Journal of Pharmacological and Toxicological Methods xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

Renal studies in safety pharmacology and toxicology: A survey conducted in the top 15 pharmaceutical companies

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ARTICLE INFO

Available online xxxx

Keywords:
Safety pharmacology
ICH S7A
Kidney
DIKI biomarkers
Strategy

ABSTRACT

Introduction: With the recent development of more sensitive biomarkers to assess kidney injury preclinically, a survey was designed i) to investigate what strategies are used to investigate renal toxicity in both ICH S7A compliant Safety Pharmacology (SP) studies after a single dose of a compound and within repeat-dose toxicity studies by large pharmaceutical companies today; ii) to understand whether renal SP studies have impact or utility in drug development and/or if it may be more appropriate to assess renal effects after multiple doses of compounds; iii) to ascertain how much mechanistic work is performed by the top 15 largest pharmaceutical companies (as determined by R&D revenue size); iv) to gain an insight into the impact of the validation of DIKI biomarkers and their introduction in the safety evaluation paradigm; and v) to understand the impact of renal/urinary safety study data on progression of projects. **Methods:** Two short anonymous surveys were submitted to SP leaders of the top 15 pharmaceutical companies, as defined by 2012 R&D portfolio size. Fourteen multiple choice questions were designed to explore the strategies used to investigate renal effects in both ICH S7A compliant SP studies and within toxicology studies. **Results:** A 67% and 60% response rate was obtained in the first and second surveys, respectively. Nine out of ten respondent companies conduct renal excretory measurements (eg. urine analysis) in toxicology studies whereas only five out of ten conduct specific renal SP studies; and all of those 5 also conduct the renal excretory measurements in toxicology studies. These companies measure and/or calculate a variety of parameters as part of these studies, and also on a case by case basis include regulatory qualified and non-qualified DIKI biomarkers. Finally, only one company has used renal/urinary functional data alone to stop a project, whereas the majority of respondents combine renal data with other target organ assessments to form an integrated decision-making set. **Conclusion:** These short surveys highlighted areas of similarity: a) urinary measurements are most commonly taken on repeat-dose toxicity studies, and b) renal SP studies are less often utilised. The two major differences are a) lack of consistent use of DIKI biomarkers in urinary safety studies and b) the way large pharmaceutical companies assess renal function. Finally, suggestions were made to improve the safety assessment methods for determining the safety of compounds with potential renal liability.

Abbreviations: α-GST, alpha-glutathione S-transferase; B2M, beta-2 microglobulin; BUN, blood urea nitrogen; CROs, contract research organisations; Cr, creatinine; CysC, cystatin C; DIKI, drug-induced kidney-injury; EFPIA, European Federation of Pharmaceutical Industries and Associations; EMA, European medicines agency; ERBF, effective renal blood flow; FDA, food and drug administration; GFR, glomerular filtration rate; GLP, good laboratory practice; ICH, International Conference on Harmonisation; IND, Investigational New Drug application; KIM-1, kidney injury molecule-1; NAG, N-acetyl Glucosaminidase; NCE, novel chemical entity; NGAL, neutrophils gelatinase-associated lipocalin; NHP, non-human primate; PAH, para-aminohippurate; PMDA, Pharmaceuticals and Medical Devices Agency; PSTC, Predictive Safety Testing Consortium; R&D, Research & Development; RPA-1, renal papillary antigen-1; SAFE-T, IMI Safer and Faster Evidence Based Translation; SCr, serum creatinine; SP, safety pharmacology; TFF-3, trefoil factor-3; uTP, urinary total protein.

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http://dx.doi.org/10.1016/j.vascn.2015.01.004
1056-8719/

1. Introduction

The kidney is a complex and crucial excretory organ that plays an important role in numerous regulatory processes that include fluid and electrolyte balance (ultrafiltration, reabsorption and secretion), control of blood pressure and volume, acid-base balance, removal of waste products and endocrine function (Stockham & Scott, 2008). The kidneys receive 25% of cardiac output and filter large volumes of plasma and are key contributor to drug disposition, metabolism and excretion (Choudhury & Ahmed, 2006). It is not surprising therefore that drug-induced kidney injury (DIKI) is associated with significant discontinuation in pre-clinical and clinical drug development (Garrett & Workman, 1999; Kola & Landis, 2004; Lesco & Atkinson, 2001; Liano & Pascual, 1996; Mehta et al., 2004; Redfern et al., 2010). The mechanisms by which drugs produce acute and/or chronic kidney injury are poorly understood and currently histopathology is considered by many to be the 'gold standard' by which DIKI is established.

The nonclinical safety study recommendations for the marketing approval of a pharmaceutical usually include safety pharmacology (SP) studies and repeat dose toxicity studies, amongst other study types, and these are covered by the International Conference on Harmonisation (ICH) S7A (Anon, 2001) and ICH M3(R2) (Anon, 2009) guidelines, respectively. Under ICH S7A, the assessment of renal function is considered as supplementary and therefore might not be performed by all sponsors. The ICH S7A guidance states *"urinary volume, specific gravity, osmolarity, pH, fluid/electrolyte balance, proteins, cytology, and blood chemistry determinations such as blood urea nitrogen, creatinine and plasma proteins"* (Anon, 2001) can be used to assess drug effect on renal function; such parameters are typically measured in a study consisting in a single dose administration of a test compound to conscious animals with the compound at levels up to the maximum tolerated dose. Under the ICH M3(R2) guidance, there is reference to routine inclusion of serum creatinine (SCr) and blood urea nitrogen (BUN) in clinical pathology/biochemistry panels in non-clinical safety studies supporting clinical trials (Anon, 2012) in particular the 28 days ('one month') pivotal rodent and non-rodent toxicology studies. Such parameters can be helpful to assess functional consequences of histopathological changes (or vice versa), and can be informative for clinical safety monitoring.

