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Emerging Pharmacological Treatments for Cerebral Edema: Evidence from Clinical Studies

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Abstract

Cerebral edema, a common and often fatal companion to most forms of acute central nervous system disease, has been recognized since the time of ancient Egypt. Unfortunately, our therapeutic armamentarium remains limited, in part due to historic limitations in our understanding of cerebral edema pathophysiology. Recent advancements have led to a number of clinical trials for novel therapeutics that could fundamentally alter the treatment of cerebral edema. In this review, we discuss these agents, their targets, and the data supporting their use, with a focus on agents that have progressed to clinical trials.

INTRODUCTION

Cerebral edema, defined as a net increase in brain water mass, is present in most types of acute central nervous system (CNS) injury or insult. In ischemic stroke, severe cerebral edema can increase mortality to nearly 80% (1) and is an independent risk factor for poor outcomes (2). In traumatic brain injury (TBI), brain swelling accounts for nearly 50% of all mortalities (3). In glioblastoma, peritumoral edema is a strong independent predictor for reduced survival (4–6). And in intracerebral hemorrhage (ICH), perihematoma edema volume is associated with increased morbidity and mortality (7).

All current therapies for cerebral edema are nonspecific to the underlying pathophysiology. Instead, they primarily seek to minimize critical downstream consequences of edema: mass effect and increased intracranial pressure (ICP). For example, decompressive craniectomy does not inhibit the formation of edema fluid but rather enables the brain to expand further, thereby reducing pressure. While hyperosmotic therapies such as mannitol do reduce edema fluid volume, they simply compete with, rather than inhibit, the driving forces that promote edema formation. As a consequence, these therapies are typically given only after the ICP reaches a critical level and when brain perfusion is threatened. Ideally, antiedema therapy would be given prophylactically, thereby avoiding any risk to tissue perfusion. However, this paradigm requires new antiedema drugs that block edema formation itself.

Several pharmacological agents have shown promise in preclinical models and are currently being tested in clinical trials. In this review, we briefly present the pathophysiology of cerebral edema. We then discuss several potential antiedema drugs (**Table 1**), but only those that have progressed to clinical trials, focusing on their mechanisms of action and the data that support their efficacy.

CEREBRAL EDEMA PATHOPHYSIOLOGY

General Concepts: Ischemia and Trauma

For a detailed description of cerebral edema pathophysiology, please refer to Stokum et al. (8). Briefly, cerebral edema develops in several stages following CNS injury, although the precise details depend on the type and severity of the insult. Within minutes after injury, the neuroparenchyma exhibits cytotoxic edema (used here to refer only to cellular swelling), which consists mainly of astrocyte swelling (9, 10). Multiple ion transporters contribute to cytotoxic edema formation by mediating astrocyte osmolyte uptake, which in turn drives astrocyte water uptake. Examples of ion transporters include the sulfonylurea receptor 1–transient receptor potential melastatin 4 (SUR1-TRPM4) channel (11, 12), the sodium-potassium-chloride transporter subtype 1 transporter (13, 14), the sodium-hydrogen exchanger (15), and the excitatory amino acid transporters (16).

As an isolated rearrangement of parenchymal water, cytotoxic (cellular) edema by itself does not directly produce brain swelling. However, cytotoxic edema does generate the major driving force for downstream edema formation. By depleting extracellular sodium ions (Na^+), cytotoxic edema generates a new Na^+ gradient across the blood–brain barrier (BBB) that favors the influx of vascular Na^+ (17). Various Na^+ transporters expressed by brain endothelial cells then enable Na^+ osmolytes to follow this new electrochemical gradient inward across the BBB (18–20). Water follows, resulting in the formation of a subtype of cerebral edema called ionic edema, which does result in brain swelling. In reality, cytotoxic edema is not thought to occur in isolation from ionic edema, but conceptually separating the two processes aids in understanding the role of distinct molecular mechanisms that contribute separately to the two processes.

