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New Avenues for Treatment of Intracranial Hemorrhage

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Opinion statement

The mortality and morbidity from intracerebral hemorrhage (ICH) remain high despite advances in medical, neurologic, and surgical care during the past decade. The lessons learned from previous therapeutic trials in ICH, improved understanding of the pathophysiology of neuronal injury after ICH, and advances in imaging and pre-hospital assessment technologies provide optimism that more effective therapies for ICH are likely to emerge in the coming years. The potential new avenues for the treatment of ICH include a combination of increased utilization of minimally invasive surgical techniques with or without thrombolytic usage to evacuate or reduce the size of the hematoma; utilization of advanced imaging to improve selection of patients who are likely to benefit from reversal of coagulopathy or hemostatic therapy; ultra-early diagnosis and initiation of therapy in the ambulance; and the use of novel drugs to target the secondary injury mechanisms, including the inflammatory cascade, perihematomal edema reduction, and hemoglobin degradation products-mediated toxicity.

Introduction

Intracerebral hemorrhage (ICH) has high morbidity and mortality despite advances in medical, neurologic, and surgical care. There is desperate need to find effective and novel therapies to improve the outcome of this devastating condition. Recent advances in our understanding of the pathophysiolo-

gy of neuronal injury after ICH and the development of multiple ongoing research and clinical efforts to target ICH lend hopeful optimism that effective therapies and strategies are underway. In this review, we discuss new promising avenues for the treatment of ICH.

Epidemiologic considerations

ICH is a stroke subtype with particularly high morbidity and mortality. It comprises approximately 10 %–15 % of all incident ischemic and hemorrhagic strokes [1], a proportion that has remained stable over the past few decades [1–3]. Pooled data from a systematic review and meta-analysis estimated the annual incidence at approximately 25/100,000 [2]. Despite advances in treatment and some studies suggesting decreased incidence rates, more updated analyses suggest that those have remained relatively stable or with nonsignificant decreases over the past few decades [1–3]. A decrease in ICH rates among patients aged 75 or younger seems to be largely attenuated by increased rates among those 75 years or older [1], highlighting the societal and economic burden of ICH in an aging population.

The 1-month ICH case fatality rate is approximately 40 %, rising to 55 % in 1 year [2]. The 10-year survival rate has been estimated at 20 %–25 % [4]. Despite advances in therapy, survival rates have not improved [1, 2] in the last decades. The rate of functional independence after ICH at 1 year varies from 12 % to 39 % in various studies [2].

Racial differences in ICH have been a point of particular interest in the past with evidence suggesting increased incidence among blacks compared with whites [5]. However, in a more updated, detailed systematic review and meta-analysis, only Asians and East Asians were found to have increased incidences of ICH compared with Whites, Blacks, and Hispanics, with an OR of 2.1 [2]. Similarly, gender as a risk factor has attracted attention with incongruent results among studies. In one study, the crude RR of ICH was 3.73 for men [6]. Subsequent meta-analyses, however, reported a much more attenuated effect of gender with a nonsignificantly lower risk for females (OR 0.85, CI 0.61–1.18), sex explaining only 2.1 % of variance in ICH incidence [2]. In addition, age [2, 6] hypertension (especially for deep hemorrhages) [5], increasing antithrombotic use [7], and cerebral amyloid angiopathy [8] have been causally related to ICH.

Pathophysiology of neuronal injury after ICH

Understanding the pathophysiology and natural history of ICH is of utmost importance as it provides the basis for identifying potential therapeutic targets. ICH results from vessel rupture and blood extravasation in the brain parenchyma, leading to hematoma formation, mechanical disruption and tearing of neighboring blood vessels, leading to growth of the hematoma and culminating in cessation of neuronal function. This primary insult is followed by a cascade of secondary events including edema formation, pre-

cipitated by the growing mass of blood and toxic effects of blood degradation products, over the ensuing days-to-weeks resulting in delayed (secondary) neuronal injury.

