Off-target Blood Pressure Effects in Biopharmaceutical Therapeutic Treatment Development: Points to Consider

Cardiac safety has been a primary component across all therapeutic indications within the pharmaceutical / biologic development lifecycle and approval process. Within the regulatory arena, specific guidance in ICH-E14 has provided the framework on approaching cardiac safety specific to a drug's electrophysiological effect. This is presently based on the evaluation of the drug's effect on the QT interval as defined in both the dedicated thorough (TQT) study and intensive QT study, along with ECG data collected during other trials within the clinical trial phases. Over the past five years, there has been an increasing interest in blood pressure as a cardiovascular safety endpoint. There is presently no specific regulatory guidance for the industry that provides a framework as to evaluating a compound which may have an "off-target" blood pressure response. It is important to note that most of the recent discussions on blood pressure have been associated with increases in blood pressure, but we should not overlook that some compounds (non-anti-hypertensive) may generate a blood pressure lowering effect, which may also be a consideration based on patient population and therapeutic indication. Another point to highlight is that the blood pressure response does not and should not be defined only as a hypertensive response when looking at potential cardiac safety risk. The focus should be to define the increase in blood pressure associated with exposure to the compound/treatment and how it relates to the indication and patient population.

When discussing any cardiac safety endpoint, it is always important to review potential issues from a benefit-risk perspective. The Sentinel Initiative from the FDA provides a good reference point for the discussion. "Using medical products brings benefits and risk. Although marketed medical products are required by federal law to be safe for their intended use, safety does not mean zero risk."[1]

As noted previously, the safety consideration of an off-target change in blood pressure can be associated across therapeutic indications.[2-4] A good example of a clinical trial that was designed to determine the "off-target" blood pressure effect within an oncology development programme was presented at the European Society for Medicinal Oncology in 2010.[2] The title of the poster was Axitinib pharmacokinetics and blood pressure changes in front-line metastatic renal cell carcinoma patients. From the study, they were able to conclude:

- Axitinib-induced increases in dBP and sBP occurred early, by day four of treatment, and remained consistent two weeks after initiation of axitinib therapy, supporting early monitoring and management of BP
- The observed BP responses appear to be independent of axitinib plasma concentration
- The relationship between BP and plasma exposure will be further explored in this ongoing trial

In determining how to approach defining an off-target blood pressure response in a biopharmaceutical under development, there are a series of questions which will assist in the design of the study.

Is the change in blood pressure related to dose concentration?

It is important to evaluate whether the observed change in blood pressure shows a dose dependency with the compound. This becomes valuable information as with other safety and efficacy measures, as to defining whether or not there is an association between increased study compound concentration in the body and the increase in blood pressure. Is there a specific concentration threshold that can be associated with the blood pressure response?[5]

Does the blood pressure response disappear and/or return to baseline upon discontinuation of study medication?

Upon discontinuation of biopharmaceutical treatment, blood pressure responses may return back to baseline. Even though reversibility of blood pressure effects may exist, it is often not tested. However, it is important because medications are often prescribed for a limited duration and a sponsor will want to know if the effect on blood pressure will resolve itself or if additional intervention (in the form of a secondary medication) will be required in order to safely use the drug in a specific population.[5]

Additional questions may include:

- Is the blood pressure response acute or gradual?
- Does the response plateau, or, with each exposure is there an additional change (increase or decrease) in blood pressure?

Having a preliminary understanding of the blood pressure response, based on early clinical study data, will provide direction and insight into the design and blood pressure monitoring technology that would be an appropriate means for collecting blood pressure data to define the blood pressure response.

One specific question which may be of interest to the research and medical community is associated with the adolescent/paediatric population and the long-term effect of exposure to a compound with an "off-target" blood pressure increase. Does the early exposure, and

specifically if it is for an extended treatment period (chronic treatment) have a long-term effect and potential to increase cardiovascular risk as an adult?

Blood Pressure Monitoring Options:
There are a number of methodologies that can be implemented to capture blood pressure readings. These include:

Ambulatory blood pressure monitoring (ABPM) – This blood pressure monitoring methodology provides the ability to capture blood pressure data over a 24-hour period, thus providing visibility to the circadian rhythm. ABPM has become a recognised standard for defining a study participant's blood pressure classification, as the ABPM data can be used to generate a mean daytime/nighttime and 24-hour average for the individual.[6] ABPM provides a means of removing the "white coat" hypertensive response and to capture blood pressure data during daily activity. The ABP automated readings can be configured to take readings at a pre-defined interval throughout the monitoring period, thus standardising the blood pressure data capture across all study participants. ABP monitoring can also be included in an early phase trial and provides a means of conducting an "intensive BP" study with a focus on capturing blood pressure readings in association with pharmacokinetic (PK) sampling to assist in identifying if there is a blood pressure response associated with a drug/compound concentration effect. In addition, ABPM devices may also have the ability to capture central systolic pressure, pulse wave velocity and arterial compliance, as well as capturing body position and activity levels.