Table 1 Prior and ongoing clinical trials of antiedema drugs

Trial	Trial details	Drug	Studied population	Salient results (references)
NCT03000283	Ongoing pilot, goal of 7 participants	Conivaptan	Patients with ICH greater than 20 cc not due to infection, thrombolysis, SAH, trauma or tumor who are expected to survive more than 48 hours	Currently recruiting
NCT02002390	Phase 2 completed in 2014, 22 participants	Fingolimod	Patients with either supratentorial ICH of 5–30 cc or ischemic stroke Excluded if taken for surgical evacuation or if ICH due to coagulopathy, trauma, or thrombocytopenia	In ICH, fingolimod improved neurological function and reduced edema (41) In stroke, fingolimod reduced lesion volume and lesion growth and improved neurological function at 90 days (160)
NCT00526214 (ACE-ICH)	Pilot completed in 2009, 44 participants	Celecoxib	Patients presenting with supratentorial ICH not due to trauma, aneurysm rupture, or anticoagulation Excluded if planned surgical evacuation within 24 h	Celecoxib reduced hematoma expansion and perihematoma edema expansion (40)
NCT01268683 (GAMES-PILOT)	Phase 2a completed in 2013, 10 participants	Glyburide	Patients with large (82–210 cc) acute MCA or MCA/ACA ischemic stroke Excluded if patients had prior commitment to DC, treatment with IA rtPA or mechanical thrombectomy, herniation signs, or hemorrhage	Glyburide was feasible and well tolerated with no symptomatic hypoglycemia (119) Glyburide reduced radiographic markers of vasogenic edema (120) and improved clinical outcomes (161)
NCT01794182 (GAMES-RP)	Phase 2 completed in 2016, 83 participants		Patients with large (82–300 cc) acute MCA ischemic stroke Excluded if patients had prior commitment to DC, treatment with IA rtPA or mechanical thrombectomy, contralateral infarction, signs of herniation, or hemorrhage	Primary and secondary outcomes not met In adjudicated posthoc analysis, glyburide reduced midline shift, serum MMP9, NIHSS, edema-related deaths, and 30-day all-cause mortality (43, 44, 121)
NCT02864953 (CHARM)	Ongoing phase 3, goal of 680 participants		Patients with large (80–300 cc) acute MCA ischemic stroke or large hemispheric infarction with NIHSS $\geq$10 Excluded if patients likely to have withdrawal of care on day 1, have prior commitment to DC, or have contralateral infarction	Currently recruiting
No identifier	Phase 1 completed in 1998, 17 participants	Xerecept	Patients with primary or secondary brain tumor with evidence of edema on CT; included patients had stable steroid dose and were not submitted to concomitant chemotherapy or radiation	Xerecept was well tolerated and improved neurological symptoms (137)
NCT00088166	Phase 3 completed in 2008, 200 participants		Patients with histologically malignant brain tumor and $\geq$1 steroid side effects; included patients had stable steroid use and were not treated with surgery, radiosurgery, or radiation within 5 weeks of enrollment	Primary outcome not met Secondary outcomes met significance Xerecept reduced dexamethasone requirements, improved myopathy, and reduced risk of Cushing syndrome (138)
No identifier	Phase 2 completed in 2007, 32 participants	Bevacizumab	Patients with histologically confirmed progressive or recurrent grade III-IV glioma, post radiation therapy; patients not concomitantly treated with surgery, radiation, or chemotherapy	Bevacizumab reduced tumor cross-sectional area, radiographic markers of edema, and glucocorticoid requirements and resulted in neurological improvement (153)
NCT00943826 (AVAglio)	Phase 3 completed in 2015, 921 participants		Patients with newly diagnosed, histologically confirmed glioblastoma, and stable or decreasing glucocorticoid use Excluded if patients had hemorrhage or prior treatment for glioblastoma	Bevacizumab reduced glucocorticoid use and increased the time-to-initiation of glucocorticoid treatment (146)
NCT00305656 (NCT00254943)	Phase 2 completed in 2012, 31 participants	Cediranib	Patients with histologically confirmed glioblastoma and stable dose of corticosteroids	Cediranib reduced glucocorticoid use (151) Cediranib induced vessel normalization and reduced radiographic edema (152)

Abbreviations: ACA, anterior cerebral artery; CT, computed tomography; DC, decompressive craniectomy; IA, intra-arterial; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; MMP9, matrix metallopeptidase 9; NIHSS, National Institutes of Health stroke scale; rtPA, recombinant tissue plasminogen activator; SAH, subarachnoid hemorrhage.