Hematoma expansion (HE)

Although the initial hematoma volume is the single most important predictor of 30-day mortality and functional outcome, HE is a consistent predictor of early deterioration and mortality, with each milliliter increase in absolute volume increasing the chance of dependence by 7 % [9]. This association between the extent of hematoma expansion and clinical outcome has been shown in several studies [10–12]. HE has been widely investigated as a therapeutic target in ICH given its modifiable nature.

Various definitions for HE have been used, ranging from any increase in hematoma size, to >33 % relative increase in size using the ABC/2 method on CT imaging [13]. Estimating the frequency of HE is largely dependent on the definition used and timing of imaging. Pooling data from studies focused on hematoma expansion utilizing similar definitions but heterogeneous imaging time points reveals that HE frequency ranges from 23 %–38 % [14]. Taking timing into account, HE is detected in 13 %–32 % of patients scanned within 6 hours of symptom onset [10], while scanning within 3 hours reveals HE of any degree in up to 73 % of patients, with "significant" expansion affecting one third of them [9].The frequency decreases to 11 % for those presenting after 6 hours and 20 % for those with unknown exact time of ICH onset [15].The above data demonstrate that early presentation is associated with higher likelihood of HE, and indicates that targeting HE as a therapeutic target is time sensitive and urgent.

The risk factors and pathophysiologic processes underlying HE are not completely understood. Although it has been traditionally conceptualized as continuous blood leakage from a single ruptured vessel, supporting histopathologic evidence is lacking. An alternative model suggests multiple small vessels with ongoing bleeding in the periphery of the hematoma [13, 16]. Early identification of patients at high risk for significant HE and interventions to arrest hematoma growth have been the "Holy Grail" of the vast majority ICH investigations to date. There appears to be a relationship between initial hematoma volume and subsequent expansion: the larger the hematoma on presentation, the more likely it is to expand [10, 17]. Oral anticoagulant use has also been linked to HE [18, 19]. Molecular and genetic factors have been investigated as well; Apolipoprotein E ε2 is associated not only with increased risk of ICH but also with increased risk for HE [20], likely by increasing vessel wall fragility. Interleukin-6, cellular fibronectin, matrix metalloproteinase-9, and tumor necrosis factor (TNF-α) are also associated with HE [21].

The "spot-sign", a hyperdense sign thought to represent contrast extravasation within the hematoma in CT angiography, has been shown to be an independent predictor of HE and poor outcome [22, 23, 24•]. It provides a potential imaging strategy to identify patients who are likely to benefit from interventions targeting HE. Despite the robust data from the PREDICT trial, further refinement of the spot sign is necessary, as the low sensitivity of 50 % [24•, 25] cannot be overlooked, as well as issues with inter-rater reliability

[25] and indications that hematoma volume affects the accuracy of prediction, being more reliable for hematomas >30 mL [26].

Secondary injury and perihematomal edema

Besides the primary neurologic insult caused by the hematoma itself, by tissue disruption and displacement, there is increasing evidence that a significant part of the pathologic process in ICH occurs as a result of a complex cascade of phenomena that follow the initial injury; the whole process has been characterized as "neurohemoinflammation." Thrombin appears to have a key role in the early stages of the process: it is produced as a result of activation of the coagulation cascade. In low doses it has a neuroprotective, hemostatic effect, limiting ongoing hemorrhage and hematoma expansion [27]. At higher doses, thrombin has a deleterious effect, affecting several different cell populations [28]; its detrimental effect on brain endothelial cells leads to blood–brain barrier disruption and formation of perihematomal edema [29]. Furthermore, it can activate Src Kinase with further effects on vascular permeability and excitotoxicity [30], as well as initiate apoptotic pathways for neurons and astrocytes [31].

