Early QT assessment – how can our confidence in the data be improved?

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Exposure–response (ER) analysis has emerged as an important tool to interpret QT data from thorough QT (TQT) studies and allows the prediction of effects in the targeted patient population. Recently, ER analysis has also been applied to data from early clinical pharmacology studies, such as single and multiple ascending dose studies, in which high plasma concentrations are often achieved. In line with this, there is an on-going discussion between sponsors, academicians and regulators on whether ‘early QT assessment’ can provide sufficiently high confidence in assessment of QT prolongation to replace the TQT study. In this article, we discuss how QT assessment can be applied to early clinical studies (‘early QT assessment’) and what we believe is needed to achieve the same high confidence in the data as we currently obtain from data from the TQT study. The power to exclude a QT_c effect exceeding 10 ms in small sample sizes using ER analysis will be discussed and compared with time-matched analysis, as described in the ICH E14 guidance. Two examples of early QT assessment are shared; one negative and one positive, and the challenge in terms of demonstrating assay sensitivity in the absence of a pharmacological positive control will be discussed. Finally, we describe a recent research proposal, which may generate data to support the replacement of the TQT study with data from QT assessment in early phase 1 studies.

Introduction

Since the adoption in May 2005 of the ICH E14 guidelines ‘The Clinical Evaluation of QT/QT_c Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs’ [1], the ‘thorough QT/QT_c study’ has been a key component for the clinical assessment of whether a drug has the potential to prolong the QT interval. The thorough QT (TQT) study was initially perceived as a challenge for industry [2], but with increasing experience and through a continued dialogue between regulators and sponsors, these studies can today be conducted more effectively and with high confidence in the data generated. It has also become clear that there is an expectation from regulators that a TQT study should be conducted for all small molecules in development, as well as for polypeptides. For large, targeted molecules, there is no clear requirement for a TQT study, but some degree of ECG assessment is expected [3], whereas drugs that cannot be safely administered to healthy volunteers (e.g. oncology drugs) need to be evalu-

ated in patients [4]. The TQT study is generally performed in healthy volunteers and is designed to demonstrate that a drug-induced effect on the heart rate corrected QT interval (QT_c) is less than 10 ms. In addition to the investigational compound, the study should also include a negative (placebo) and a positive control, in most cases 400 mg oral moxifloxacin [5]. ECGs are recorded serially at baseline and post-dosing, in most cases by the use of continuous 12-lead recording devices (Holter monitors), from which ECGs are extracted at protocol-specified time points in a schedule designed to capture the anticipated peak plasma concentrations of the drug and of the positive control. Given the variability of the QT measurement with standard techniques and assuming a small underlying effect of the drug of around 3 ms, sample sizes of around 40 to 80 subjects for a crossover design and four times as many in a four group parallel designed study are often used [6, 7].

The TQT study has as its sole objective to rule out a small drug-induced effect on the QT interval and other ECG intervals. A long-standing criticism of this approach has

been that it is not effective from a resource management perspective and it has been argued that the TQT study may not be cost-effective [8]. A more efficient approach would be to collect the same quality QT data in clinical studies that are standard components of the clinical development programme, thereby, reducing the number of clinical studies needed during development without compromising the evaluation of this important safety biomarker. The studies that are likely to be most suitable for the purpose of 'early QT assessment' are the first time in man single ascending dose (SAD) and multiple ascending (MAD) studies in healthy volunteers. These studies have as their main objectives tolerability/safety and pharmacokinetics of the new drug and doses up to the maximum tolerated dose (MTD) are often used. This means that these studies often achieve plasma concentrations above those that will be seen during the later stages of development.

The role of the exposure–response relationship

Even before the implementation of ICH E14 guidelines in 2005, modelling the exposure–response (ER) relationship has played an important role in characterizing QT prolonging effects during clinical development and regulatory review of drugs such as anti-arrhythmic agents [9–14]. In the TQT study the ER relationship allows for the characterization of the QT_c effects over the observed range of drug concentrations obtained by administering therapeutic and supratherapeutic doses. Consequently, the role of the ER relationship for non-cardiac drugs has expanded to include:

- Project QT_c prolongation with doses and formulations not directly evaluated in the TQT study,
- Project QT_c prolongation in specific populations that have increased exposure to a drug due to their intrinsic and extrinsic factors and
- Clarify ambiguous results in the TQT study.

