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Regulatory Feasibility of Novel Kidney Biomarkers

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Introduction

The development of a new drug is a lengthy and expensive process. On average it takes 10-15 years, with an estimated cost of £1-2 billion for a potential drug to be approved for use. Analysis of clinical trial data from 2010 to 2017 show that 30% of compounds that reach Phase I clinical trials fail due to unmanageable toxicity, and many of those fail due to nephrotoxicity and acute kidney injuries (Sun et al. 2022).

In patients presenting with acute kidney injury, it is estimated that up to 26% is caused by drug-induced nephrotoxicity in adults and 16% in children (Awdishu and Mehta 2017). This demonstrates that the current non-clinical assessments are not sufficient or capable of showing early injury or toxic insult to the kidney. This paper examines the alternative kidney biomarkers available and the regulatory feasibility of using them non-clinically and clinically to determine safety.

Acute Kidney Injury (AKI)

Acute kidney injury (AKI) may result from many conditions, the most common being ischemia leading to the death of tubular epithelial cells. AKI is potentially reversible if caught early enough as tubule epithelium has high regeneration capabilities (Andrianova et al. 2019). Following toxic insult, the tubular cells undergo a cascade of cellular mechanisms and result in the accumulation of proteins in the urine and blood. Moreover, the aftermath of toxic insults on tubular cells involves a complex cascade of cellular mechanisms, further elucidating the intricate pathophysiology of AKI. Upon exposure to nephrotoxic substances, such as certain medications, heavy metals, or harmful chemicals, tubular cells initiate a series of responses aimed at neutralising and eliminating the toxic threat (Orr and Bridges 2017). However, these protective mechanisms can inadvertently lead to cellular stress and damage (Jaishankar et al. 2014). One notable consequence of toxic insult is the activation of pathways that promote inflammation, oxidative stress, and apoptosis within the renal tubular epithelium. Inflammation plays a pivotal role in amplifying the injury, recruiting immune cells to the site of damage, and exacerbating tissue destruction (Rabb et al. 2016). Concurrently, oxidative stress, characterised by an imbalance between the production of reactive oxygen species (ROS) and the cell's ability to detoxify them, contributes to cellular damage and dysfunction (Pavlakou et al. 2017). The culmination of these events often results in apoptosis, a programmed cell death process, further compromising the structural and functional integrity of tubular epithelial cells.

As the tubular cells succumb to the toxic insult, the repercussions extend beyond the confines of the renal tubules. Proteins that are normally retained within the tubular cells may leak into the surrounding interstitial space, leading to their subsequent appearance in the urine, a phenomenon known as proteinuria (Saraf et al. 2020). Additionally, damaged tubular cells release proteins and enzymes into the bloodstream, contributing to the elevation of serum biomarkers associated with renal injury.

The accumulation of proteins in both urine and blood serves as a critical clinical marker for the severity and progression of AKI following toxic insults. Monitoring these biomarkers not only aids in the diagnosis of AKI but also provides valuable insights into the underlying mechanisms of renal damage. This understanding is instrumental in tailoring therapeutic interventions to address the specific molecular pathways activated during toxic-induced AKI, with the ultimate goal of mitigating injury, promoting repair, and preserving renal function. Researchers and clinicians alike are actively engaged in unravelling the intricacies of toxic-induced AKI to pave the way for more effective preventive and therapeutic strategies.

Creatinine

Creatinine, a byproduct originating from the breakdown of creatinine phosphate during muscle tissue metabolism and protein breakdown, is consistently released into the bloodstream. Its elimination occurs through the kidneys via glomerular filtration and tubular secretion (Shemesh et al. 1985; Waikar et al., 2009). Glomerular filtration separates waste, including creatinine, from the blood, with subsequent movement into renal tubules (Goldstein 2010). Tubular secretion actively transports creatinine from the blood into tubular fluid, ensuring effective removal and preventing bloodstream accumulation.

Monitoring blood creatinine levels is vital for diagnosing renal conditions, including chronic kidney disease and acute kidney injury (Fletcher et al. 2022).

Serum creatinine is the most common functional biomarker of the kidney and is a standard measurement on all nonclinical toxicology studies. If the filtration or function in the kidney is reduced, then creatinine levels in the blood will increase. However, serum creatinine is not an effective biomarker for showing AKI and is more relevant for a chronic kidney disease. A rise in creatinine concentrations is only observed when there is marked decrease in functioning nephrons. It is estimated that an effect on creatinine is observed when there is already a loss of approximately 70% in kidney function (Shemesh et al. 1985). To address the limitations of the current assessments of kidney function, research has focussed on markers of tubular injury following dysfunction or damage to the kidney. Due to the pathophysiology of the injury, biomarkers of tubular insult provide early detection and identification of the injury location. A number of alternative biomarkers to serum creatinine have been identified in animal models, most of which translate into the clinic. These markers are unique to specific regions of the nephron due to their different mechanistic responses to kidney insult (Zhang and Parikh 2019).