A pronounced inflammatory response follows the primary hemorrhage, resulting in activation and influx of several cell populations, including microglia, neutrophils, and monocytes, leading to reactive oxygen species and proteases production as well as further blood brain barrier (BBB) disruption [32]. This is coupled by upregulation of inflammatory chemokines such as TNF-α and Interlukin-1β as well as matrix metaloproteinases (MMP), mainly MMP-3 and MMP-9. The collective effect of the above processes is further degradation of BBB integrity, extracellular matrix breakdown and worsening of cerebral edema [33–36]. Closely related to the above phenomena is the complement cascade activation and formation of membrane attack complex affecting neuronal cells by injuring them directly, as well as indirectly, by further enhancing the inflammatory cascade and destroying erythrocytes, leading to toxic heme byproduct release, in particular iron [37, 38]. There latter process is being increasingly recognized as a major contributor to perihematoma edema (PHE) and neurologic injury after ICH [39–44]. There is also emerging evidence supporting the role of the innate immune system, in particular the toll-like receptor 4 and its downstream cascade, in the pathogenesis of secondary injury after ICH [45].

Although the influence of PHE on long-term recovery after ICH is debatable [46–50], there is evidence that early edema progression correlates with early neurologic deterioration [46, 49]. Data from several studies confirm that PHE formation is a dynamic process; it almost unequivocally undergoes enlargement, which occurs at a faster pace in the first few days, but continues for weeks after ICH [49]. Radiologic studies of the natural history of PHE have yielded conflicting results regarding the association between baseline hematoma volume and edema volume. Some authors conclude that baseline edema is only moderately correlated with hematoma volume and more importantly, subsequent edema expansion does not show correlation with hematoma enlargement [51], while others report a closer association between hematoma and PHE volumes [49, 52, 53]. The historical simplistic

viewpoint that PHE merely represents perihematoma ischemia secondary to microvascular compression has been refuted by mounting physiologic and molecular evidence. Although studies utilizing advanced imaging and including diffusivity properties of PHE support the presence of relative hypoperfusion in the periphery of the hematoma, this is self-limited and lacks hallmark imaging signs of acute ischemia, most specifically decreased apparent diffusion coefficient (ADC) values [54–58]. MRI-based studies including diffusivity measures, suggest that the initially increased ADC values (in images obtained within the first 48 hours) show a consistent tendency to decrease in later imaging (as late as 7 days) [55, 57]. In fact there is evidence from imaging studies suggesting that PHE is plasma-derived [54], in accordance with the biologic evidence of BBB disruption, inflammation, and protein extravasation. This evidence collectively suggests that an early phase of transient but not critical hypoperfusion with vasogenic edema is followed by some degree of cytotoxic edema that reflects the effect of secondary inflammatory, apoptotic, neurotoxic processes mentioned above.

Therapeutic targets in ICH

The mechanisms of neurologic injury in ICH outlined above offer numerous potential therapeutic targets, which can be summarized as follows:

(1) Reducing the size of the hematoma through surgical evacuation, or minimally invasive stereotactic aspiration.

(2) Limiting hematoma expansion, either through the use of hemostatic agents, reversal of coagulopathy, or intensive blood pressure (BP) lowering.

(3) Modifying the molecular events precipitating the secondary effects of ICH, in particular iron-mediated toxicity, and inflammation induced by hemoglobin degradation products, or accelerating endogenous hematoma resolution.

Ongoing and future avenues for the treatment of ICH

Several of the strategies outlined above have already been tested in human clinical trials, while others are either at a primary, translational or early clinical stage. In the following section we will review previous attempted treatments for ICH, with emphasis on those that are in an early, yet promising stage.