During ionic edema formation, the BBB remains impermeable to circulating plasma proteins and erythrocytes. However, as the brain injury matures, plasma proteins appear in edema fluid due to the formation of permeability pores in the BBB. A variety of mechanisms, including vascular endothelial growth factor (VEGF) upregulation (21), matrix metalloproteinase activation (22), and changes in endothelial morphology, mediate the formation of permeability pores (23). Edema fluid that contains plasma proteins but still excludes erythrocytes is called vasogenic edema.

Peritumoral Edema

Peritumoral edema, which mostly consists of vasogenic edema, is formed by the disordered and proangiogenic tumor vasculature. The relatively unique mechanisms that underlie its formation are described below.

Relative to normal tissue, tumor vessels are serpiginous, irregular, and disorganized, resulting in large avascular areas and patchy necrosis (24). Up to 15% of tumor vessels may be mosaic, wherein the luminal wall comprises both endothelial and tumor cells (25). Strangely, some tumors contain isolated networks of vessel-like channels formed directly by tumor cells (26). The cells that form the tumor vasculature are also abnormal. Glioblastoma endothelial cells are proliferative and hypertrophic (27). Furthermore, many tumor endothelial cells and pericytes are derived from tumor stem cells rather than from stromal tissue (28–30).

Despite the increased vascularity present in many tumors, tumor perfusion is generally poor (31), in part because only 50–70% of newly formed vessels are capable of carrying erythrocytes (32). The poor perfusion provided by the abnormal tumor vasculature, combined with the heightened metabolic demand of the growing tumor, results in a hypoxic tumor microenvironment that promotes angiogenesis. In newly formed vessels, the BBB is not fully developed (33) and permits the passage of molecules up to ~550 nm (33, 34). In tumor vessels, interendothelial junctional proteins are often downregulated or undetectable (30). The increased permeability of tumor vessels encourages the extravasation of plasma, i.e., formation of vasogenic edema.

Peritumoral edema is an important barrier to tumor treatment (35). The combined mass effect of the tumor plus the peritumoral edema can drive local hydrostatic pressure in excess of 12 mm Hg (36). The increased tumor interstitial pressure reduces the hydrostatic pressure gradient between blood and tumor, inhibiting the delivery of chemotherapeutics. Furthermore, increased tumor interstitial pressure promotes bulk flow of fluid away from the tumor, which limits the efficacy of convection-enhanced delivery. Unsurprisingly, the magnitude of peritumoral edema is highly predictive of reduced patient survival (37).

CLINICAL TRIAL DESIGN

A number of antiedema agents have progressed to human clinical trial. However, the design of antiedema drug trials is still evolving as lessons are learned from the recent trials focused on this target. Here, we present several aspects of trial design that are salient to antiedema drugs.

Adequate preclinical animal experiments are critical prior to any clinical trial. Experiments should be performed using multiple animal models and should be conducted in multiple laboratories to ascertain drug dosing, time window, efficacy, and drug accumulation in the target organ. Several previous trials have suffered from inadequate preclinical data. In the head injury trials (HITs), nimodipine, an L-type voltage-gated calcium channel blocker, was tested in TBI without any preclinical data (38). The HITs failed to show any therapeutic benefit, and in the case of HIT-2, nimodipine was associated with worsened outcome. In the Selfotel (CGS-19755) TBI trial where a glutamate *N*-methyl-D-aspartate receptor antagonist was tested, the primary outcome

failed. However, since it was unknown whether peripherally administered Selfotel accumulated in the CNS, the negative result was difficult to interpret (38). Exploration of intermediate or pharmacodynamic end points that may be relevant to human translation is often helpful. For example, imaging markers of water content or plasma biomarkers may help identify potential candidate biomarkers in humans.

