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Target organ profiles in toxicity studies supporting human dosing: An assessment of recovery and chronic dosing

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ABSTRACT

We have previously reported the profile of toxic effects with respect to target organs (defined as organs showing histopathological changes) observed in rodent and non-rodent toxicity studies conducted prior to first time in man (FTIM) for 77 AstraZeneca candidate drugs (CDs) across a range of therapy areas. The main objectives of the current study were twofold; to determine which target organs observed in the FTIM studies recovered after a dose free recovery period and to determine which additional target organs were observed in subsequent chronic ($\geqslant$3 month) studies required to support longer term clinical dosing. The analysis showed that $\geqslant$86% of findings in studies supporting FTIM either fully or partially resolved at the end of the recovery period, with profiles of recovery that were similar whether the CD progressed into man or not and across different therapy areas. Compared to observations in FTIM studies, chronic studies identified toxicities in an additional 39% of target organs. Overall these data demonstrate that chronic studies in both rodents and non-rodents provide valuable information for the risk assessment for longer term dosing in humans. In addition, the high levels of recovery demonstrated in this analysis suggest that inclusion of recovery assessments on FTIM studies should be on a case-by-case basis driven by a positive indication of need. This is in line with ICH non-clinical guidance that states that reversibility of severe nonclinical toxicities of potential clinic relevance should be assessed 'when appropriate', but that the evaluation can be based on a study of reversibility or on a scientific assessment.

1. Introduction

Rodent and non-rodent repeat dose toxicology studies are used to support human clinical trials to assess, limit and manage risk to human volunteers or patients and are a regulatory requirement. These studies are aimed at characterising target organ toxicity related to dose and exposure, informing clinicians of appropriate monitoring and also the potential for reversibility after a dose free period.

Nonclinical safety packages are designed in a step-wise process in accordance with regulatory guidance; in general for small molecules nonclinical toxicology studies of up to one month duration are used to support single or multiple dosing for up to a similar duration in Phase I clinical trials in human volunteers or patients (ICH M3(R2), 2009). As candidate drugs (CDs) progress to later stage Phase II and Phase III clinical trials, greater numbers of patients can be exposed for a longer duration in order to give a fuller assessment of efficacy and tolerability. These clinical trials are supported by chronic repeat dose studies of at least equivalent duration. For example, 6 month rodent and 9 month non-rodent studies would generally support dosing for longer than 6 months in clinical trials and are required for registration (ICH M3(R2), 2009). One exception to this is for clinical trials in advanced cancer patients, where dosing can continue beyond the duration of toxicology cover where there is evidence of benefit to the patient and an acceptable safety profile for the therapeutic indication (ICH S9, 2009). In the advanced cancer setting, results from repeat dose studies of up to 3 month duration are generally required prior to initiating Phase III studies and are usually considered sufficient to support a marketing application (ICH S9, 2009).

Regulatory guidance recommends that recovery from pharmacological and toxicological effects that could have potential adverse clinical impact should be assessed as part of the nonclinical safety evaluation (ICH M3(R2), 2009; ICH S6(R1), 2011; ICH S9, 2009). Consequently, it is a common practice to include recovery groups within repeat dose toxicity studies, although the optimum timing for this within the toxicology programme can vary for a variety of reasons (Pandher et al., 2012). AstraZeneca usually includes an assessment of reversibility within the pivotal studies supporting the first clinical trials in humans (FTIM) on the basis that these studies tend to use higher dose levels than could be tolerated for chronic

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administration. In addition, in a study of concordance between animal and human toxicities (Olson et al., 2000) it was shown that animal studies of up to 1 month duration detected 94% of toxicities associated with the test article when human toxicity was observed. Thus assessing recovery on the 1 month studies can provide reasonable confidence that most potential toxicities for which recovery might need to be demonstrated have already been identified (Pandher et al., 2012). Alternatively, there may be advantages to assessing reversibility in chronic studies given that new findings can be seen on extended duration of dosing (Pandher et al., 2012). Consequently, there are differences between pharmaceutical companies in routine practice for inclusion of an assessment of reversibility in the nonclinical studies (Sparrow et al., 2011), with some companies assessing recovery in the FTIM enabling studies, others in the chronic studies and others in both. More recently, the option of a scientific assessment of the likelihood of recovery rather than a study has been discussed (ICM M3 (R2) Q&A, 2013). This scientific assessment could be based on the extent and severity of the lesion, the regenerative capacity of the organ and knowledge of other drugs causing the effect.

We have previously reported an analysis of target organ profiles in FTIM toxicity studies for a set of 77 AstraZeneca candidate drugs (CDs) across a range of therapy areas (cardiovascular/gastrointestinal: CVGI; CNS/Pain: CNSP; respiratory and inflammation: RITA; oncology/infection: OI) (Horner et al., 2013). Target organ toxicity was primarily defined as compound-related histopathological changes. The analysis demonstrated the liver as the most common target organ in rodents and non-rodents in line with previous publications (Baldrick, 2008; Ballet, 1997; Greaves et al., 2004; Heywood, 1981) and also clearly demonstrated the benefit of using two species for assessing safety; changes commonly seen only in non-rodents were in target organs of high relevance for human risk assessment such as the liver, male reproductive tissues and CNS (Horner et al., 2013).