Surgical hematoma removal

Craniotomy

Surgical evacuation of the hematoma has been the subject of extensive investigation. Intuition suggests that removal of the hematoma should relieve the mechanical pressure on adjacent healthy tissue and limit secondary inflammatory, excitotoxic and apoptotic phenomena. Indeed, surgical evacuation in patients with cerebellar hemorrhage with evidence of hydrocephalus from 4th ventricle obstruction or evidence of brainstem compression from

the local effect of the hematoma can be life-saving [59]. However, the results of two large multinational randomized controlled trials [60, 61•] comparing the effect of craniotomy vs conservative therapy in acute primary supratentorial ICH did not support beneficial effects from surgery. Several reasons have been proposed to explain the lack of "expected" benefit from open craniectomy. The dogma that "time is brain" perhaps explains it partly—the surgeons were expected to undertake surgery within 12 hours, which, although a reasonable target from a logistical standpoint, it might be too late from a biologic standpoint, allowing time for the initiation of detrimental secondary injury mechanisms whose effect is only partially mitigated after hematoma removal. However, early surgery is associated with increased re-bleeding due to release of the tamponading tissue pressure. In addition, it is practically inevitable that this major invasive approach causes some healthy tissue disruption, which, although not objectively measureable, has a detrimental effect potentially outweighing the proposed benefit from removing the clot.

Minimally invasive hematoma evacuation

Given the neutral effects of craniotomy and hematoma evacuation and the inherent risks of a surgical approach, especially for hemorrhages with a deep parenchymal location, minimally invasive methods are now the subject of vigorous investigations. A small, phase 2 trial testing the safety of stereotactic aspiration and thrombolysis in 28 patients with deep basal ganglia and internal capsule hemorrhages provided preliminary evidence of reduction in ICH and improved clinical outcomes, and led to MISTIE II (Minimally Invasive Surgery plus TPA for Intracerebral Hemorrhage Evacuation) trial, a two stage multicenter randomized safety and dose-finding prospective trial, which supported the safety of this approach, and showed a statistically significant decrease in both hematoma and PHE volumes [62, 63•] DF Hanley, International Stroke Conference, Honolulu HI, 2013). The ICES (Intraoperative CT-guided Endoscopic Surgery) tier of the trial, in which endoscopic evacuation without thrombolysis was compared with medical management, showed similar results (Vespa P, International Stroke Conference, Honolulu, HI, February 2013). Planning for a phase III trial (MISTIE III, NCT01827046) to test the efficacy of this promising approach in a larger population of ICH patients is currently underway. A similar approach for patients with intraventricular hemorrhage (IVH) is currently under investigations. A phase II study comparing t-PA with placebo via external ventricular drainage catheter (CLEAR IVH) in 48 patients with IVH showed safety and an increased rate of clot lysis [64], leading to a larger ongoing phase III trial (CLEAR III, NCT00784134).

Another promising approach is to combine ultrasound with local t-PA to enhance hematoma resolution. A small single-center study tested the safety and efficacy of sonothrombolysis in primary ICH. This approach was shown to be safe with some evidence that clot lysis (intraparenchymal or intraventricular) is achieved faster than with thrombolysis alone [65]. The promising preliminary result need to be replicated and confirmed in larger scale trial.

Overall, there is guarded optimism that minimally invasive aspiration of the clot with local t-PA alone or in combination with ultrasound could provide a successful strategy to treat ICH in the future if the results of planned phase III trials support its safety and efficacy.

Limiting hematoma expansion

Hematoma expansion (HE) remains a major target to minimize neurologic deterioration and decrease morbidity and mortality after ICH. Several efforts are underway.

Hemostatic therapy

Although earlier studies showed that ultra-early use of activated Factor VIIa within 4 hours of ICH onset could reduce HE at 24 hours, the magnitude of the effect was mild and did not result in improvement in functional outcomes [66•]. Furthermore, the use of activated FVIIa was associated with an increased risk of thromboembolic complications, including ischemic stroke and myocardial infarction [67]. The lessons learned from FAST (Factor Seven for Acute Hemorrhagic Stroke Trial) highlighted two important considerations: (1) the need for improved selection and identification of ICH patients who are most likely to derive benefit from hemostatic therapy using advanced imaging or biochemical markers [21, 23]; and (2) targeting hematoma expansion is time sensitive. HE resulting in significant clinical deterioration occurs in 26 % of patients within 1 hour of ICH onset, and in an additional 12 % of patients by 20 hours [68]. In patients with ICH associated with warfarin use, the potential for HE is higher, and hematoma growth may continue beyond the first 20–24 hours [19].

