or predict proximal tubular injury, and others are used to diagnose and monitor glomerular damage. Thus, measurement of a panel of kidney safety biomarkers in parallel would help maximally capture all potential safety signals for a more informative decision to be made in drug research and development as well as for optimal selection of the drug and its dose in clinical practice.

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1. Introduction

The kidney is the most important organ responsible for the excretion of unchanged drugs and/or their hydrophilic metabolites (Williams et al., 2004) and thus is one of the major sites of drug toxicity that is manifested frequently in drug development and in patient care. Renal dysfunction and injury are common adverse effects of drug treatment (Choudhury & Ahmed, 2006). Acute kidney injury (AKI, formerly called acute renal failure) occurs in up to 20% of hospitalized patients and in 30–60% of critically ill patients in intensive care (Hoste et al.,

Abbreviations: AKI, acute kidney injury; ALB, albumin; ATN, acute tubular necrosis; AUC, area under the curve; A1M, alpha-1 microglobulin; B2M, beta-2 microglobulin; BUN, blood urea nitrogen; CLU, clusterin; CysC, cystatin C; EMA (or EMEA), European Medicines Agency; FDA, Food and Drug Administration; GFR, glomerular filtration rate; GST, glutathione-*S*-transferase; HESI, Health and Environmental Sciences Institute; ICU, intensive care unit; ILSI, International Life Sciences Institute; kDa, kilo Dalton; KIM-1, kidney injury molecule-1; mRNA, messenger ribonucleic acid; NAG, *N*-acetyl-β-D-glucosaminidase; NPAA, *N*-phenylanthranilic acid; PMDA, Pharmaceuticals and Medical Devices Agency of Japan; PSTC, Predictive Safety Testing Consortium; RPA-1, renal papillary antigen-1; sCr, serum creatinine; TFF3, trefoil factor 3; uALB, urinary albumin; uTP, urinary total protein.

☆ The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US federal government.

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2010). While acute tubular necrosis (ATN) is often multifactorial, it has been reported that nephrotoxic drugs contributed in 19–25% of cases of severe ATN in critically ill patients (Mehta et al., 2004; Uchino et al., 2005). Acute interstitial nephritis is a common cause of AKI that is thought to be drug-induced in 60–70% of patients (Perazella & Markowitz, 2010).

In an effort to minimize the potential risk for developing drug-associated nephrotoxicity, it is critical either to prevent new nephrotoxic drugs from entering the market, or to detect and manage nephrotoxicity efficiently if continued use of a drug with nephrotoxic liability is mandated by medical need (Bonventre et al., 2010). Although the low sensitivity of serum creatinine (sCr) and blood urea nitrogen (BUN) – serum indicators of whole kidney function – for detection of kidney injury has been well recognized for several decades, sCr and BUN are currently still considered as the "gold standard" to monitor renal function and to detect drug-induced nephrotoxicity. The limitations of relying on elevated sCr and BUN to monitor impairment of renal function have been well documented (Bonventre et al., 2010; Frangogiannis, 2012; Slocum et al., 2012). In addition to the delay in appearance of a rise in sCr and BUN due to the functional reserve of the kidney, other limitations include extra-renal factors influencing production and clearance of these biomarkers of renal function. In view of the poor performance of these two markers, novel renal safety biomarkers are required to identify and monitor renal injury with high specificity and sensitivity (Vaidya et al., 2010).