Here, we present a further analysis of target organs to assess which demonstrated reversibility after a dose free period, whether the toxicity profile differed by therapy area and whether the toxicity profile differed for CDs that progressed into man and those that did not. We also report which additional target organs (defined as target organs not previously noted in the FTIM enabling studies) were observed in the chronic studies that were conducted for a subset of these compounds.

2. Materials and methods

We have previously reported an analysis of target organ toxicities for a total of 155 GLP rodent and non-rodent toxicity studies, conducted to support 77 candidate drugs (CDs) intended for first time in man (FTIM) dosing (Horner et al., 2013). Of these 77 potential CDs, 68 CDs had studies in rodents (67 studies) and non-rodents (60 studies) that included an assessment of recovery. For these 68 CDs, the profile of target organ toxicities following completion of dosing and the recovery of these findings after cessation of dosing were compared. Of these 68 CDs, 53 progressed into FTIM clinical trials, whilst the remaining 15 compounds were not progressed further. Additionally, for a total of 42 out of the 77 CDs previously analysed, chronic studies of $\geqslant$3 month duration were conducted in rodents (47 studies) and non-rodents (65 studies). For these 42 CDs, we determined the incidence of new target organ toxicities seen on chronic dosing compared to that seen in the studies supporting FTIM.

Target organ toxicity was primarily defined as compound-related histopathological changes; other changes such as altered organ weights or clinical pathology findings, in the absence of associated histopathological changes, were considered not to be evidence of target organ toxicity for the purpose of this analysis. Single or multiple findings within a tissue, or the severity of the findings, were not discriminated in the analysis. In the analysis, the term recovery encompassed full or partial recovery, where full refers to a pathological lesion returning to within the normal range and partial refers to a lesion showing a trend towards reversibility by the end of a recovery period, but not yet within the normal range. The absence of recovery was defined as no evidence of recovery for the lesion. Differences between the recovery profiles for the 53 CDs that progressed into early clinical trials in humans versus the 15 CDs that did not progress were also assessed. New findings in chronic studies were defined as toxicities in target organs not previously noted in the studies supporting FTIM, rather than an exacerbation of existing toxicities or additional lesions noted in organs already defined as a target for that CD. The frequency of new findings in individual target organs in the chronic studies for a particular CD was assessed collectively across all studies in the rodent and non-rodent.

For the CDs that had a recovery period included for one or both species prior to FTIM, recovery was always assessed in the high dose group and was usually of 4 weeks duration with the following exceptions: 14–21 day recovery was conducted in one or both species for 2 CDs and 6–15 week recovery was included in one or both species for 4 CDs. The number of recovery animals on study varied but the majority (>95%) used 3 per sex for the non-rodents and 5 per sex for the rodents. All studies were conducted between 1998 and 2010 (95% of them between 2003 and 2010). A summary of included studies is shown in Table 1.

The rodent and non-rodent species used in the majority of studies were rats (Wistar-derived) and beagle dogs, respectively (Table 1), with mice, cynomolgus monkeys or marmosets used in the remaining studies. The majority of the studies used the oral route for compound administration, except for 2 compounds for which inhalation studies were conducted. To enable a full evaluation of potential effects on reproductive organs, in particular to assess effects on spermatogenesis, the animals in the majority of FTIM studies commenced dosing at an age that ensured that they were sexually mature at study termination, with the following exception: the 6 studies in cynomolgus monkeys used sexually immature animals. The dosing route, age and species are detailed in Table 1, but were not discriminated in the analysis.

The dose levels selected for use on studies supporting FTIM were based on data from appropriate dose range finding (DRF) studies. The highest dose levels tested in the GLP studies were either the maximum tolerated dose (MTD), the maximum feasible dose (MFD) based on solubility, dosing formulation or drug delivery system, or an acceptable limit dose, as defined within the regulatory guidance (ICH M3(R2), 2009).

For the 42 CDs for which chronic ($\geqslant$3 month) studies were conducted in one or both species, the majority of studies were of either 3 or 6 months duration (32 CDs), although studies of 7–12 months duration were used for a number of CDs. For some CDs, more than one chronic study was conducted and for those CDs the target organ toxicity profile across all chronic studies conducted was combined. For 3 CDs, chronic studies were conducted in both dogs and primates and for these CDs the target organ toxicity profile across both non-rodent species was combined. The dose levels selected for use in these studies were based on appropriate data from the previous studies, but were generally similar to or lower than those selected for the studies supporting FTIM. All studies were conducted between 1997 and 2011 (82% of them between 2003 and 2011) A summary of included study details is shown in Table 2.

As in our previous analysis (Horner et al., 2013) the parameters typically measured in these studies included clinical observations, body weight, food/water consumption, ophthalmoscopy, haematology (including coagulation in non-rodents), clinical chemistry,