Well-designed inclusion and exclusion criteria can strongly influence the ability of a study to detect a therapeutic effect. It is important to identify patients that are likely to have the biological target of interest. Framing the study design so that the population is enriched with patients with a high likelihood of developing the problem of interest can maximize both the chance of drug effect and the magnitude of that effect, assuming the target problem has a causal relationship with clinical outcome. In addition, patients with relatively mild or relatively severe CNS insults are very likely to either improve or deteriorate, regardless of therapeutic intervention. Thus, if patient outcome is the desired end point, the ideal cohort may consist of patients that lie on an inflection point of disease severity (38). Even with stringent inclusion/exclusion criteria, patient matching may be difficult due to disease-related heterogeneity. For example, the heterogeneity of TBI patients has complicated data interpretation in prior TBI clinical trials (39). To address this problem, some have suggested stratification by clinically important, disease-specific variables, such as hemorrhagic shock or the presence of intraventricular hemorrhage (39).

Appropriate end point selection is a major issue in antiedema drug trial design. A number of previous trials have utilized radiographic end points, such as the quantification of edema using computed tomography (NCT03000283) (40) or using edema-sensitive MRI sequences such as gradient echo and fluid-attenuated inversion recovery (FLAIR) (41). Although several radiographic measurements are broadly accepted for cerebral edema, few have been validated as a quantitative end point for clinical trials. Ipsilateral swelling, lesional swelling, and midline shift are valuable radiographic markers (42, 43), but the relationship between these parameters and the magnitude of edema has yet to be established. Conversely, a clear association between midline shift and patient survival was established in a clinical trial of intravenous (IV) glyburide in large hemispheric infarction (43, 44) (**Figure 1**).

Several antiedema drug trials have used patient outcome end points, such as in-hospital mortality (NCT03000283) and clinical improvement as measured by the modified Rankin Scale, Glasgow Coma Scale, or National Institutes of Health stroke scale (40, 43). While patient outcomes are essential in determining the ultimate efficacy of an intervention, these end points are vulnerable to confounding. For example, in the Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) trial, where patients with large hemispheric infarction were treated with IV glyburide versus placebo to reduce edema, the primary end point was the proportion of patients with a modified Rankin Scale (mRS) score of $\leq$4 at 90 days without decompressive craniectomy (43). The study was complicated by significant intercenter variability in the application of decompressive craniectomy, with over 90% of the surgeries performed by approximately 50% of the study sites. Intercenter variability has complicated other trials, such as the TBI tirilazad trial in which intercenter variability accounted for over 40% of the study variance (38). This is especially true for nonrandom variability that occurs postrandomization.

Glyburide: a sulfonylurea drug that inhibits SUR1-containing channel complexes, including the SUR1-TRPM4 channel

ARGININE VASOPRESSIN AND THE VAPTANS

Arginine Vasopressin Is a Central Mediator of Brain Edema

Arginine vasopressin (AVP), a nine–amino acid peptide primarily produced by the posterior pituitary, was detected in mammalian cerebrospinal fluid (CSF) in 1978 (45, 46). In early experiments, CSF AVP increased after CSF harvest, which indicated a possible role for AVP in the regulation of brain water content (45, 46).

