Dynamic Data

James McRedmond of Java Clinical Research explores the ways in which improving the volume, quantity and accuracy of the pharmacodynamic data can add value to clinical trials

Clinical trial costs are increasing, and are a limiting factor in the drug development process (1). Pressure to reduce the expense of trials may lead to trial designs and protocols that are tailored to meet regulatory requirements, but miss opportunities to acquire additional useful data about the investigational drug. Crucial decisions are made on the basis of trial data, including whether it is worthwhile proceeding with the next phase of clinical research, which is usually more expensive than the current study. For this reason, reducing the cost of clinical trials at the expense of generating data may be a false economy; acquiring data about how the study drug behaves is, after all, the purpose of the clinical trial. Indeed, more accurate data may allow trials with fewer patients to produce equivalent results, becoming cost neutral as a result or even reducing costs overall.

The major factor increasing expense in many trials is the number of patients. For each patient, there are largely inflexible associated costs, including payments for study site resources to conduct procedures and investigations, locally or centrally performed assays required to determine safety, efficacy and pharmacokinetics, sample shipping costs, and so on. Any additional investigations for each patient push the cost of the trial over the minimum. These might include assays that are considered 'nice-to-have' rather than 'required'. Of course, the 'fixed' costs are also subject to pressure, leading to trends such as the outsourcing of trials to countries where such patient costs may be lower. Here, however, the focus is on additional costs incurred per patient.

Acquiring additional or more accurate data about drug effects in a trial will make it more informative. Phase II trials will often have broad objectives such as 'assessing the safety and tolerability' of a new compound in the target population. These trials are not typically powered to demonstrate statistically significant differences in clinical outcomes between groups, particularly if the event is rare, or develops over a long period. For this reason, surrogate markers for the clinical effect are often measured to gauge effectiveness, and the drug's fate will depend on how it affects these markers. These surrogate markers are often scrutinised in a substudy of the main trial, with additional samples taken or assays performed only in a subset of sites. Some surrogate markers have well-established correlations with clinical outcomes (such as LDL cholesterol and atherothrombosis, or elevated blood pressure and stroke), but in many cases the relationship between markers and clinical outcome is uncertain, and the predicted effect of the drug is subject to interpretation. Indications of the study drug's effects from a number of different sources may aid the decision-making process.

Phase III trials typically have a primary endpoint that determines their success or failure. However, other data or subsidiary endpoints may be analysed to provide more information on the drug's mechanism of action or effects in certain patient populations. In a successful Phase III trial, this extra information may make trial results more compelling, providing mechanistic information that explains the drug's beneficial effect. Crucially, in all trials, more accurate data with less variability may allow the use of fewer patients and actually reduce the cost of clinical research.

We shall discuss the ways in which the volume, quality and accuracy of crucial pharmacodynamic data may be improved in clinical trials. We focus on two indications in the cardiovascular area: antiplatelet and antihypertensive drugs. In both cases, the use of technological approaches facilitates the collection of additional, high quality data. Generally, to ensure that the information-rich approach is incorporated into trial designs to maximise the yield of useful data, appropriate expertise must be brought into the clinical trial process at an early stage. Typically this will involve expertise from outside the pharmaceutical company developing the drug, and often outside the CRO entrusted with managing the trial.