Over recent years, seven novel urinary biomarkers have emerged and qualified for use in rat studies (Dieterle, Perentes, et al., 2010; Ferguson, Vaidya, & Bonventre, 2008; Ozer et al., 2010; Rouse et al., 2011; Sasaki et al., 2011; Yu, Jin, Holder, Ozer, & Villarreal, 2010). Their appearance/excretion in urine offers the promise of greater sensitivity over functional kidney biomarkers, and greater utility to detect early stages of drug-induced kidney stress, before histopathologically-defined DIKI has occurred.

Therefore, with the recent development of the tools to assess kidney injury preclinically this survey was designed i) to investigate what strategies are used to investigate renal toxicity in both ICH S7A compliant SP studies after a single dose of a compound and within repeat-dose toxicity studies by large pharmaceutical companies today; ii) to understand whether renal SP studies have impact or utility in drug development and/or if it may be more appropriate to assess renal effects after multiple doses of compounds; iii) to ascertain how much mechanistic work is performed by the top 15 largest pharmaceutical companies (as determined by R&D revenue size); iv) to get an appreciation of the impact of the validation of DIKI biomarkers and their introduction in the safety evaluation paradigm; and v) to understand the impact of renal/urinary safety study data on progression of projects.

2. Method

Safety pharmacology leaders (e.g., heads of SP departments) within the top 15 pharmaceutical companies, as defined by R&D revenue figures in 2012 (Table 1, Pharmaprojects®, 2012 Citeline), were invited to participate in two short anonymous surveys designed to investigate what strategies are used to study renal effects of candidate drugs in both ICH S7A compliant SP studies and within repeat-dose toxicology studies. The surveys were created using Survey Monkey™. There were a total of 14 questions to answer across the two surveys, each of which was set out in a multiple choice format with the option to select multiple answers for some questions (i.e., questions 1–6, 8 and 10–12) furthermore some questions had a separate field for free text (i.e., questions 4, 6–8 and 12; Table 2). This enabled individuals to add clarity to any answer provided. Participants received the questions via e-mail with a link to the website and were asked to complete the surveys within one month of receiving the invitations in October 2013 and June 2014.

Table 1
List of the top 15 pharmaceutical companies as defined by R&D portfolio size in 2012. Pharmaprojects®, 2012 Citeline.

Company	Ranking	No. of R&D products 2012	No. of originated products
GlaxoSmithKline	1	257	147
Pfizer	2	225	152
Merck & Co	3	223	150
Novartis	4	218	151
Hoffmann-La Roche	5	198	147
Sanofi	6	178	90
Takeda	7	149	80
Bristol-Myers Squibb	8	146	113
AstraZeneca	9	144	85
Johnson & Johnson	10	142	85
Eli Lilly & Co.	11	125	102
Astellas	12	104	66
Abbott Laboratories	13	96	67
Amgen	14	91	79
Bayer	15	91	62

Once the deadline for survey completion had been reached, the responses were collated and reviewed. The results were shared during a teleconference, with participants contributing to the discussion and interpretation. The participants unanimously agreed to release the results of the survey in the public domain.

3. Results

Ten out of the 15 invited pharmaceutical companies participated in the first survey and eight participated in the second survey (67 and 53%, respectively). The first question explored the types of renal studies that organisations conduct as part of the submitted regulatory package (Fig. 1). There were ten respondents to this question. Five companies (50%) conduct renal SP studies including excretory functions, but one of the respondents commented that they only run renal SP studies that include renal excretory function measurement and renal hemodynamic parameters when the compound being tested is thought to have a renal liability, and then studies are only performed in larger species such as dog or non-human primate (NHP). All of the five respondents that conduct renal SP studies also investigate renal excretory measurements after repeated doses of a compound (urinary collection on repeat dose toxicology studies). Nine companies (90%) conduct renal excretory measurements in toxicity studies. Two companies (20%) responded that they do not conduct any renal or urinary supplemental SP studies or renal endpoints in toxicology studies as part of their regulatory packages, however of these two, one respondent also stated that they can perform renal SP studies and renal excretory measurements in toxicology studies, so it has to be inferred that although they do have the capability to run these study-types they do not include renal SP studies as part of their standard regulatory package.

The second survey had eight respondents, who all stated that they conduct renal/urinary studies, thus inferring that the two respondents from the original survey who stated that they did not perform any

Please cite this article as: Benjamin, A., et al., Renal studies in safety pharmacology and toxicology: A survey conducted in the top 15 pharmaceutical companies, *Journal of Pharmacological and Toxicological Methods* (2015), http://dx.doi.org/10.1016/j.vascn.2015.01.004