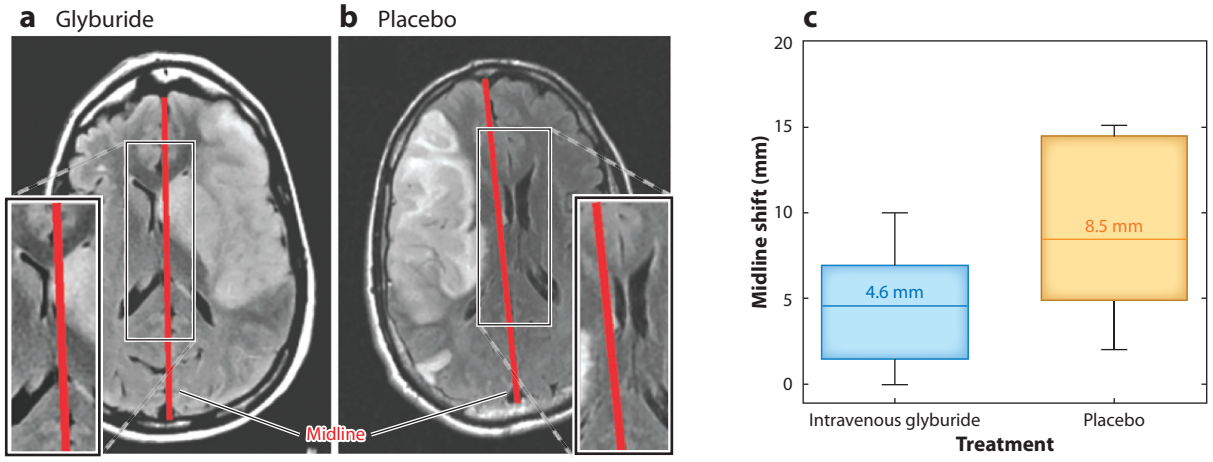

Figure 1

(*a*,*b*) Axial brain T2 fluid-attenuated inversion recovery MRI images from the Glyburide Advantage in Malignant Edema and Stroke study (NCT01794182) showing midline (*red bar*) shift in patients with large middle cerebral artery territory ischemic stroke who were given intravenous (IV) (*a*) glyburide or (*b*) placebo. (*c*) Graph showing the reduced median midline shift in patients given IV glyburide, with boxes depicting interquartile range, whiskers representing 10th to 90th percentiles, and bars showing 95% confidence intervals. Figure adapted with permission from Reference 43.

In the mammalian CNS, vasopressin exerts its effects primarily via the V1 receptor (47, 48), which is widely expressed throughout the adult brain (49, 50). AVP reaches the neuroparenchyma through multiple routes: Circulating AVP can be transported across the BBB via a carrier-mediated system (51); AVP can be centrally secreted by neurons and the choroid plexus epithelium (52, 53); and hypothalmo-extrahypophyseal vasopressin pathways innervate the ventricular walls, which may release AVP into ventricular CSF (54).

In the healthy brain, exogenous AVP delivered into the ventricles modestly increases brain water content by ~1.3% (55). AVP mediates changes in brain water content by regulating capillary permeability (56), astrocyte volume (57, 58), CSF production and absorption (59, 60), and cerebral blood flow (61). In contrast to its modest role in the healthy brain, central AVP signaling is a potent regulator of edema in the injured brain. In models of cerebral ischemia and TBI, AVP and its V1 receptor are upregulated (53, 62, 63). Experiments have consistently shown that AVP worsens cerebral edema in models of ischemic stroke (47, 48, 62, 64), after brain cryoinjury (65), and in models of TBI (66).

Circulating AVP also worsens brain edema, albeit indirectly. Among all hospitalized patients, hyponatremia, even when asymptomatic, is associated with increased brain edema and worsened mortality (67, 68). Hyponatremia is present in ~10% of patients with TBI and in ~20% of patients with subarachnoid hemorrhage (69). The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the underlying etiology of hyponatremia in ~62% of neurosurgical patients (69). SIADH occurs mainly through AVP stimulation of renal V2 receptors, resulting in antidiuresis and euvolemic hyponatremia (70).

Vaptans: a class of small-molecule vasopressin receptor inhibitors that include conivaptan and tolvaptan

Vaptans: Arginine Vasopressin Receptor Antagonists

Vaptans are nonpeptide small-molecule inhibitors of vasopressin receptors, with varying receptor subtype specificity. Two vaptans—conivaptan, a V1a and V2 receptor antagonist, and tolvaptan, a V2 specific antagonist—are currently approved to treat hyponatremia (71).

Preclinical experiments have shown that vasopressin receptor inhibition effectively reduces cerebral edema formation after CNS injury. Vasopressin antagonism reduces brain edema formation after cardiac arrest (72) and in models of ischemic stroke (47), subarachnoid hemorrhage (73), and TBI (66, 74, 75). Additional studies have found that vaptans exert their antiedema effects mainly via the inhibition of V1 receptors (47, 48) and through the regulation of aquaporin-4 (48), an aquaporin expressed in the CNS that plays a major role in edema dynamics (8).

Currently, there are limited clinical data supporting the use of vaptans for the treatment of brain edema. One case report demonstrated reduced ICP in a patient with occlusive carotid dissection treated with a vaptan (76). Another case report showed reduced edema in a patient with a midbrain and thalamic hemorrhage who was treated with a vaptan (77). There is an ongoing clinical trial (NCT03000283) to test the efficacy of conivaptan in the treatment of cerebral edema in patients with nontraumatic ICH.