In the TQT study, ER analysis is performed by pooling data across individuals in the placebo and dose groups and applying a mixed effect model that best describes the relationship. To avoid complex models accounting for diurnal variation in the QT_c interval as proposed by Piotrovsky [15], the model can be simplified by using the baseline-corrected QT_c or placebo- and baseline-corrected QT_c interval depending if the data were obtained from parallel or crossover studies, respectively [16, 17]. For non-cardiac drugs, the relationship is usually described by linear models using either observed concentrations or logarithmic-transformed concentrations. There are, however, few cases of non-linear relationships and delayed effects requiring more sophisticated pharmacokinetic-pharmacodynamic modelling approaches [18, 19]. To

increase the confidence in the modelling approach, it is important that bias introduced by the analyst is minimized. This can be achieved by pre-specifying the criteria used for model selection and evaluation.

The same modelling approach can be applied to data obtained in SAD and MAD studies. The time-matched concentration and baseline-corrected QT_c data can be pooled across the placebo and dose cohorts to assess the relationship. The precision in the concentration– QT_c relationship can be increased by using data obtained from a wide range of doses and minimizing the within-subject variability in QT_c interval (methods to decrease variability are discussed in later sections). The ER relationship can then be used to project the QT effects at doses to be used in subsequent clinical trials assessing efficacy and safety. Two examples of the use of the concentration– QT_c relationship in SAD and MAD studies are provided below.

Early QT assessment as applied on SAD/MAD studies

The first example is a first time in man, SAD study, which was conducted at one study site with large experience of QT assessment studies. It was a typically designed SAD study with six subjects on active treatment and two on placebo in each dosing group. In total, seven doses were studied with a 120-fold range between the lowest and the highest tested dose, resulting in 42 subjects on active treatment and 14 on placebo. Continuous 12-lead ECGs were recorded and ECGs were extracted at prespecified time points at which subjects had been resting supine for at least 10 min at baseline (predose) and serially at nine time points post-dosing up to 24 h. Blood draws for pharmacokinetic sampling were performed after each time window for ECG extraction. Ten replicate ECGs were extracted from a 5 min time window immediately preceding the protocol-specified time point. QT intervals were measured using a high precision QT measurement technique on all beats from the 10 replicates [20]. When exploring the relationship between plasma concentrations and the placebo-adjusted, change from baseline Fridericia corrected QT_c ($\Delta\Delta QT_c F$), a linear ER model with an intercept fitted the data best, based on Akaike information criteria and visual inspection of goodness of fit plots [21]. Figure 1 shows the model based prediction of $\Delta\Delta QT_c$ across the plasma concentration range observed in the study with model based estimates (black line) and two-sided 90% confidence interval (CI, grey shaded area) of the QT_c effect. The slope of the ER relationship was slightly negative and not statistically significant (-0.00026 ms per $ng\ ml^{-1}$; 90% CI $-0.00063, 0.00010$). The upper bound of the CI was clearly below 10 ms at all concentrations observed in the study, meaning that the drug did not cause QT prolongation exceeding the threshold of concern. The average variability of the QT estimate over all time points, measured as

Figure 1

The model based estimate (solid black line) with 90% CI (grey shaded area) is shown across the range of plasma concentrations observed in the SAD study. The horizontal red line shows the plasma concentration divided into deciles and the vertical, red bars show the observed $\Delta\Delta\text{QT}_c\text{F}$ with 90% CI within each plasma concentration decile (plotted at the median concentration of each decile). As shown by the upper bound of the 90% CI, a drug-induced effect on the QT_c interval exceeding 10 ms could be excluded at all observed plasma concentrations. —■—, median concentration quantiles; —, mean (90% CI) predicted QT_cF prolongation

the between-subject standard deviation of change from baseline QT_cF ($\Delta\text{QT}_c\text{F}$), was 6 ms. The study illustrates that ER modelling applied to data derived from a typical SAD study with a carefully designed ECG schedule can, despite the small sample size in each dose group, achieve sufficient power to exclude a QT_c effect exceeding the regulatory concern, i.e. 10 ms.