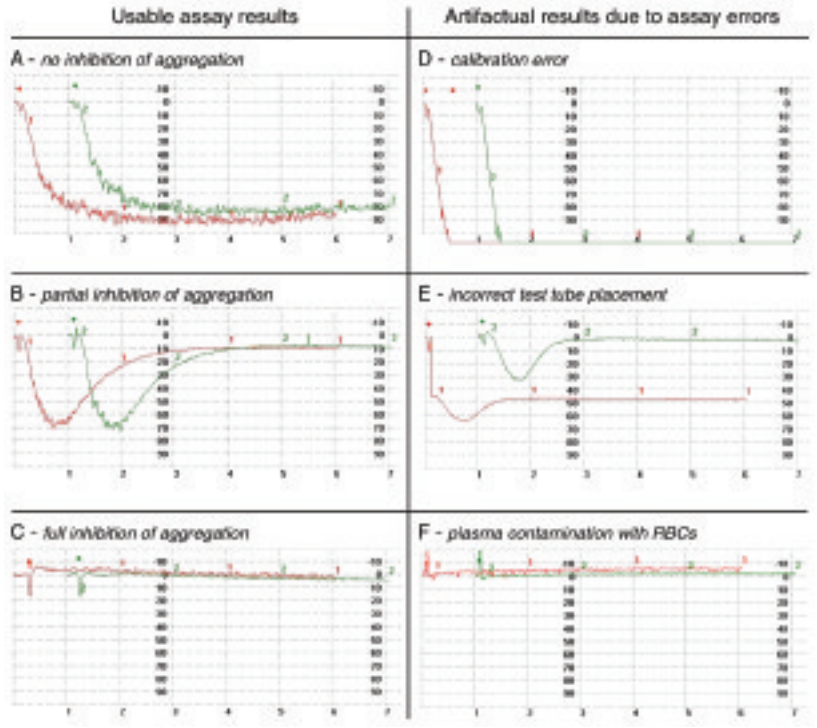
LIGHT TRANSMISSION AGGREGOMETRY FOR ASSESSMENT OF PLATELET FUNCTION

Light transmission aggregometry (LTA) is a procedure for determining the platelet function status of *ex vivo* samples from patients in clinical trials (2). Through the use of specific agonists, LTA is customisable to the platelet activation pathway of interest. While other assays of platelet function are available, LTA is considered the gold standard (3). No other assay provides comparable assessment of pharmacodynamics when studying an antiplatelet agent with a novel mechanism of action, such as a protease activated receptor (PAR – a thrombin receptor) antagonist. In preclinical, Phase I and Phase II trials, it is likely that there will be no other indication of the effectiveness of an antiplatelet drug. Phase III outcome trials in this area typically require tens of thousands of patients to demonstrate a benefit over current treatment (4). The need to acquire early and useful indications of drug effects with pharmacodynamic assays is essential.

The platelet response measured by LTA acts as a surrogate endpoint for thrombosis. For this reason, LTA may be widely

performed preclinically and in Phase I trials of antiplatelet agents, and in intensive substudies during Phase II and III. Note that thrombosis *in vivo* is a complex, multi-stage process with many contributing factors. Platelet aggregation performed *ex vivo* provides a readout of the patient's platelet function status, but does not completely mimic thrombosis. For instance, aggregating platelets are stirred in a test tube, not subject to the turbulent haemodynamic forces found in an atherosclerotic blood vessel. Importantly, a single agonist is used to trigger aggregation, whereas there are multiple stimuli for thrombosis *in vivo*; the assay therefore focuses on a single platelet activation pathway of interest.

Figure 1: Platelet aggregation data from a clinical trial. A – C: typical range of subject responses. D – F: artifactual responses that do not reflect the action of study drug



In any case, LTA is a somewhat specialised procedure, and many trials sites will not have staff skilled in performing the assay. Suitable training enables unskilled staff to perform the procedure, but without quality control of the resultant data, inappropriate, artifactual results will sometimes be produced. These will increase the variability of the aggregation data if they are included in analyses. Notably, other assays that produce crucial trial information, such as ECGs and biochemical assays, are quality controlled, and the same stringency should be applied to LTA data. Electronic recording and transmission of LTA results allow close to real-time review of the data by independent experts, identifying artifacts, and limiting the recurrence of mistakes by providing feedback to assay operators. This feedback improves data quality, and by identifying artifacts, the review process reduces the variability in the LTA dataset, allowing useful conclusions to be drawn from fewer datapoints. This reduces the number of patients (and possibly sites) required, and hence the cost of intensive substudies involving LTA. Figure 1 shows typical data from trial sites performing platelet aggregometry; a range of normal responses are seen to placebo and different study drug doses, but scrutiny is required to identify assays containing artifacts indicative of performance errors that make the results meaningless.

Platelet function assessment by LTA is used to demonstrate that the study drug inhibits the pathway of interest by challenging platelets with appropriate agonists (for example ADP for antagonists of the P2Y12 receptor). This qualitative effect is expected, and the quantitative response is often of greater interest (such as determining the degree of inhibition at different dose levels). However, if LTA is being performed, the major expense of recruiting a patient into an intensive substudy is already incurred, and additional useful information may be gained at small extra cost. For instance, multiple platelet aggregation assays challenging platelets with other agonists (such as collagen and thrombin) or combinations of agonists or antagonists could easily be performed using modern multichannel instruments with the same patient blood sample. These extra tests may indicate how well the study drug will inhibit platelet function in response to the complex stimuli that lead to thrombosis *in vivo* (where platelets are exposed to several activating agents, and positive feedback loops play an important role). This additional information may inform decisions about the most appropriate dose to investigate in later trial stages, and be used to support submissions to regulatory agencies. Such comprehensive data would also be persuasive to key opinion leaders in the field, and help to differentiate the study drug from others in the same class. Notably, there are now multiple antagonists of major platelet receptors in clinical development (the ADP receptor P2Y12 and the thrombin receptor PAR1) (5). Small differences in the performance of these agents, as demonstrated in clinical trial samples, may determine which are most clinically and commercially successful.