As a result, several ongoing trials are reinvestigating the role of hemostatic therapy in ICH patients based on the presence of the spot sign on CT angiography as an inclusion criterion. The Spot Sign for Predicting and Treating ICH Growth Study [STOP-IT] and the Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy [SPOTLIGHT] trials are currently re-examining the utility of activated Factor VIIa as a potential treatment for ICH in "spot sign" positive patients only (STOP-IT, NCT00810888, SPOTLIGHT, NCT01359202), while the Spot Sign and Tranexamic Acid On Preventing ICH Growth - Australasia Trial is studying tranexamic acid (STOP-AUST, NCT 01702636).

In addition, the use of hemostatic therapy, in particular prothrombin complex concentrates (PCCs), for rapid correction of coagulopathy and reversal of elevated INR in patients with warfarin-associated ICH continues to be under investigations. Although several studies have clearly demonstrated that PCCs can rapidly normalize INR within 20–30 minutes of its administration, the effects of PCCs on functional outcomes and mortality remain equivocal [69, 70]. Future and ongoing studies, such as the International Normalized Ratio (INR) Normalization in Coumadin Associated Intracerebral Hemorrhage (INCH, NCT00928915) trial, a randomized prospective trial studying the use of PCCs and fresh

frozen plasma in anticoagulation-related ICH, are likely to refine the selection of patients who are most likely to benefit from rapid reversal of coagulopathy. It is also likely that future studies will incorporate CTA and the spot sign to guide therapeutic decisions.

Intensive blood pressure lowering

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) [71] and the Antihypertensive Treatment in Acute Cerebral Hemorrhage (ATACH) [72] trials showed that early intensive systolic blood pressure lowering to less than 140 mm Hg is clinically feasible, well tolerated, and seems to reduce HE in ICH. Meanwhile, the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure (ADAPT) Trial demonstrated that rapid SBP lowering to less than 150 mm Hg after ICH does not reduce perihematoma cerebral blood flow as assessed by perfusion CT [73]. The recently completed phase-3 INTERACT-2 trial in 2839 patients confirmed the safety of rapid lowering of SBP within 6 hours of ICH onset to less than 140 mm Hg; reported a strong trend, albeit nonsignificant, toward reduced 90-day mortality and severe disability with intensive blood pressure lowering; and showed significantly improved functional outcomes in the treatment arm in a secondary ordinal analysis of 90-day modified Rankin Scale scores [74•]. However, the magnitude of benefit from intensive BP lowering in INTERACT-2 was small, and seemed to be unrelated to reduction of HE. The results from INTERACT-2 raise important questions as to whether earlier and more prolonged intensive lowering of blood pressure could be more beneficial. The following ongoing studies are likely to provide additional valuable information to optimize blood pressure management in ICH patients in the future: (1) ATACH-2 study, a multi-center, phase-3, trial designed to evaluate the therapeutic benefit of intensive systolic blood pressure lowering to less than 140 mm Hg with intravenous nicardipine within 4.5 hours of symptom onset [75]; (2) Field Administration of Stroke Therapy-Blood Pressure Lowering (FAST-BP, NCT01811693) study, an open label, pilot, dose-escalation study of glyceryl trinitrate (Nitroglycerin) administered by paramedics in the field within 2 hours of symptom onset to severely hypertensive stroke patients; and (3) Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT, ISRCTN 66434824), a prospective, randomized, single-blind, parallel-group, controlled trial designed to test the safety and effect of transdermal glyceryl trinitrate initiated within 4 hours of stroke onset by the paramedics for 7 days on blood pressure in patients with hyperacute stroke.

