Commentary

Preclinical randomized controlled multicenter trials (pRCT) in stroke research: a new and valid approach to improve translation?

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Provenance: This is a Guest Commentary commissioned by Section Editor Mingzhu Gao, MD (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

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Over the last decades, based on the improved knowledge of the pathophysiological mechanisms involved in ischemic stroke and neuronal degeneration, many experimental studies were carried out using drugs targeting the different steps of the degenerative process. Thus, drugs with anti-excitotoxic, antioxidant, anti-apoptotic and anti-inflammatory properties were investigated as potential protective therapeutic agents in animal models of stroke. In spite of the large evidence for neuroprotection of many of the tested compounds, a systematic review of the literature by Kidwell *et al*. reported that none of the more than 49 agents studied in clinical trials made the expected jump from bench to bedside (1). Therefore, since up to now new therapeutic agents have not been identified despite this intense research activity, thrombolysis with tissue plasminogen activator (tPA) remains the only clinically approved therapy for ischemic stroke (2). However, the discovery of new pharmacological tools is urgent because tPA has important contraindications which limit the number of stroke patients taking advantage from this treatment (3), leaving brain ischemia as one of the leading cause of death and disability.

Different explanations were claimed as responsible for the failure in translation of the many positive results in animal models, including the time of drug administration (minutes *vs*. hours or days), the dose of drug administered, the assessment of different biochemical or behavioral endpoints in clinical trials, and the use of young animals (old people are the most affected by stroke). In addition, in preclinical studies other factors, including different animal strains and models of ischemia, design of the experiments, criteria of inclusion or exclusion of animals in the experimental groups and data analysis, make it difficult to compare the results obtained by the different groups working in experimental ischemia (4).

The preclinical randomized multicenter trial (pRCT) described in the paper by Llovera *et al*. (5) represents an attempt to overcome some problems and limitations of independent preclinical in vivo studies. The study utilizes the process of randomized, controlled clinical trials to the preclinical situation, and was directed to fill the gap between experimental animal research and clinical trials. Authors used this new approach to study an antibody (anti-CD49d) proven to possess anti-inflammatory activity by inhibition of leukocyte migration into the brain. The study has a rigorous design for statistics, analysis and reporting. According to the authors, this approach allows a better control and assessment of the preclinical efficacy before exploring its effect in long-lasting and expensive clinical trials. Using this strategy and two animal models of stroke, authors selected the infarct volume as a primary endpoint, and functional outcomes and invasion of leukocytes into the brain as secondary endpoints, in line with the STAIRS recommendations for what concerns outcome measurements (6). Besides the innovative approach, the results are interesting for two additional reasons. (I) Six independent European research centers, operating as a "single Unit", have now described in more detail the

differences in the anatomical regions involved in the two most used models of experimental stroke, i.e. permanent *vs* transient occlusion of the middle cerebral artery. (II) The drug used in the pRCT reduced the infarct volume but only in the coagulation (permanent) model. The fact that in the endovascular filament (transient) model no statistically significant effect on the infarct volume was observed, may be indicative of a more robust inflammatory process in the permanent occlusion model (5).

It is currently hard to know if the pRCT approach used by the authors will be successful for a better translation of preclinical studies in stroke. For sure, the approach helps to reduce variability in the experimental results and leads to a better characterization of the drug(s) effect. The use of different animal models, additionally, gives further helpful information for planning clinical trials (e.g. a better selection of patients based on the kind of stroke that is more responsive to the testing drug), improving, therefore, the translational process. However, this approach only addresses some of the different important issues that may be responsible for the many failures in this area of research, leaving many others open (4,7). In humans stroke is heterogeneous, and a drug effective on one patient could be not suitable for another one. The time of administration can be critical, and depending on the stage of the neurodegenerative process, the same drug could be either protective or could promote neurodegeneration. In this complexity, it should be considered that the more rational approach to stroke would not be a single drug but combinations of drugs with different mechanisms of action and with selective administrations at poststroke intervals. Hypothermia, a non-pharmacological neuroprotective strategy, should be probably considered in addition to the pharmacological therapy (8-9). Of course, this approach requires more efforts in studying the different mechanisms responsible for the evolution of the injury, and additionally in developing new preclinical strategies and animal models that may better support translation. Imaging methodologies (e.g., MRI) should be considered in preclinical models in order to get more reliable measurements of the infarct volume. Imaging methodologies can offer the advantage to follow the evolution of the brain damage in the same groups of living animals immediately after injury and for days and weeks after the ischemic insult. This approach may confirm or even improve the histological results using a smaller number of animals compared to the histological approach alone, and may allow to correlate injury and neurological deficits in the same animal (10). Another advantage is that the same method(s) can also be used in clinical trials, allowing a more effective translation process. pRCT studies, which allow to use the competences and technologies of different research groups, should also go in this direction.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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