Preclinical Phase III Trials in Translational Stroke Research

Call for Collective Design of Framework and Guidelines

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Our understanding of basic stroke pathophysiology, risk factors promoting the disease and its sequela in the central nervous and peripheral organ systems have progressed tremendously for the past decades. Preclinical research has identified a multitude of potential therapeutic targets to replenish our arsenal for fighting ischemic stroke. Although the efficacy of numerous therapeutic strategies was demonstrated preclinically, clinical trials failed to confirm this efficacy in patients, putting translational stroke research into crisis. However, the translational failure raised our awareness of the pathophysiological complexity of ischemic stroke and underpinned the importance of experimental quality. We also realized that context- and model-dependent efficacy might have confounded preclinical stroke research. Hence, measures to improve study quality, such as blinding, randomization, and attention to systemic physiology, are increasingly used and gradually become a prerequisite for publication. The majority of these measures can be easily implemented in most laboratories. However, some more complex but equally important aspects are harder to address by individual groups or even larger centers. For example, it is hardly possible to reproduce the wide range of age and weight, genetic heterogeneity, comorbidities, immunologic conditions, and preexisting medications typically found in patient populations with stroke (diversity factors). Neglecting diversity factors could jeopardize our chances to translate basic research findings successfully into novel stroke treatments and eventually limit the willingness of the public and industry to support preclinical stroke research. In response, Dirnagl et al have recently proposed the concept of phase III preclinical trials. It aims to link groups and centers globally, which agree on common quality standards to achieve sufficient power/depth conjointly for adequate preclinical implementation of diversity factors. To resemble the situation of comparable clinical multicenter studies, all research activities may be governed by a supervising committee, featuring central randomization and data analysis. Intercenter comparability, for example, on blinded analysis of functional and imaging data sets, could be ensured by preclinical round robin trials.

This strategy is not intended to replace the identification of novel pathophysiological processes and related therapeutic candidates (preclinical phase I) or any initial safety and efficacy studies (preclinical phase II) conducted by individual groups. Instead, the instrument shall provide the stroke research community with the option to assess safety and efficacy of a given concept rigorously before the initiation of early stage clinical trials.

The collective approach will aim on identification of treatment concepts with a potentially lower efficacy in humans or being beneficial to a particular subset of patients with stroke and thus is intended as a more efficient path for drug development from bench to bedside. Assembling a group of experts in experimental stroke research is certainly a valid approach to define how such phase III preclinical trials should be organized and performed in the future. However, we think that enrollment of the global stroke research community provides additional benefits in this process with respect to relevance, acceptance, and widespread adoption of this novel approach within the experimental stroke community. To this end, we have launched a Website (www.p3pt.de) as an invitation to the community to provide their position on preclinical/experimental phase III trials and potential suggestions how those should be organized and performed. The Website will be open for contributions until June 30, 2014. All input will be reviewed and is intended to be published in comprehensive summary. We think that the contribution from the greater stroke research community will help to create both practicable and effective terms of multicenter preclinical research, to optimize our joint research endeavors, and to create a readiness to participate.

Disclosures

None.

References


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