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Webinar EVER Pharma (June 14, 2020)

The Renaissance of Neuroprotection in Times of Recanalization Therapies

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Moderator

Topic: The Role of Cerebrolysin in Cases of Unsuccessful Recanalization Therapy in Severe Stroke.

Topic: The Neuroprotective Effects of Cerebrolysin in Thrombolysis and Thrombectomy - Scientific Rationale and Clinical Development

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Introduction

N. V. Ramani

Dr. Ramani anchored the webinar with an outline of the major problems facing stroke care in Asia, the region which has the highest burden of stroke in the world. High incidence due to poorly controlled risk factors, high mortality after a severe stroke, lack of specialized stroke care in certain geographical areas, and high disability burden as measured by DALYs are all hallmarks of stroke in Asia. The newest standards of stroke care are certainly available, but appear insufficient to tackle the growing epidemiological problem. The approaches that reduce mortality and disability due to stroke include recanalization therapies (urgent iv thrombolysis and thrombectomy) and decompressing craniectomy (in malignant cerebral edema, large cerebral infarctions) for selected patients as well as organized stroke care for every stroke patient. However, the data from global stroke trials indicate that even with the best standard of care only about 40% of patients after thrombolysis and thrombectomy return to good functional grade, while the remaining 60% do not recover as expected. This efficacy gap remains to be addressed in the clinic. Effective recanalization does not guarantee functional recovery. In Asia, access to both thrombolysis and thrombectomy varies widely between countries and there is a need for improving the early admissions and affordability of these procedures in many regions. The poor access to the advanced recanalization technology adds to the inherent clinical problem mentioned earlier. This is why it is so important to discuss the complementary role of adjunctive stroke therapies, which is the focus of this webinar.

State-of-the-art in acute ischemic stroke treatment

N. Bornstein

Dr. Bornstein joined the conversation explaining that it is his goal to discuss the scientific rationale and clinical development for one such adjunctive therapy - treatment with Cerebrolysin, a multimodal, neuroprotective, and neurotrophic agent. First, he overviewed the development in the recanalization treatment standards and discussed the advantages and limitations of these approaches. Then, he addressed major issues related to the development of neuroprotective adjunctive therapies. Finally, he showed how certain complementary approaches, including Cerebrolysin, can be used to overcome important limitations of the recanalization.

What we have learned from the thrombolysis trials is that time is brain. The sooner we apply thrombolysis the higher is the probability of clinical success in both recanalization and clinical outcome. The meta-analysis of the individual patient data from randomized trials¹ showed that the successful application of rtPA can be extended to 4.5 hours post-stroke and that such factors like the age and the severity (up to NIHSS 22) of stroke are not negating its clinical benefits. The most recent meta-analysis² (of EXTEND, ECASS4-EXTEND, and EPITHET trials) evaluated the possibility of further extending the therapeutic window of thrombolysis using diffusion imaging in patients with symptoms present beyond 4.5 hours from the stroke onset or on waking up. These patients benefited from thrombolysis when treated up to 9 hours post-stroke if salvageable brain tissue was identified with diffusion imaging. The results were consistent across age, time, and large vessel strata. Having these positive advances in mind, we should be aware of certain drawbacks, still present when using alteplase. One major issue is the increase in the symptomatic intracranial hemorrhage rate. Another is the fact that rtPA does not always help in the cases of large vessel occlusion (LVO). For such patients, thrombectomy is the method of choice. Usually (in 80% of

patients), it is combined with rtPA to effectively remove the LVO³. Meanwhile, the DAWN and DEFUSE 3 studies have shown that applying specified herein neuroimaging criteria permits using thrombectomy in certain patients for up to 24 hours after stroke onset. These successful efforts to extend therapeutic windows for recanalization therapies allow us to treat more patients and therefore constitute major milestones in stroke care. Nevertheless, some significant limitations do apply. While final recanalization status correlates strongly with clinical outcomes, not all patients with therapeutic recanalization show positive recovery. Although recanalization in stroke is mandatory (whenever possible), in many cases it is still insufficient for clinical success. In the case of rtPA, several factors contribute to this failure and all appear to be related to its negative impact on the microcirculation. rtPA induces blood-brain barrier (BBB) permeability leading to symptomatic and asymptomatic hemorrhagic transformation. Alteplase was also shown to induce fibrin deposition in the microvasculature. This contributes to blocking the downstream microcirculation and also provokes pro-inflammatory processes that further exacerbate BBB leakage. In many cases, these side effects can offset the benefits related to successful recanalization achieved after thrombolysis and thrombectomy.