The second example is a multiple ascending dose study with an investigational compound administered at three dose levels for 7 days to healthy volunteers. Based on an earlier clinical 'signal', the design was to some extent adapted and subjects received either placebo or two dose levels of the drug in a fixed sequence, in all resulting in eight subjects on the lowest dose and 16 subjects on the two higher doses and on placebo. ECGs were extracted in 10 replicates from continuous 12-lead recordings at baseline (pre-dose) on day 1 and at seven time points after the morning dose on day 7, designed to capture the anticipated peak plasma concentration of the drug and several time points with substantially lower plasma concentrations. ECG intervals were measured using the methodology outlined above and the achieved between-subject standard deviation of $\Delta\text{QT}_c\text{F}$ was 7 ms on active treatment and 8 ms on placebo. A linear ER model with intercept provided the best fit to the data using the same criteria as in the first example. A concentration-dependent effect of

the drug on $\Delta\Delta\text{QT}_c\text{F}$ was demonstrated with a statistically significant slope of 0.0185 ms per ng ml^{-1} (CI 0.014, 0.023, $P < 0.0001$, Figure 2). This means that for every 100 ng ml^{-1} increase in plasma concentration, the QT_c interval can be expected to increase by 1.9 (90% CI: ± 0.45) ms. The drug clearly has an effect on the QT_c interval and the upper bound of the CI by far exceeded 10 ms within the ranges of plasma concentrations observed in the study. In cases such as this, a similar approach as the one applied to data from TQT studies [17] [16] can be used to estimate the QT_c effect in patients with impaired clearance and high plasma concentrations of the drug. There seems to be little to gain in repeating the QT assessment with a thorough QT study, since the consequence for further development of the compound most likely will be the same: the QT_c effect must be further characterized in the targeted patient population. This example therefore illustrates how a QT_c effect can be detected using ER modelling and thereby potentially waive the need for a TQT study [22].

It should be acknowledged that the QT_c effect in the latter example was large and detection or exclusion of smaller effect levels will pose more of a challenge and will require a high precision of the QT estimate. In addition to the precision of the QT interval measurement itself [20], several components of the study conduct, which are routinely applied in TQT studies, have an impact on the

Figure 2

As demonstrated with an increase of approximately 1.85 ms (90% CI ± 0.45) per 100 ng ml⁻¹ increase in plasma concentration. At plasma concentrations around 1 $\mu\text{g ml}^{-1}$, the predicted QT_c effect is around 18 ms with an upper bound of the CI of 23 ms. ■, observed QT_cF (mean $\pm$ 90% CI); —, model predicted effect on QT_cF (mean $\pm$ 90% CI)

variability of the data [5]. Experimental conditions must be strictly standardized with regard to meal intake and composition and physical activity. At prespecified time points for ECG recording/extraction, subjects should be resting supine for at least 10 min in an undisturbed environment with no TV or videos available. The use of continuous 12-lead ECG recordings (Holters) is preferred as it allows extraction of replicate ECGs around prespecified time points with optimal signal-to-noise ratio. Replicate ECGs should be serially recorded at baseline and at several time points post-dosing to capture the anticipated peak plasma concentration and several time points thereafter, including those with low plasma concentrations, e.g. 24 h after dosing. Blood samples for PK analysis should always be paired with ECG recordings and should be done after the recording to avoid heart rate effects.