There is compelling evidence to support the notion that every minute counts in ICH, just like its ischemic stroke counterpart. Early neurologic deterioration en route to the hospital or in the emergency department occurs in 20 %–25 % of ICH patients, and its predictors include: higher blood pressure at the scene, ICH onset time under 3 hours, initial body temperature ≥37.5 °C, intraventricular extension, and radiologically evident herniation or midline shift greater than 2 mm [76, 77]. Ultra-early management of the factors leading to deterioration before the patient reaches the hospital setting

is essential to reduce the morbidity and mortality of ICH. Recent advances in pre-hospital assessment of stroke patients, including the introduction of mobile stroke units equipped with CT scanners, point-of-care laboratories, and telemedicine capabilities [78] indicates that greater involvement of the paramedics in the diagnosis and treatment of ICH is expected in the not too distant future.

Targeting the secondary injury

The secondary injury after ICH is multifactorial and includes direct effects of the primary insult (eg, mass effect and physical disruption), physiological response to the hematoma (eg, inflammation) and release of clot components (eg, hemoglobin and iron). Unlike HE, which is time sensitive, the secondary injury after ICH tends to be delayed and lasts from days to weeks, thus, providing a longer time window for intervention. A few studies targeting the secondary events after ICH are currently underway. If successful, they could supplement the previously mentioned ongoing efforts targeting the hematoma and its expansion to treat ICH. A summary of these potential interventions follows.

Minocycline

Minocylcine is a tetracycline-based antibiotic that has attracted significant attention due to its ability to achieve satisfactory CNS penetration. Several lines of evidence suggest that minocylcine has a pleiotropic neuroprotective effect in ICH models, reducing inflammation and oxidative stress (likely by acting as a free radical scavenger), inhibiting apoptosis and blocking the activity of matrix metalloproteinases [79]. Daily systemic administration of minocylcine in rat ICH models showed reduced inflammatory marker activation, preserved BBB permeability, and reduced cerebral edema [80, 81]. Some authors suggest that the neuroprotective effect might be limited to the critical first 3 hours after hemorrhage [82]. Minocycline is an attractive therapeutic agent for ICH, and is currently being investigated in the Minocycline in Intracerebral Hemorrhage Patients (MACH- NCT01805895) trial; a pilot study assessing the safety and potential efficacy of minocycline in acute ICH—24 patients will be randomly assigned (1:1) to either 400 mg of minocycline or placebo for 5 days.

Hypothermia

Hypothermia has established neuroprotectant properties, both in animal models of cerebral ischemia [83] and human victims of cardiac arrest, in whom it reduces mortality and improves chances of a favorable neurologic outcome [84]. In animal models of ICH, the results have been mixed thus far, with some experiments suggesting decreased cerebral edema but not improved functional outcome [85]. A time-dependent effect might exist, with delayed onset of hypothermia having a beneficial effect both in terms of tissue loss and functional outcome, while early onset hypothermia (earlier than 12 hours) did not offer any advantage [86]. A small nonrandomized study of mild prolonged hypothermia (35 °C for 8–10 days) in 25 patients

with large supratentorial ICH suggested that hypothermia arrested the progression of PHE and reduced 3-month mortality compared with historical controls. Shivering and pneumonia (96 %) were the most frequent side effects, although the latter was reportedly adequately controlled with antibiotic treatment [87]. This is being followed by the Cooling in INtraCerebral Hemorrhage (CINCH) trial; a phase II randomized trial, planning to recruit 50 patients with basal ganglia or thalamic ICH to test prolonged mild hypothermia (35 °C for 8 days) vs normothermia for the primary endpoints of hematoma volume and 30-day mortality [88]. The safety and feasibility study of Targeted Temperature Management after ICH (TTM-ICH NCT01607151) is another randomized study aiming to test the safety of 72 hours of hypothermia (32 °C–24 °C) vs normothermia in patients with supratentorial ICH. Based on the same principle, an open label, randomized, study (Aggressive Fever Control With Intravenous Ibuprofen After Nontraumatic Brain Hemorrhage NCT01530880) is currently evaluating the efficacy of fever control by continuous intravenous infusion of ibuprofen vs conventional measures.