Fingolimod: a sphingosine-1-phosphate (S1P) receptor modulator that acts as a functional S1P receptor antagonist

SPHINGOSINE-1-PHOSPHATE AND FINGOLIMOD

Sphingosine-1-Phosphate Signaling and Cerebral Edema

Sphingosine-1-phosphate (S1P) is a sphingolipid derivative that signals through S1P receptor subtypes 1–5 (S1P1–5) (78). Circulating S1P is derived from multiple sources, including platelets (79), erythrocytes (80), and endothelial cells (81). In the healthy CNS, S1P receptors are widely expressed by all cell types (82). Following CNS injury and during neuroinflammation, S1P and S1P receptors are upregulated in the CNS (83, 84).

S1P signaling is complex and has different roles in different cell types. Classically, S1P was considered critical in the regulation of lymphocyte trafficking. Via S1P1, S1P signaling is necessary for the egress of lymphocytes from peripheral lymphoid tissues (85). Consequently, S1P1 knockout lymphocytes become sequestered in lymphoid tissues (86).

There is growing recognition of the nonimmunological roles of S1P signaling. In endothelial cells, the major S1P receptor subtypes are S1P1, S1P2, and S1P3 (87), which regulate vascular and BBB permeability. S1P1 receptor signaling is particularly important in the development and maintenance of the vascular barrier via its effects upon the actin cytoskeleton and endothelial morphology (88). S1P1 knockout mice die around embryonic day 12–14 from hemorrhage due to inhibited vessel maturation (89). In conditions of anaphylaxis, histamine stimulation, or inflammation, erythrocyte-derived S1P stimulates endothelial S1P1 to help maintain vascular integrity (90).

Interestingly, in contrast to S1P1, endothelial S1P2 disrupts intercellular adherens junctions and promotes increased vascular permeability (91). During inflammation, S1P2 is upregulated, which could reflect a mechanism that enables context-specific tuning of endothelial permeability (87). Vascular S1P3 regulates vascular tone and perfusion by mediating cytoskeletal changes and activation of endothelial nitric oxide synthetase (92, 93).

Fingolimod: S1P Receptor Modulator

Fingolimod (FTY720) is an S1P receptor modulator that was approved in 2010 to treat multiple sclerosis (94–98). In vivo, FTY720 is activated to fingolimod phosphate by sphingosine kinase 2. Upon ligation of S1P1 and S1P3–5 receptors, fingolimod briefly acts as an agonist (99). However, upon fingolimod stimulation, S1P receptors are internalized, thereby quenching their biological activity (86). Thus, fingolimod ultimately acts as a functional S1P receptor antagonist.

In preclinical experiments, fingolimod reduced cerebral edema in models of ICH (100, 101) and ischemic stroke (102). Unfortunately, due to the pleiotropic roles of S1P in the cerebral vasculature and circulating immune cells, the precise mechanism of its antiedema effects is unclear.

There is growing clinical evidence in support of fingolimod as an antiedema drug, particularly following ICH. In one study that included 23 patients with ICH, fingolimod was shown to improve neurological status, perihematomal edema, and three-month mRS scores (41, 103). In a second study that included 22 patients with acute ischemic stroke, fingolimod improved neurological status and reduced microvascular permeability (104). Fingolimod is relatively well tolerated in patients, although it is linked with some instances of minor infections, bradycardia, and decreased pulmonary function (99).

Celecoxib: a nonsteroidal anti-inflammatory drug inhibitor of cyclooxygenase-2

CYCLOOXYGENASE AND NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Cyclooxygenase (COX) enzymes process arachidonic acid to generate proinflammatory prostaglandins and thromboxanes and come in three isoforms: COX1–3. Inflammation plays a key role in the pathophysiology of many CNS injuries and is particularly important in ICH (105). After ICH, COX2 is upregulated in the endothelium and invading leukocytes (106). In animal models of ICH, COX2 worsens neuronal death, neurological outcome, infarct volume, and brain edema (107, 108).

Two studies have examined the efficacy of the COX2 inhibitor celecoxib in reducing hematoma volume and cerebral edema after ICH. In a retrospective study of patients with ICH given celecoxib versus no celecoxib, celecoxib was found to reduce edema volume and hematoma expansion (109). In a randomized prospective study where patients with ICH were treated with celecoxib ($n = 20$) versus standard therapy ($n = 24$), celecoxib reduced perihematomal edema and hematoma expansion (40).