Comparing the power of exposure response and E14 time-matched analyses

The ICH E14 requests that data are analyzed in a so-called time-matched way, which means that a QT_c effect (meas-

ured as the placebo-adjusted change from baseline, $\Delta\Delta\text{QT}_c$) exceeding 10 ms must be excluded at each post-dosing time point without regard to plasma concentrations of the drug. As discussed above, assuming the use of standard techniques for QT measurements, the power of this statistical analysis is high if 40 to 60 subjects are included [23], but entirely insufficient at the sample sizes normally used in SAD/MAD studies (six to eight subjects per dose group). In the ER analysis, all observed QT_c intervals at given plasma concentrations of the drug are analyzed in one model and this approach is therefore considered to provide more power to detect or exclude an effect. In a simulation study based on moxifloxacin and placebo data from five crossover designed TQT studies, different underlying QT_c effect levels (no effect, 3 ms and 5 ms) were simulated and the power to exclude a QT_c effect was compared between the E14 time-matched (TM) analysis and ER analysis using 1000 and 3000 resamples of the data [24]. A negative study was concluded if the upper bound of the two-sided 90% CI was below 10 ms at the geometric mean peak plasma concentration. When a small underlying effect of 3 ms was simulated, ER provided 76 to 99% power to exclude a 10 ms effect with nine subjects, whereas the power of the TM approach was clearly lower

(26 to 67%). If no underlying effect (placebo) was simulated, the power of ER to exclude an effect above 10 ms was 92 to 100% with nine subjects and that of TM 43 to 87%. These numbers will differ depending on the data set and likely also on the ER model used, but illustrate that ER provides much higher power than the E14 TM approach, and can therefore more effectively be used in SAD/MAD studies of typical size.

Demonstration of assay sensitivity without using a pharmacological positive control

It seems unlikely, and undesirable, that the use of moxifloxacin or any other pharmacological positive control will become a standard element of SAD/MAD studies. At the same time, it must be acknowledged that the use of moxifloxacin as a positive control in TQT studies has been a key factor for achieving a high confidence in the study's ability to demonstrate the absence of a drug effect. If the QT_c response after 400 mg moxifloxacin meets prespecified criteria [25] and a drug effect above 10 ms can be excluded, then there is high confidence that this represents a true absence of a clinically concerning effect on cardiac repolarization. The key question is therefore whether the same level of assurance can be obtained through other methods. In our view, this can only be achieved by analysis of data from each study, as a concept with 'validated' study centres will not provide assurance that studies conducted some time apart will all have the same ability to exclude small QT effects based on various factors, such as staff turn-over, differences across study populations, or just variability of the data. Efforts in the direction of demonstrating that study-specific quality criteria may replace the positive control have been recently published [26]. In brief, the within- and between-subject variability across several, complete baseline days was assessed on data from TQT studies and the proposed analyses seem to enable the differentiation between studies of high and poor quality. Even though small changes related to diurnal variability is not the same as small drug-induced change, the analyses seem promising and efforts are on-going to explore whether they can be applied to SAD/MAD studies of standard design. Clearly, some way of demonstrating that a study reliably can detect a small QT prolongation, should there one exist, will be needed also for early QT assessment.

Can the early phase QT replace the TQT study?

More than 7 years after the implementation of the ICH E14 guidance in May 2005, several hundreds of TQT studies that basically follow the E14 guidance have been

performed and submitted to regulatory authorities. As an example, FDA's Interdisciplinary Review team for QT studies (IRT) has evaluated 288 (October 2012) TQT studies between 2005 and 2011. In about 5% of these, the assay sensitivity test with moxifloxacin failed [27] but for the majority of the studies, the confidence in the data is very high. Although it is difficult to prove, it is generally accepted that the TQT study has been very effective in terms protecting patients by identifying 'QT liability' for new drugs [22], with consequent regulatory actions (precautionary state QT assessment' is therefore challenging and will most likely include several steps. These steps will, in our view, include generating data to demonstrate that 'early QT assessment' can provide results with high confidence, that assay sensitivity can be demonstrated without the use of a pharmacological positive control, that results from ER analyses using predefined models can replace the E14 time-matched analysis and that standard SAD/MAD studies with tightly controlled experimental conditions and ECG methodologies can provide sufficiently precise QT estimates to allow exclusion of small drug-induced QT effects with the sample sizes normally used in these studies.