Remote tele-monitored home blood pressure monitoring – This form of standardised/centralised blood pressure monitoring can be a very valuable tool in defining a blood pressure response and can be seen as complementary to ABP monitoring. The strength of tele-monitored home blood pressure is that it can provide a longitudinal capture of an individual's blood pressure data without having the study participant return to the clinic for evaluation. These platforms can be configured to provide for threshold notifications to the study sites if a blood pressure reading is outside of pre-defined blood pressure ranges, allowing for ongoing visibility and safety monitoring. The methodology is well suited for late-phase blood pressure monitoring. In studies that have compared office, home and ABP blood pressure assessment, there was a correlation between the ABPM and remote tele-monitored home blood pressure data.[7]

Centralised automated office blood pressure monitoring (C-AOBP) - The clinic blood pressure is always an important component of screening and study participant assessment. However, within clinical research and clinical management there have been ongoing questions as to the ability to ensure consistency in technique and standardisation between study sites. From an "off-target" blood pressure response perspective, blood pressure assessment, although a standard procedure, is not always the primary focus or endpoint for studies. Solutions to this challenge include providing the study sites with standardised automated blood pressure devices for clinic evaluation; moreover, this provides the sites with devices and platforms that automatically set the blood pressure reading sequence for the office pressures and then transmit them to a study-specific centralised database. This removes a number of variables that historically have created challenges within the clinical research arena, from device/technique variability to transcription errors and source documentation.

Non-invasive pulse wave form assessment (PWA) - PWA provides a non-invasive means of measuring additional haemodynamic endpoints beyond the brachial systolic and diastolic values. Measurements from PWA include central systolic blood pressure, pulse wave velocity and arterial compliance. These additional measurements can provide additional insight associated with an "off-target" blood pressure response. PWA measurements can be completed in the office setting, as a component of ABPM and remote home blood pressure monitoring.[8]

Industry and Regulatory Insight
There has been a dedicated interest related to the "off-target" blood pressure response within biopharmaceutical development. References in the literature can be seen within specific therapeutic indications such as oncology.[9-10] From a clinical development best practices and trial design perspective, the cardiac safety research consortium (CSRC), which is a public-private consortium consisting of regulatory, academic, and industry representation, generated a paper which addressed the question of how best to approach, and considerations associated with, the "off-target" BP response. The CSRC conducted a think tank on the topic as well, which was held in July 2012. The paper provided a decision tree related to defining the potential increase in BP, which included reference to study phase and potential BP assessment methodologies.[11]

The CSRC paper also provides the industry and researchers a great resource and reference. Below are some of the consensus points identified in the paper:

- Methods of blood pressure measurement may impact precision of the signal. ABPM is favoured; automated methods can be useful in other settings
- Changes in BP (drug-induced off target changes) differences should be evaluated according to baseline blood pressure, age, sex, CV comorbidities, and mechanism
- Dedicated BP studies during Phase II could have value, depending on the mechanism of action of the study drug, the population being studied, and the need to understand the need for safety monitoring during Phase III
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Summary
Blood pressure has been a primary diagnostic cardiovascular indicator, a biomarker throughout medical and scientific investigations within haemodynamic assessment.[12-13] It is well recognised that reducing elevated blood pressure (hypertension) to a normal range provides health benefits and improved cardiac outcomes. The other component of the development process is the safety endpoint. This article provided an introduction to the potential "off-target" increase in blood pressure, study considerations and assessment methodology associated with biopharmaceutical products where the primary intent of the compound is not a cardiovascular indication. There are a number of open questions related to the potential risk associated with an "off-target" increase in blood pressure; however, over the last five years there has been a good deal of productive discussion around the best approach to defining the potential benefit-risk considerations when a biopharmaceutical treatment, in addition to treating the disease, generates an increase in the blood pressure response.

References

1. The Sentinel Initiative May 2008, Department of Health and Human Services U.S. Food and Drug Administration Office of Critical Path Programs
2. 2Fishman M, Carducci M, Bair A, Chen Y, Rini B. Axitinib pharmacokinetics and blood pressure changes in front-line metastatic renal cell carcinoma patients. 15th annual Congress of the European Society for Medical Oncology (ESMO) October 8-12 2010, Milan Italy.
3. White W, Derosier F, Thompson A, Adams B, Goodman D. Evaluation of the migraine treatment sumatriptan/naproxen sodium on blood pressure following long-term administration. J Clin Hypertens (Greenwich). 2011; 13:910-916.
4. Elliott WJ. Drug interactions and drugs that affect blood pressure. J Clin Hypertens (Greenwich) 2006; 8(10):731-7.
5. Geiger M. Off target blood pressure changes and evaluation in drug development: safety, clinical and regulatory considerations. 49th annual meeting of the Drug Information Association (DIA) June 23-27 2013 Boston MA USA.
6. O'Brien E, Turner JR. Assessing blood pressure response to noncardiovascular drugs: the beneficial role of ambulatory blood pressure monitoring. J Clin Hypertens (Greenwich) 2013; 15(1): 55-62.
7. Denolle T, Waeber B, Kjeldsen S, Parati G, Wislon M, Asmar R. Self-measurement of blood pressure in clinical trials and therapeutic applications. Blood Pressure Monitoring 2000; 5:145-149.
8. Scanlon E, Mankad R, Davis, J. Non-Invasive cardiovascular imaging for cardiovascular risk assessment in rheumatoid arthritis. EMJ Rheumatol. 2016; 3 (1): 106-113.
9. Maitland M, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010; 102:596-604.
10. Larochelle P, Kollmannsberger C, et al. Hypertension management in patients with renal cell cancer treated with anti-angiogenic agents. Curr Oncol 2012; 19 (4): 202-208.
11. Sager P, Heilbraun J, Turner JR, et al. Assessment of drug-induced increases in blood pressure during drug development: Report from the cardiac safety research consortium. Am Heart J 2013; 165:477-488.
12. Giles T. Blood pressure – the better biomarker: delay in clinical application. J Clin Hyperten 2007; (12): 918-920.
13. O'Brien E, Fitzgerald D. The history of blood pressure measurement. J Human Hyperten 1994; 8: 73-84.

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