SUR1-TRPM4 AND GLYBURIDE

SUR1-TRPM4 is a monovalent cation channel that is de novo upregulated after CNS injury. The pore-forming subunit of the SUR1-TRPM4 channel is composed of TRPM4, a constitutively expressed monovalent cation channel that opens in response to increased intracellular calcium (11, 110, 111). After injury, SUR1, an adenosine triphosphate (ATP)-binding cassette, is de novo upregulated and coassociates with TRPM4, which doubles TRPM4 calcium sensitivity and sensitizes TRPM4 to intracellular ATP depletion (11, 110, 112).

In conditions of ATP depletion, such as acute CNS injury, SUR1-TRPM4 mediates the influx of Na^+ osmolytes, resulting in oncotic cell swelling and cell death (11, 12, 113). This ionic redistribution promotes transcapillary ion and water influx, driving brain edema and brain swelling (8). Furthermore, SUR1-TRPM4 also mediates the oncotic cell death of the capillary endothelium, resulting in capillary fragmentation, secondary hemorrhage, and worsened edema (114).

Glyburide is a sulfonylurea drug that inhibits SUR1-containing channel complexes. When given after cerebral ischemia, glyburide inhibits newly expressed SUR1-TRPM4 channels in the BBB (20). Glyburide reduces brain edema in animal models of ischemic stroke (20, 115), TBI (116), and subarachnoid hemorrhage (117). SUR1 inhibitors were also found to decrease peritumoral edema in animal models of cerebral metastases (118).

Several clinical trials have sought to assess the efficacy of glyburide for the treatment of malignant cerebral edema after large hemispheric infarction. In the first trial—the GAMES pilot—10 patients with large anterior circulation stroke were treated with IV glyburide, demonstrating treatment feasibility (119). A follow-up analysis of the GAMES pilot data showed reduced T2 FLAIR ratio and reduced water diffusivity in the ischemic tissue, indicating that glyburide reduced vasogenic edema (120). In the phase 2 GAMES-RP trial (43), patients 18–80 years old with large

(80–300 cm^3) anterior circulation infarctions were randomized to glyburide ($n = 41$) versus placebo ($n = 36$). The primary outcome was the proportion of patients with mRS scores of 0–4 at 90 days without decompressive craniectomy. Secondary outcomes included the proportion of patients that underwent decompressive craniectomy or were dead within 14 days and the change from baseline in ipsilateral hemispheric or lesional swelling within 72–96 h measured by MRI. The primary end point was not met, possibly due to high intercenter variability in the application of surgical decompression (90% of the surgeries in the trial occurred in half of the trial sites). However, glyburide was shown to improve mortality at 30 days, reduce median midline shift from 8.5 to 4.6 mm (**Figure 1**), and lower total plasma matrix metallopeptidase 9 levels. Furthermore, posthoc analyses showed significantly reduced adjudicated neurological and edema-related deaths as well as favorable long-term outcomes in patients <70 years old (44, 121). The phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (IV glyburide) for Severe Cerebral Edema Following Large Hemispheric Infarction (CHARM) is currently recruiting patients (NCT02864953). The prespecified outcome in the CHARM trial does not include surgical decompression and instead includes the mRS score at 90 days and the reduction of midline shift at 72 h.

Dexamethasone: a corticosteroid commonly used to treat peritumoral edema

Xerecept: a synthesized form of the endogenous hypothalamic human corticotrophin-releasing factor developed to treat peritumoral edema in patients with severe steroid side effects

CORTICOSTEROIDS AND XERECEPT FOR PERITUMORAL EDEMA

Dexamethasone

The first documented use of corticosteroids to treat edema was in 1957 when they were used in patients with cerebral breast cancer metastases (122). However, their use did not become widespread until the work of Joseph Galicich. In 1958, Dr. Galicich noted that BBB permeability varied diurnally with plasma cortisol levels, an observation that prompted him to treat peritumoral edema with corticosteroids (123). In 1961, his seminal work demonstrated the efficacy of dexamethasone for the treatment of peritumoral edema (124). Importantly, dexamethasone was the first drug taken to US Food and Drug Administration (FDA) approval by a neurosurgeon. While all subsequent randomized trials have tested dexamethasone for the treatment of peritumoral edema surrounding brain metastases (125–127), corticosteroids are now used in a variety of brain neoplasms.