Dr. Bornstein underlined that an adjunctive treatment counteracting these side effects at the level of the microcirculation - Cerebrolysin - is already available for clinical use. The extensive research conducted by Dr. Michael Chopp showed that Cerebrolysin reduces BBB leakage as well as the production of pro-inflammatory cytokines, that mediate BBB leakage induced by rtPA and fibrin, in the human cerebral endothelial cells. These data create a strong scientific rationale for using Cerebrolysin in conjunction with rtPA and thrombectomy. While the brain tissue perfusion depends on the microcirculation patency as well as on the integrity and functionality of BBB, the brain tissue protection and recovery depend on the preservation or reopening of the latent collateral circuits and on the restoration of the blood flow throughout the affected region. Downstream Microvascular Thrombosis (DMT) has been singled out as a major contributing mechanism precluding the restoration of the blood flow downstream from the major occlusion, as it can persist even after successful recanalization. The risk and intensity of DMT appear to be related to the presence of pro-inflammatory or procoagulant states. Cerebrolysin exhibits anticoagulant, anti-inflammatory, and pro-fibrinolytic properties and appears to be uniquely suited for enhancement of the recanalization standard (**Fig. 1**).

Fig. 1. The mechanisms through which Cerebrolysin enhances recanalization therapies

The general aim of neuroprotection is to prevent the death of neurons in penumbra irrespective of recanalization. On top of the described here effects at the level of microvasculature, Cerebrolysin provides neuroprotective capacity that predisposes the affected brain tissue for accelerated recovery. This is a unique therapeutic feature that was missing in many of the past trials investigating more than 1000 potentially neuroprotective agents. The reasons for this failure were broadly discussed, but two elements stand out as the most likely culprits. First is the failed availability of the neuroprotectant due to the lack of collaterals delivering the blood to the penumbra in the treated patients. This could explain a weak or nonexistent response to the investigated agents. Another problem relates to the nature of the investigated compounds themselves. Mostly, these were inadequate molecules (monomodal compounds) targeting a single chosen mechanism of the complex pathophysiological processes occurring after ischemic stroke. The effective neuroprotection, as we understand it today, requires multimodal drugs with trophic and regenerative effects, such as Cerebrolysin, that target an array of key mechanisms of the pathophysiological cascade (**Fig. 2**).

In support of this rationale, a new clinical trial investigating Nerinetide (ESCAPE-NA1)⁴, a promising agent showing previously neuroprotective effects in pre-clinical studies and a phase II trial, included ischemic stroke patients (stratified against thrombolytic treatment) with preserved good-to-moderate collaterals (assessed by multiphase CT Angiography). Although Nerinetide did not significantly improve functional independence (mRS 0-2) in the entire treated population (in comparison with placebo), the results suggested a neutralizing effect of alteplase as the reason for the lack of therapeutic benefit. Alteplase caused a significant reduction in Nerinetide levels in all thrombolysed patients leading to inhibition of the treatment effect. This most recent example of a neuroprotection trial confirms the importance of both modern diagnostic modalities and the choice of adequate therapeutic agents for the successful application of neuroprotection in stroke.

Fig. 2. The effective neuroprotection requires multimodal drugs with trophic and regenerative properties

1. Lancet. 2014; 384: 1929-1935
2. Lancet. 2019 Jul 13;394(10193):139-147
3. BMJ 2016;353:i1754
4. Lancet, Vol 395, Issue 10227; P878-887, March 14, 2020

The role of Cerebrolysin in cases of unsuccessful recanalization therapy in severe stroke

Z. Poljakovic

The role of Cerebrolysin in cases of unsuccessful recanalization therapy in severe stroke patients was explored in investigations conducted by Dr. Poljakovic. The fast reperfusion is an obvious but sometimes elusive goal for recanalization therapies. Impaired cerebral autoregulation, BBB disturbances, hypo-perfusion volume, re-occlusion, microvascular dysfunction, high baseline NIHSS score, advanced age, and prolonged delay in treatment have all been associated with futile reperfusion seen in up to 40% of cases. On the other hand, reperfusion is sometimes achieved even without recanalization. There are also the cases when after successful recanalization and reperfusion patients deteriorate anyway, due to the reperfusion-triggered injury. The symptomatic intracranial hemorrhage is the most dangerous scenario resulting in a high mortality rate (up to 40%). The direct causes and risk factors of reperfusion injury are partially understood and include low collateral score, reperfusion of the hypo-perfused brain tissue, low ASPECT score, high baseline NIHSS score, and advanced age. All these problematic cases of futile recanalization and reperfusion injury require appropriate interventions with safe adjunctive treatments and one of the agents considered for this role is Cerebrolysin. In recently published publications^{1,2}, including a meta-analysis of clinical trials (Bornstein et al., 2017), Cerebrolysin showed high safety profile as well as efficacy in early recovery post-stroke. In a study more specifically associated with recanalization, Cerebrolysin was used as an adjunctive treatment to thrombolysis (CERE-LYSE trial; Lang et al., 2013)³. This study showed that combination treatment resulted in faster recovery than in the case of alteplase alone. This advantage was seen across all severity groups, but in the most severely (NIHSS 15-25) affected patients it was most pronounced (**Fig. 3**). Cerebrolysin was safe in the combination with alteplase, induced faster improvement in all assessed efficacy parameters (in comparison with rtPA alone) and this effect