Albumin

Albumin exerts multiple neuroprotective effects in animal models of ICH and ischemic stroke. In rat models of experimental ICH, treatment with albumin improved neurologic function and maintained integrity of the blood–brain barrier [89] without affecting hematoma volume or edema [90]. Despite the negative results of the albumin in acute ischemic stroke (ALIAS) clinical trial [91], the potential benefit of albumin in ICH is currently under investigation in the Albumin for ICH Intervention (ACHIEVE, NCT00990509) study, a placebo-controlled trial aiming to evaluate the positive and negative effects of albumin in patients with ICH within 24 hours of symptom onset with the primary outcome measure being the frequency and severity of blood brain barrier disruption based on pre- and postcontrast magnetic resonance imaging.

Deferoxamine mesylate

Hemoglobin degradation products, in particular iron, are major contributors to secondary injury after ICH [92]. The neurotoxic effects of iron resulting from the hemolysis of red blood cells are mediated via several mechanisms, including: autophagy, oxidative stress and hydroxyl radical formation, and exacerbation of excitotoxicity [41, 93]. The iron chelator, deferoxamine mesylate, has been shown to reduce the secondary injury after ICH in rat and pig models [94, 95]. Deferoxamine has anti-apoptosis, anti-oxidative stress, anti-phagocytosis, and anti-inflammatory effects, and blocks hemoglobin-mediated accentuation of glutamate excitotoxicity. Animal studies have shown that DFO reduces hemoglobin-induced neurotoxicity in vitro and in animal models of hemorrhage, and improves neurologic function after experimental ICH [94, 96–98]. The safety of deferoxamine in patients with ICH was investigated in the Dose Finding and Safety Study of Deferoxamine in Patients with ICH (DFO in ICH) Study, a phase I open label study evaluating the safety and tolerability of varying doses of DFO to determine a maximum tolerated dose. Repeated daily infusions of DFO in doses up to 62 mg/kg/day (up to a maximum daily dose of 6000 mg per day) in patients with

acute spontaneous ICH were safe and not associated with increased adverse events or mortality [99]. A larger, phase II, randomized, placebo-controlled, blinded, multi-center, trial (High dose deferoxamine in ICH [HI-DEF] trial, NCT01662895) is currently underway to determine whether treatment with deferoxamine mesylate is of sufficient promise to improve outcome before pursuing a larger phase III clinical trial to examine its effectiveness as a treatment for ICH.

Pioglitazone

Pioglitazone is an agonist of the peroxisome proliferator-activated receptor gamma. Preclinical work demonstrates that the transcription factor peroxisome proliferator-activated receptor gamma plays an important role in augmenting phagocytosis while modulating oxidative stress and inflammation [100], suggesting that targeted stimulation of phagocytosis to promote efficient removal of the hematoma without harming surrounding brain cells may be a therapeutic option for ICH. The Safety of Pioglitazone for Hematoma Resolution In ICH (SHRINC) study [101], a prospective, randomized, blinded, placebo-controlled, dose-escalation safety trial, was recently completed, and its results should inform the design of future phase II/III evaluation of pioglitazone as a potential therapy for ICH.

Conclusions and future directions

Several studies aimed at improved selection and identification of ICH patients for hemostatic therapy and reversal of coagulopathy, and investigations of novel agents targeting the mechanisms of secondary injury after ICH are currently underway, and their results could have important implications for the management of ICH in the future. Future avenues for the treatment of ICH are likely to combine strategies aiming at reducing the size of the hematoma and its expansion with those targeting the mechanisms of secondary injury, and are likely to involve increased utilization of pre-hospital services for early diagnosis and initiation of therapy. Future research is likely to focus on better understanding of the role of the innate immune system in the pathogenesis of secondary injury after ICH and the development of new drugs to target chemotactic signals downstream of toll-like receptor 4.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Shruti Sonni declares no potential conflicts of interest relevant to this article. Dr. Vasileios-Arsenios Lioutas declares no potential conflicts of interest relevant to this article. Dr. Magdy H. Selim is the principal investigator for a NINDS-sponsored trial (U01 NS074425).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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