To address this need, it is required to discover and qualify novel renal safety biomarkers that would be used to predict and monitor drug-associated nephrotoxicity. In 2010, the Critical Path Institute Predictive Safety Testing Consortium (also known as C-Path PSTC) Nephrotoxicity Working Group selected 23 exploratory renal biomarkers (Sistare et al., 2010) and systematically evaluated the utility of the most promising biomarkers in multiple mechanistically distinct models of kidney injury in rats dosed with well-established nephrotoxicans (Bonventre et al., 2010; Dieterle et al., 2010a, 2010b; Ozer et al., 2010; Vaidya et al., 2010; Warnock & Peck, 2010; Yu et al., 2010). Seven of these urinary safety biomarkers were proposed to the regulatory authorities for qualification as kidney safety biomarkers for preclinical toxicology assessments (Dieterle et al., 2010b; Goodsaid & Papaluca, 2010; Mattes et al., 2010; Sistare et al., 2010; Warnock & Peck, 2010). Later, the ILSI–HESI (International Life Sciences Institute, Health and Environmental Sciences Institute) Committee on Biomarkers of Nephrotoxicity evaluated a panel of renal safety biomarkers in two strains of male rat, and demonstrated that renal papillary antigen-1 holds high specificity for collecting duct injury, superior to all reference biomarkers being tested (Harpur et al., 2011). As a result of the efforts of these two consortia, these eight biomarkers – albumin (ALB), β2-microglobulin (B2M), total protein (TP), cystatin C (CysC), kidney injury molecule-1 (KIM-1), clusterin (CLU), trefoil factor 3 (TFF3), and renal papillary antigen-1 (RPA-1) – were judged by regulatory authorities to be acceptable in specified contexts of non-clinical development for detection of acute drug-induced renal toxicity and to provide additional and complementary information to the currently available standard parameters (FDA, 2008, 2010; EMA, 2009, 2010; PMDA, 2010). These newly qualified safety biomarkers are anticipated to facilitate early identification and elimination of drug candidates that are potentially nephrotoxic through sensitive and specific prediction of human nephrotoxicity in preclinical drug safety screening. It is also expected that, with better understanding of their diagnostic performance in humans, they will contribute to better safety monitoring and help prevent drug-induced kidney injury in clinical trials. Clearly, thorough knowledge and better understanding of biochemical characteristics and clinical significance of each nephrotoxicity biomarker would significantly improve translation of potential safety signals into the prediction and management of nephrotoxicity and enhance renal function monitoring as well.

2. The eight qualified renal safety biomarkers

As summarized below, these eight biomarkers provide differential information on renal injury related in part to their location within the nephron (Fig. 1) and in part to their physiological behavior.

2.1. Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1), a trans-membrane glycoprotein with a mucin domain in the extracellular region, has been widely studied in both animals and humans over the past 10–15 years. These studies have shown it to hold great promise as a sensitive and specific marker of renal tubular injury (for reviews see Vaidya et al., 2008a; Slocum et al., 2012).

2.1.1. Non-clinical studies

KIM-1 mRNA levels have been shown to be expressed at a low level in normal kidney tissue but markedly increased in proximal tubular cells following ischemic or toxic injury in rodents (Ichimura et al., 1998; Amin et al., 2004). Following tubular injury from a variety of causes, the mucin ectodomain is shed into the urine where it is stable for prolonged periods of time (Bonventre, 2008). KIM-1 can be detected in urine in several models of nephrotoxicity (Ichimura et al., 2004). Vaidya et al. (2006) found that urinary KIM-1 levels were elevated after cisplatin or ischemic injury in rats at times when other routinely used urinary biomarkers of injury or blood-based markers of renal function had not changed, showing the potential sensitivity of KIM-1 to monitor tubular injury. Recent studies have provided evidence that urinary KIM-1 is a highly sensitive and specific biomarker for the early detection of nephrotoxicant-induced proximal tubular injury, regardless of the mechanism underlying that injury (Zhou et al., 2008; Hoffmann et al., 2010; Ozer et al., 2010; Tonomura et al., 2010; Vaidya et al., 2010; Togashi et al., 2011). Increased urinary KIM-1 reflected increases in gene/protein expression and histopathological alterations in the renal tissues earlier than functional alterations (raised BUN or sCr) were manifested (Hoffmann et al., 2010). Further evidence for the superior sensitivity of urinary KIM-1 over whole kidney functional assessment by sCr or BUN was provided by Ozer et al. (2010) and Vaidya et al. (2010). Tonomura et al. (2010) found that KIM-1 was the best biomarker for proximal tubular injury based on its early and time-dependent increase as well as the large magnitude of the increase. The data generated by Vaidya et al. (2010) which demonstrated that KIM-1 out-performed traditional markers (sCr and BUN) were reviewed by regulatory authorities before deciding that KIM-1 was qualified for the detection of acute drug-induced nephrotoxicity in rats. In addition, urinary KIM-1 may also reflect recovery from tubular injury in rats (Rouse et al., 2011).

2.1.2. Clinical studies

Many of the basic properties of KIM-1 that have been demonstrated in rodents also obtain in humans. Thus KIM-1 is expressed at high levels in proximal tubular cells and the cleaved ectodomain of KIM-1 can be detected in the urine of patients with ATN (Han et al., 2002). Human studies also indicate the promise of KIM-1 as a diagnostic biomarker of AKI (for reviews see Coca et al., 2008; Vaidya et al., 2008a; Slocum et al., 2012). Urinary KIM-1, in combination with a number of other biomarkers, demonstrated prognostic value in AKI, identifying those patients at greater risk of requirement for renal replacement therapy or death (Vaidya et al., 2008b). Moreover, increased KIM-1 expression in kidney biopsies correlated significantly with declining renal function in renal transplant recipients (Zhang et al., 2008).