Fig. 3. Cerebrolysin in combination with rtPA accelerates recovery of ischemic stroke patients

was most noticeable at day 10 of the treatment. The efficacy of the combination increased with the severity of the stroke.

In the follow-up to these promising results, Dr. Poljakovic's team wanted to look into the therapeutic potential of Cerebrolysin in patients with futile recanalization (TICI score of 2A or less on control angiography) and those at high risk of the reperfusion injury. The parameters of this prospective study included population with NIHSS ≥ 8 (moderate and severe stroke), dosage and administration regimen according to CERE-LYSE trial (30 ml/day, starting within 24 hours post-stroke, lasting for minimum 14 and maximum 21 days), long-term observation (up to 12 months) as well as various outcome measures (functional outcome, complications, and mortality). The investigators wanted to test the hypothesis that Cerebrolysin improves the outcome in severe stroke patients who do not experience clinical improvement (≥ 2 points in NIHSS) after recanalization therapy (either with only rtPA or rtPA and thrombectomy) in the first 24 hours after the treatment. The study included the matched group of patients as a control. The study groups were well balanced and paired with a small difference in stroke etiology and age (the investigational group was slightly older and with more cardioembolic strokes). The early functional outcome defined as mRS score at day 10-30 (at discharge) and at day 90 (**Fig. 4**) showed differences in ordinal scale vs differences in dichotomized scale for mRS.

Fig. 4. The impact of Cerebrolysin on the functional outcome and mortality of stroke patients after unsuccessful recanalization

The strongest effect was seen in the group with mRS 3 (moderate disability but able to walk without assistance) reflecting this quality of life component as the most decisive differentiating factor (in accordance with the QOL utility-weighted version of the mRS). Concerning the late mRS score (at 12 months), the statistically significant difference in mortality rate was observed (**Fig. 4**) between the investigational and control groups (13% vs 43% respectively). For the group of Prof. Poljakovic, the most important complication to be monitored in their study was hemorrhagic transformation. There the advantage of Cerebrolysin treatment was also recorded in a statistically significant reduction in the rate of these hemorrhagic transformations (**Fig. 5**). In discussing the results of the study, Dr. Poljakovic underlined the favorable safety profile of Cerebrolysin, its long-term impact on functional outcome, and lowering the mortality rate which might be attributed to the reduction of both symptomatic and asymptomatic hemorrhagic transformation. The study confirmed the neuroprotective profile of Cerebrolysin as add on to recanalization therapy in cases of futile recanalization and in the prevention of reperfusion injuries.

The future plans of Dr. Poljakovic include investigating Cerebrolysin treatment in patients with aneurysmal subarachnoid hemorrhage (SAH) as add on to intraventricular thrombolysis. This kind of complication is one of the most frustrating to interventional neurologists and occurs after fast and complete securing of an aneurysm. The most common secondary complication in these patients is vasospasm and the resulting delayed ischemic neurological deficit which could be addressed with appropriate neuroprotective therapy, like Cerebrolysin. Intraventricular thrombolysis in patients with SAH is routinely performed in the medical center in Zagreb. To date, Cerebrolysin was used in three such cases with very good preliminary results (significant reduction of diffuse edema after 24 hours and fast reduction of hemorrhage volume in subarachnoid space) and this success prompted preparation of the dedicated clinical trial which, by now, is ready for launch.

Fig. 5. The reduction of hemorrhagic transformation rate by Cerebrolysin in patients with futile recanalization

1. Neurol Sci. 2018 Apr;39(4):629-640
2. J Neurosci Rural Pract. 2019 Oct;10(4):576-581
3. Int J Stroke. 2013 Feb;8(2):95-104.