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

One of the most widely researched of these proteins is Neutrophil gelatinase-associated lipocalin (NGAL). NGAL is a glycoprotein bound to metalloproteinase-9 in neutrophils and is part of the lipocalin family, involved in the transport of hydrophilic compounds and maintaining cellular homeostasis (Flower 1996). NGAL is expressed in multiple tissues including the lung, gastrointestinal tract, liver and kidney; and is induced in epithelial cells in response to injury or inflammation (Zhang and Parikh 2019). NGAL has been shown to inhibit bacterial growth by binding to bacterial siderophores, and defends against pathogens by sequestering iron. In animal studies, NGAL exhibited a 10-fold increase in expression in murine kidney cells following viral infection; demonstrating its role within the immune system (Hraba-Renevey et al. 1989). Genetic profiling studies in rodents identified NGAL as one of the most upregulated genes in the kidney after tubular injury, especially in the nephrons (Supavekin et al. 2003).

NGAL has been studied in both the blood and urine and it was shown that the urinary NGAL is more predictive of kidney injury, therefore this is less useful in animal models, as routine monitoring is not practical. In order to obtain a urine sample in animals, they have to be transferred to specific urinary collection cages and house singularly. Removing an animal from their home cage causes stress and needs to be limited as much as possible, therefore any additional procedures should be considered carefully.

Kidney Injury Molecule-1 (KIM-1)

Kidney Injury Molecule-1 (KIM-1), also known as HAVcr-1 and TIM-1, is a type one transmembrane glycoprotein that is part of the T-cell immunoglobulin and mucin domain family. It is primarily expressed in the lymphocytes and epithelial cells (Karmakova et al. 2021). KIM-1 expression is ten times greater in the kidney when compared to other tissues, specifically in the proximal tubular cells (The Human Protein Atlas n.a.). Many studies looking at AKI have shown that KIM-1 expression on the surface of the epithelial cells in the renal proximal tubules, is induced by ischemia and toxic insult (Ichimura et al. 2004). The release of KIM-1 is thought to be an adaptive response and reparation of damage to the tubules following injury (Zhang et al. 2008), therefore in healthy kidneys only trace amounts of KIM-1 are present. In injured kidneys, there is a considerable increase in KIM-1 in the urine and blood. There is a direct correlation between the extent of damage and levels of KIM-1 in the blood (Bonventre 2009).

According to a recent meta-analysis examining the results of clinical investigations conducted between 2008 and 2013, sensitivity and specificity of urinary KIM-1 as a predictor of AKI were 81.8 and 83.8%, respectively (Shao et al. 2014). KIM-1 has been demonstrated to be a highly specific marker of kidney injury in animal models, and has shown to be translatable across species (Sabbisetti et al. 2014; Vaidya et al. 2006). Urinary and serum KIM-1 levels serve as a non-invasive, rapid and sensitive method to detect early kidney injury in both non-clinical and clinical studies. It has the potential for high-throughput screening of compounds in preclinical drug development and for risk-benefit profiling of pharmaceutical agents (Vaidya et al. 2006).

Current Research

Researchers have identified alternative biomarkers detectable in serum that provide additional insights into kidney function beyond traditional markers. These include Cystatin C, Fibroblast growth factor 23 (FGF-23), beta-2 microglobulin, and troponins, which are currently under investigation (Chen et al. 2020; Mizdrak et al. 2022). Cystatin C is widely recognised as a sensitive indicator of renal function, offering valuable insights into the kidney's filtration efficiency (Shlipak et al. 2021). Furthermore, FGF-23 is intricately linked to phosphate and calcium metabolism, furnishing crucial information about the mineral balance concerning renal health (Khanijou et al. 2022). Additionally, beta-2 microglobulin functions as an indicator of renal dysfunction, reflecting disruptions in the normal functioning of the kidneys (Mizdrak et al. 2022).

It is noteworthy that troponins, typically associated with cardiac health, may also exhibit elevation in cases of AKI, as emphasized in the comprehensive study by Rangaswami et al (Rangaswami et al. 2019). Moreover, the exploration of practical alternatives for collecting routine urine samples has emerged as a significant and evolving area of interest in the realm of nephrology research (Cheng et al. 2022; De Baetselier et al. 2019). The development of methods that are not only less invasive but also more convenient and readily accepted by patients holds the potential to substantially improve the feasibility and regularity of monitoring renal biomarkers (Kukkar, Chhillar, and Kim 2023). In the pursuit of more patient-friendly approaches, researchers are actively investigating non-invasive methods, such as wearable devices for continuous monitoring, as well as the creation of user-friendly, at-home testing kits (Sequeira-Antunes and Ferreira 2023). These advancements aim to revolutionise the landscape of urine sample collection, promoting increased patient engagement and compliance in renal health monitoring.

