BIA 10-2474: some lessons are clear but important questions remain unanswered

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Phase I clinical trials in healthy volunteers are generally safe. The incidence of worrying drug-related serious adverse events has been estimated at 0.05%, with less than half of these thought to be related to the study drug[1] and deaths are much rarer still. However, unfortunately, there are occasional disasters involving serious harm and even deaths of healthy subjects participating in such trials. The most recent disaster occurred in 2016 during the first-in-human study of BIA 10-2474 and the results of that study are published in this issue of *Clinical Pharmacology & Therapeutics* (CPT)[2] with an accompanying commentary written by a group of highly experienced phase I study investigators who had no involvement in the study.[3] **(Figure 1)**

Events such as this are terrible tragedies for all involved and must become opportunities to question if there are ways to further improve the safety of phase I studies. The first requirement is full transparency with respect to the study protocol, the events that occurred during the study, and all the collected data. In the case of the BIA 10-2474 study, the protocol was released publicly soon after the disaster, although

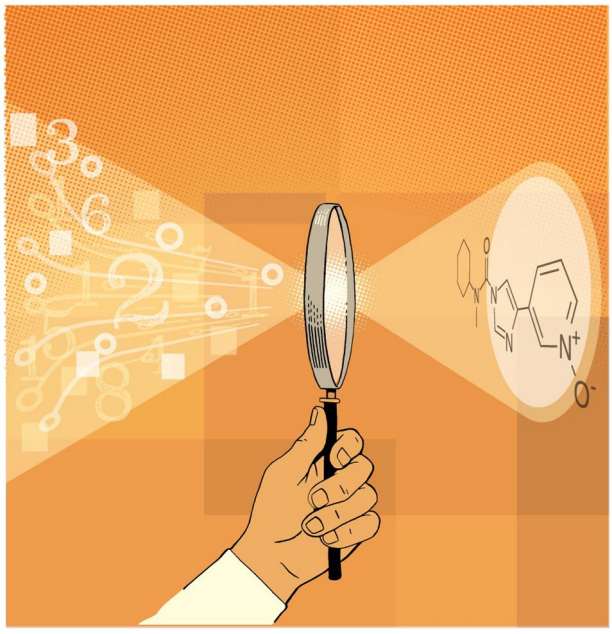

Figure 1 CPT February 2022 cover image: BIA 10-2474.

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it is no longer available. Some of the clinical data were presented at conferences and the hospital team that cared for the subjects have published their findings.[4] It is very important that the full results of the study have now been published too. However, the investigator brochure, summarizing all the available preclinical data, a critical document for understanding what was already known about the drug at the time of the development of the study protocol, has not been made available to the scientific community. The reviewers and editors of CPT asked that this be included as a supplement to the publication, but we were informed that this was not possible because the case remained under legal review in France. Instead, a comprehensive list of all the data that has since been published was provided. Although this is helpful, we support the recommendation of Cohen *et al*. that the investigator brochure should also be made available as soon as possible to improve understanding of what was known at the time and to facilitate further investigation.[3]

The investigator brochure was made available to the Temporary Specialist Scientific Committee (TSSC) established by the Agence Nationale de Sécurité du Médicament et des Produits de Santé to advise on likely causes of the tragedy and how to avoid a recurrence. Their report[5] contains several hypotheses of causality and makes recommendations for modifications to the design of future studies. Perhaps the most important of these, which was been adopted by the European Medicines Agency (EMA) in their updated guideline on the design of first-in-human studies,[6] is to restrict the maximum dose to a small multiple of the dose that achieves the maximum desired pharmacological activity. This is emphasized in the commentary from Cohen *et al*. and we agree that such an action would have prevented the serious adverse events and death in this study. We agree that measures of pharmacological activity should be included in first-in-human studies and the results reviewed before each dose escalation decision. If such measurements cannot be performed, the drug concentrations expected to produce the maximum desired pharmacology should be estimated and dose escalation stopped at a small multiple of these concentrations. The EMA guidance also requires that dose escalation be halted after one possibly drug-related serious adverse event. Whereas that would not have prevented the fatality from BIA 10-2474, it could have prevented the other serious injuries.

A lower limit on the maximum dose to be administered would have prevented the BIA 10-2474 disaster but it is not enough to minimize the risk of a similar event occurring again because, unfortunately, the mechanism of toxicity remains unknown. The TSSC report favored the hypothesis of nonselective inhibition of another serine hydrolase or perhaps direct neuronal toxicity via another mechanism but acknowledged there was no proof, other than the knowledge that BIA 10-2474 was less selective than previous inhibitors of fatty acid amide hydrolase (FAAH), the intended target.[5] After the TGN1412 disaster in 2006, the expert group commissioned by the British Secretary of State for Health was able to identify the underlying mechanism of toxicity and make recommendations to prevent a recurrence.[7] Similarly, after fialuridine caused unexpected toxicity leading to the deaths of five patients in its first phase II trial, an investigation involving the US Food and Drug Administration (FDA), National Institutes of Health (NIH), and sponsor led to a report from the Institute of Medicine, establishing the mechanism and enabling avoidance of anything similar.[8] However, the mechanism of BIA 10-2474 toxicity remains unknown and no systematic attempt to discover it has been commissioned. This is unfortunate, as potentially useful methods are available. For example, modern systems biology techniques are shedding light on the mechanisms of unexpected adverse events[9] and such approaches could be helpful for BIA 10-2474. Two obvious questions to consider are whose responsibility is it to ensure mechanistic investigations are undertaken and who funds the work? In some previous cases, national authorities in the country of the study site have taken accountability, sometimes with the involvement of the sponsor. Sponsors have an incentive to understand the mechanism of toxicity for drugs they wish to continue developing and where they believe the toxicity is manageable, but this may not be a consideration for drugs whose development is terminated due to the serious, unexplained, and unmanageable human toxicity. Another option for cases such as BIA 10-2474 might be that all sponsors of healthy volunteer studies should contribute to a central fund established for the purpose of enabling appropriate investigation of this and any similar disasters that may occur in the future. Whatever solution is identified, it is in the interest of all involved in clinical trials to have an agreed mechanism in

place to investigate the mechanisms of toxicity underlying tragedies, such as BIA 10-2474.

Another way to have avoided the deaths and serious injuries from BIA 10-2474 administration, would be never to have taken it into clinical development. Several FAAH inhibitors had previously been studied in humans and shown to be ineffective. The consequence of inhibition of FAAH is to increase the concentrations and pharmacological effects of endogenous cannabinoid receptor ligands. Importantly a systems pharmacology model developed for one of them, PF-04457845, showed that complete inhibition of FAAH was insufficient to raise the endogenous ligands enough to produce significantly increased pharmacological activity, thereby explaining the lack of efficacy.[10] No hypothesis has been put forward to suggest that BIA 10-2474 would have avoided this problem so it must be asked why it was ever approved for clinical development?

A final lesson from this case is for all involved in phase I studies, especially first-in-human studies, to remain vigilant at all times. Apparent safety of previous drugs with the same pharmacological target is not a guarantee of safety with a different molecule. Nor is keeping drug exposures in humans well below the levels associated with no toxicity in animals. Nor does having achieved higher exposures in other volunteers earlier in the study. These things may provide some reassurance, but all were true for BIA 10-2474, and serious harm was still incurred. At the end of the day, investigators must remain alert throughout the duration of the phase I study, as it is not possible to have a wholly comprehensive understanding of the on- and off-target effects, and no matter how thorough the preclinical studies, important differences remain between animals and humans.

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