The ICH E14 definition of a negative TQT study is that the drug's effect on the QT_c interval should be smaller than 5 ms, as evidenced by the upper bound of the two-sided 90% CI of the placebo-adjusted change from baseline QT_c being lower than 10 ms. It is this 'threshold of concern' that the confidence that a drug with a negative TQT study truly is devoid of pro-arrhythmic propensity in patients, including those with risk factors, is based. The same threshold (exclusion of a 10 ms QT_c effect) has been applied when ER has been used to project whether a small QT_c effect will translate into a concerning effect level in patients with high exposures to the drug. Based on this experience, it seems highly unlikely that a different threshold will be widely accepted without substantial further advancement of our knowledge of the relationship between mild QT prolongation and its consequences in large populations. In our view, this will not happen in the foreseeable future. We therefore propose that the same threshold is used to define a negative result of early QT assessment based on ER analysis, i.e. the upper bound of the two-sided 90% CI of the QT_c estimate is lower than 10 ms at concentrations that are relevant in targeted patient population.

In order to gain confidence in the early QT assessment, more research is needed that can facilitate our understanding of the potential and limitations of applying ER analysis to QT data generated from SAD/MAD studies. Individual examples, as the two shown here, will always remain anecdotal and subject to selection bias. Instead of a tedious retrospective analysis of concordance between QT assessment in phase 1 and TQT studies, a research proposal presented by the QT group of the International Consortium for Innovation and Quality in Pharmaceutical Development [28] is interesting and may eventually generate

data to demonstrate the concordance between TQT studies and early QT assessment (personal communication, Dr Nenad Sarapa, formerly Clin Pharm, Roche). The proposal is to study prospectively a number of marketed drugs with a positive TQT study in a study design that would mimic the standard SAD/MAD study as closely as possible. The studies would be conducted in eight to 12 subjects in a carefully controlled experimental setting and with enhanced ECG monitoring, i.e. serial ECGs at baseline and post-dosing, paired with blood sampling of drug plasma concentrations. Data will be analyzed using an ER approach according to a prespecified statistical analysis plan, i.e. explored ER models and decision criteria for their selection will be prospectively defined. The proposal is under discussion and many details are still lacking. However, what is proposed at this stage is that a group of TQT study positive drugs, of which moxifloxacin may be one, will be selected to undergo the 'concordance test', with the primary objective of demonstrating that the rate of false negatives remains acceptably low, i.e. that TQT study positive drugs do not come out negative in the test. Stated differently, if all TQT study positive drugs also come out positive in the test, and assay sensitivity is demonstrated, the assumption is that this would provide evidence to support replacing the TQT study with early QT assessment. The project seems very promising and may be a significant step towards understanding to what extent QT assessment as part of standard SAD/MAD studies may generate data with the same level of confidence as the TQT study.

It seems very unlikely that the TQT study will disappear to be replaced with other forms of QT assessment over-night. It also seems unlikely that ICH E14 will be revised before a sufficient amount of data have convinced all participating parties that alternative approaches can provide data at the same level of confidence. We therefore see this as a step-wise, staggered approach, in which the request for a TQT study can be waived for some compounds with certain characteristics, while others will have to undergo a TQT study. Examples of the former may include compounds from a pharmacological class known to have no members with QT liability, a clean non-clinical safety pharmacology package and robustly negative ER analysis of SAD/MAD data with the upper bound of the two-sided 90% CI of the projected QT_c effect below 10 ms at concentrations that are relevant in the targeted patient population. Other drugs, such as those with a small underlying effect or where early QT assessment has not provided a sufficiently precise estimate of the QT effect, would still require an E14-compliant TQT study. The pace and extent of this process is obviously unknown at this stage, but alternative ways of QT assessment that all involve ER analysis, are generating an increased level of interest and it seems likely that the TQT study eventually will be down-played as the only source of valid QT data.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, BD has specified a relationship with iCardiac Technologies in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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