AMBULATORY BLOOD PRESSURE MEASUREMENT

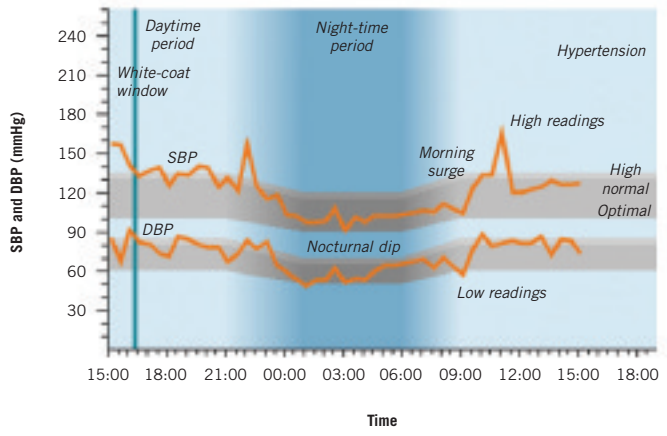
Ambulatory blood pressure measurement (ABPM) is carried out by a portable blood pressure recording device that is fitted on a patient, typically for 24 hours (6). The device measures brachial blood pressure at prespecified intervals throughout the day and night, and has considerable advantages over traditional blood pressure measurements, particularly in clinical trials of antihypertensive regimens. These advantages include:

- More accurate measurement of blood pressure
- Lack of operator bias

- Identification of 'white coat effect' and measurement of underlying pressure in such individuals
- Measurement of circadian variation (including nocturnal 'dipping' status, morning surge, and others – these may have different biological causes and responses to drugs)
- Assessment of drug efficacy over 24 hours and identification of optimal dosing times
- Many other indices derived from measurements throughout the 24-hour period (7)

A typical ABPM data summary (see Figure 2) illustrates some of the features in a patient's blood pressure profile that could not be observed with traditional measurement, such as white coat effects, nocturnal dipping and morning surge.

Figure 2: Visual summary of 24-hour ambulatory blood pressure measurement with notable features annotated



While somewhat more expensive per patient, ABPM will produce data with less variability than traditional measurement if properly implemented, and therefore allows smaller treatment group sizes (and hence less expensive trials) to demonstrate an antihypertensive effect (8). This is due both to its intrinsically greater accuracy of measurement, and the elimination of white coat effects. In addition, the wealth of additional information may be used to identify notable drug effects, or sub-populations particularly suited to receive the study drug (such as patients with nocturnal hypertension, who may benefit from particular therapeutic strategies). This data may also lead to the development of, or demonstrate the effectiveness of, therapies targeted for particular populations (such as formulation of treatments to target aspects of the circadian variation in hypertension) (9).

ABPM is recorded electronically and may be uploaded for a central, independent quality review. This ensures that sufficient recordings are present for the measurement to be valid (if not, the patient is requested to repeat the 24-hour measurement) and also allows for a safety review during the trial. Thus, the number of patients producing usable data is maximised, and patient safety is monitored more effectively than with traditional blood pressure measurements.

OTHER AREAS

Clinical trials in many other areas may also benefit from the acquisition of more and higher quality data, often through the use of emerging technologies. Some of these include:

- Continuous glucose monitoring to provide comprehensive information on glycaemic control in trials of antidiabetic therapies (10)
- Motion detection devices coupled with wireless sensors to monitor activity, falls, and so on in geriatrics (11)
- Genomic guided trials in oncology, whereby the assignment of post-surgical treatment is partially based on the gene expression profile of the cancerous cells following initial systemic chemotherapy (12)

CONCLUSION

Pressure on costs may result in clinical trial protocols that stick to tried-and-tested approaches and eschew additional patient assessments and the use of more expensive methodologies. However, this may limit the value of the resultant trial, giving ambiguous results and missing potentially useful additional insights into the study drug's actions. Acquiring higher quality, more accurate data, and assessing different aspects of the study drug's effects has multiple potential benefits. Firstly, this approach allows the use of fewer trial subjects (and hence reduces trial costs). Secondly, data providing mechanistic evidence for drug effects may prove intellectually or commercially compelling during drug marketing. Finally, additional data identifies pharmacodynamic effects of the study drug that allow better decision-making as it progresses to the next stage of clinical development.

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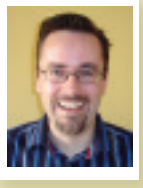

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