The Neuroprotective effects of Cerebrolysin in thrombolysis and thrombectomy – scientific rationale and clinical development

N. Bornstein

The pharmacological profile of Cerebrolysin has evolved throughout the years and allowed to establish solid evidence of its safety and efficacy in acute and post-acute phases of stroke. Dr. Bornstein reviewed the most important results of the clinical trials performed to date. The CASTA trial, in which Dr. Bornstein was involved, included 1070 patients with acute ischemic stroke in a broad range of severity¹. The patients were treated within 12 hours after acute ischemic stroke (AIS) for 10 days, with 30 ml daily intravenous Cerebrolysin. The composite endpoint (consisting of mRS, NIHSS, and BI at day 90) of the study was neutral. Nevertheless, further analyses of the results revealed important clinical observations. Primarily, the ceiling effect of mild stroke clearly disturbed the observed treatment effect. The pre-planned subgroup analyses of patients with more severe stroke (of >12 and >17 NIHSS at baseline) unmasked the significant treatment effect of Cerebrolysin, which suggested its potential for supporting the early mobilization of stroke patients. The same phenomenon was observed in the safety analysis. Cerebrolysin treated patients (NIHSS>12 subgroup) had a cumulative death rate of 10.5% in comparison with 20.2% for placebo (**Fig. 6**).

These remarkable safety and efficacy results suggested that the combination of the standard of care therapies (e.g. recanalization, early mobilization, and rehabilitation) with Cerebrolysin should be explored in future investigations.

In addition to obvious physical disability and motor function impairment, stroke patients experience serious cognitive, emotional, communication, and personality changes, which often lead to depression. This “non-physical” component of disability is often neglected in the clinic despite the fact that it has an enormous impact on the quality of life after stroke. It was, therefore, impor-

Fig. 6. The results of the CASTA trial suggested improved outcomes and safety of more severely affected patients treated with Cerebrolysin

tant to find out if Cerebrolysin could contribute to improved recovery of stroke patients also through amelioration of non-physical disabilities. The CARS trial aimed to clarify this matter in the context of the impact of Cerebrolysin (50 ml daily for 21 days) on motor rehabilitation². Apart from confirming beneficial treatment effect on the functional recovery (ARAT, mRS, NIHSS, BI), the study showed a significant impact of Cerebrolysin on decreasing depression rate among treated patients in comparison to placebo (**Fig. 7**).

Complementing this favorable pharmacological profile, the Cochrane review of six Cerebrolysin trials in vascular dementia documented its impact on ameliorating cognitive decline post-stroke in dosages ranging from 10 to 30 ml per day³. The safety aspects of Cerebrolysin were comparable to placebo, thus suggesting a favorable benefit-risk ratio in patients with mild-to-moderately severe vascular dementia. Summarizing collected to date results from all trials investigating Cerebrolysin treatment of dementia, Dr. Bornstein suggested that Cerebrolysin combines symptomatic action with long-term treatment effects. It improves cognitive functions, in early Alzheimer's disease (AD) stages, when used in lower doses (10-30ml). At higher doses (60ml) Cerebrolysin improves behavioral symptoms (in later AD stages). When used along with the symptomatic AD treatment, Cerebrolysin was shown to be as effective as cholinesterase inhibitors (ChEI) and, additionally, it was safe and well-tolerated also in combination with ChEI. Importantly, Cerebrolysin was effective in both in-patient and out-patient settings and, as an injectable drug, had a better compliance profile than oral drugs. This favorable pharmacological profile of Cerebrolysin, combining improvement in functional outcome with improved quality of life, led to a proposal of a new study initiated by Dr. Bornstein in Sharee-Zedek Medical Center, in Tel-Aviv. The study aims at assessing the efficacy of Cerebrolysin as an add-on therapy to thrombolysis and thrombectomy with a major focus on post-stroke depression and cognitive decline. It will include up to 50 patients and the treatment group will receive Cerebrolysin in 30 ml daily dose for 7 days. Cognitive parameters will be assessed with MoCA and depression with GDS, both at day 90. All patients will receive a standardized post-stroke treatment.

Fig. 7. Cerebrolysin significantly improves functional outcomes and decreases the rate of depression among patients undergoing motor rehabilitation

1. Stroke. 2012 Mar;43(3):630-6.
2. Cochrane Systematic Review - Intervention Version published: 31 January 2013 <https://doi.org/10.1002/14651858.CD008900.pub2>
3. Stroke. 2016 Jan;47(1):151-9.