Whilst helpful in the clinical setting, these advances have not translated into animal models yet.

Surrogate Endpoints

The role of a regulatory agency is to ensure that all medicines have been shown to be safe and effective; and part of that responsibility is oversight of clinical trials. Clinical trial endpoints measure the outcome of a trial.

An investigator can choose an endpoint that directly measures the clinical outcome they want to evaluate. Alternatively, they can choose an endpoint that is a 'surrogate' for the outcome they wish to measure. Some surrogate endpoints are biomarkers, defined as a characteristic that is measured as an indicator of normal biological processes, pathological processes, or responses to an exposure. Biomarkers may be used for several different purposes such as identifying patients for clinical trial enrolment, monitoring safety or efficacy. KIM-1 and NGAL would be classed as surrogate endpoints. The Food and Drug Administration (FDA) has a Biomarker Qualification Program that was established to develop biomarkers that aid in the drug development process. In this program, companies request regulatory qualification of a biomarker for use within their drug development program (FDA - Surrogate Endpoint Resources for Drug and Biologic Development 2018).

Surrogate endpoints that are used in clinical trials can be submitted to support either traditional or accelerated approval of drugs and biologics. Under Section 507 of the Federal Food, Drug, and Cosmetic Act, as amended by the 21st Century Cures Act, the FDA must make public a list of "surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or biological product." At present, KIM-1 and NGAL are not on the Table of Surrogate Endpoints (FDA - Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure 2022). The FDA requires developers to seek advice from the relevant Center for Biologics Evaluation and Research (CBER) or Center for Drug Evaluation and Research (CDER) division of such novel endpoints early in development by scheduling a Prescription Drug User Fee Act (PDUFA) VI Type C meeting to discuss the use of the surrogate endpoint in their planned clinical trials. The acceptability of a surrogate endpoint for an individual drug or biologic development program will be determined on a case by case basis.

Regulatory Opinions & Approvals

However, in 2007, a submission was made for the approval of seven novel kidney biomarkers for use in preclinical models of nephrotoxicity by the Predictive Safety Testing Consortium's (PSTC) Nephrotoxicity Working Group; these include KIM-1, albumin, total protein, cystatin C, clusterin, trefoil factor 3, and urine alpha1-microglobulin (α1M).

Following a lengthy approval process, in 2010, the FDA, European Medicines Agency (EMA) and Japanese counterparts, collaboratively qualified this panel of urinary biomarkers of kidney injury for limited use in nonclinical and clinical drug development to help guide safety assessments. The limitations set by the agencies include that the novel biomarkers must be used voluntarily and in conjunction with the standard biomarkers and histopathology; and developers must establish prespecified cutoff values within a clinical setting (Dieterle et al. 2010).

Following the approval of the PSTC submission, the Health and Environmental Sciences Institute (HESI) submitted an application to the Committee for Medicinal Products for Human Use (CHMP) for approval of further novel kidney biomarkers, urinary clusterin and renal papillary antigen (RPA-1) and urinary alpha-glutathione S-transferase (α-GST). The CHMP qualification opinion was that the findings within the HESI submission 'increase the level of evidence supporting the use of Urinary Clusterin' and that it 'can be included along with traditional clinical chemistry markers and histopathology in Good Laboratory Practice (GLP) toxicology studies which are used to support renal safety in clinical trials. In addition, the CHMP stated that the data indicates that urinary RPA-1 may be used to detect acute drug-induced renal tubular alterations, particularly in the collecting duct, and can be included along with standard clinical chemistry markers and histopathology in GLP toxicology studies. The CHMP support the use of urinary α-GST in detecting proximal tubule injury in male rats.

However, the conflicting effects of proximal and collecting duct injury on α-GST levels created uncertainty about its usefulness (CHMP Opinion 2010). The process of obtaining a CHMP opinion has previously been described by Scendea in 'Novel Methodologies for Modern Drug Development'.

Conclusion

The regulators are open to and support the use of novel biomarkers, however more evidence is needed before they become a standard test in non-clinical and clinical studies. Without developers adopting the biomarkers, and investing in them, the progression into mainstream toxicology will be slow. Contract Research Organisations (CROs) have analytical methods validated for many of the novel biomarkers and are able to conduct non-clinical studies to meet GLP requirements. These markers are translatable across species and into the clinic, and if they reduce the level of drug failure, then developers should consider using them in their drug programmes.

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