Q&A Session

N. V. Ramani

The questions and answers session began with the issue of the optimal time window for Cerebrolysin in the context of acute stroke treatment and its use as add on to recanalization therapies. Dr. Poljakovic suggested that “as early as possible”, including in the ambulance, is probably the optimal approach. She explained that in her study Cerebrolysin was administered after 24 hours, just to ensure the futility of recanalization. However, in everyday clinical practice, the evidence suggests that the earlier the treatment with Cerebrolysin the more pronounced is the therapeutic benefit for a patient.

The following question from Dr. Ramani explored the rationale of administering Cerebrolysin when rtPA cannot be used due to late admission or eligibility issues. Dr. Poljakovic stated that Cerebrolysin should be used in any case, irrespective of recanalization status because its pharmacological profile addresses immediate as well as delayed events in the complex pathophysiological sequelae of stroke. Particularly, its neuroprotective, anti-inflammatory, and neuroregeneration properties can help in cases where recanalization therapy failed or wasn't available, as was indicated in Dr. Poljakovic's study.

The next question dealt with the possibility of using neuroprotective agents to extend the therapeutic window of rtPA. For example, using Cerebrolysin in the ambulance could theoretically allow for the safer alteplase administration within a longer than currently approved time window. Dr. Poljakovic agreed that the reasoning is right. We often lose time waiting for the results of diagnostic evaluation and, therefore, the idea of using Cerebrolysin before a decision is made about recanalization therapy is backed by strong merit. However, extending the time window for thrombolysis using neuroprotective agents requires appropriate clinical evidence which currently is lacking.

The question for Dr. Bornstein addressed the best standard for establishing the collateral status of a patient as used for exclusion and inclusion criteria for the trials. The multiphase CTA appears to be the current best standard in this case, as it allows for the most precise evaluation of collateral blood flow in stroke patients. After more than 30 years of experience with clinical trials in neuroprotection, we now understand that the major issue was the failed delivery of the agent to the place of its supposed action - the ischemic penumbra. Therefore, the favorable collateral status appears as an important inclusion prerequisite in future neuroprotective trials. Dr. Bornstein commented also on extending the time window of thrombolysis. At his medical center, the wake-up stroke protocol is used for the identification of eligible patients, with an excellent outcome and no additional safety concerns. Using Cerebrolysin as an add on to this protocol appears as a good option, as it could provide additional assistance for late-stage thrombolysis protocols.

The next question addressed using mRS 0-3 in place of mRS 0-1 or 0-2, which are more commonly used cut-points for positive functional outcome in stroke trials, in Dr. Poljakovic's study. Using the dichotomized scales instead of the ordinal approach is a matter of historical choice, but not necessarily the best one, said Dr. Poljakovic. It is debatable what should be considered a good outcome in stroke patients. In her view, as mRS 3 indicates a patient capable of walking independently, it is the last point on the mRS scale clearly connected to improved quality of life after treatment. The difference between mRS 3 and mRS 4 is often considered as the biggest from the standpoint of quality of life after stroke. This is the reason why mRS 3 was used as a positive outcome cut-point in her study. Dr. Bornstein chimed in confirming that "ask the patient" approach to assess good clinical outcome is currently seen as a required paradigm shift in stroke care. Listening to what a patient says about their quality of life is more important than just technical evaluation of their status based on outcome scales.

Whether acute rehabilitation was used for patients in Dr. Poljakovic's study was the next question posted. The standard of care protocols were used for all patients, said Dr. Poljakovic. However, not all patients receive acute rehabilitation in her center. This depends on the discharge status of a patient, with those unable to take care of themselves undergoing rehabilitation in a specialized rehab institute.

The following question explored potential safety concerns of Cerebrolysin treatment if there are any. Dr. Bornstein stated that throughout all clinical trials completed to date, no concerns were detected regarding Cerebrolysin in any treatment protocol. The safety profile was similar to that of placebo in all RCTs. Dr. Poljakovic agreed with this statement and added that it is very comfortable to work with Cerebrolysin as it can be tried safely in various personalized protocols as required in clinical practice for any individual patient.

Dr. Bornstein commented also on acute rehabilitation as a concept. Current guidelines call for rehabilitation in all but severe patients and after 24 hours post-stroke. The data from the Lang study (combination Cerebrolysin with rtPA) indicates that adding Cerebrolysin very early can accelerate functional recovery and enable earlier rehabilitation (or early mobilization). This is just another argument supporting the idea of using thrombolysis together with Cerebrolysin.

The lecturers thanked the audience for the active participation and asked them to stay tuned for further news about investigating Cerebrolysin in various clinical protocols, including the combination therapies and also the mono-therapy for neuroprotection and recovery after stroke.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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