Dexamethasone, which diffuses freely across the BBB (128), exerts pluripotent effects on the cerebral vasculature. Corticosteroids downregulate proinflammatory cytokines (129), reduce endothelial VEGF production (130), increase vascular differentiation (131), and induce expression of tight junction proteins (132). Together, these changes reduce the permeability of tumor microvessels (133).

Unfortunately, the side effect profile of corticosteroids is a major limiting factor to their use. Peripheral edema, hyperglycemia, and Cushing's syndrome occur in up to 15%, 72.3%, and 15% of patients, respectively (134). Thromboembolism, infections, delayed wound healing, gastrointestinal ulcers, and psychiatric issues are other common side effects (134).

Corticotrophin-Releasing Factor (Xerecept)

The side effect profile of corticosteroids prompted the development of the so-called steroid-sparing therapies. Human corticotrophin-releasing factor (hCRF), alternatively called corticorelin acetate and Xerecept, is a synthesized form of the endogenous 41–amino acid hypothalamus-derived peptide. When given peripherally, hCRF stabilizes the brain endothelium and reduces vasogenic edema in cold injury (135), and it reduces vascular permeability in rat models of glioma (136).

hCRF has been tested in human patients with brain tumors. A phase 1 trial showed improved neurological examination in 10 out of 17 patients following hCRF treatment. Hypotension was

reported as a side effect in 2 out of 4 patients treated with high-dose hCRF (137). In a second study of 200 patients given hCRF versus placebo, hCRF significantly reduced dexamethasone requirements, improved myopathy symptoms, and reduced the rate of Cushing's syndrome (138). With further study, hCRF could help to control peritumoral edema in patients with severe steroid side effects.

Bevacizumab: a monoclonal immunoglobulin G humanized antibody targeted against vascular endothelial growth factor A

Cediranib and enzastaurin: small-molecule inhibitors of the vascular endothelial growth factor receptor

VEGF, BEVACIZUMAB, AND RECEPTOR TYROSINE KINASE INHIBITORS

Antiangiogenic Therapies for Glioblastoma

Tumor angiogenesis and peritumoral edema formation is primarily driven by the overexpression of VEGFs (139), which include VEGF-A–D (140). VEGFs bind to the receptor tyrosine kinase VEGF receptor (VEGFR) 1–3 and can also activate a number of alternative coreceptors (140). VEGF is a potent mediator of angiogenesis. Only 30 min after the intraparenchymal infusion of VEGF, 90% of neighboring brain vessels develop interendothelial gaps, lose basement membrane integrity, and become permeable to albumin (141). VEGF is highly upregulated in brain tumors, and its expression is strongly correlated with tumor grade (142).

Anti-VEGF Therapy Does Not Improve Survival

Various VEGF inhibitors have been developed due to its strong role in tumor angiogenesis. Bevacizumab is a monoclonal immunoglobulin G humanized antibody targeted against VEGF-A. Cediranib and enzastaurin are notable examples of small-molecule inhibitors of the tyrosine kinase VEGFR.

There have been several clinical trials assessing VEGF inhibitors for the treatment of glioblastoma. Initial findings were encouraging. In the BRAIN study, there was improved, progression-free survival (PFS) in patients with recurrent glioblastoma who were treated with bevacizumab plus irinotecan versus irinotecan alone at 6 months (42.6% versus 50.3%) (143). A follow-up trial showed 29% PFS at 6 months with bevacizumab plus irinotecan (144). These two trials led the FDA to approve bevacizumab for the treatment of recurrent glioblastoma in 2009.

Unfortunately, no follow-up study has shown any improvement in overall survival with anti-VEGF therapy (145). Both the AVAglio and RTOG 0825 studies failed to show improved survival in patients with newly diagnosed glioblastoma who were treated with anti-VEGF therapy (146, 147). Studies of receptor tyrosine kinase inhibitors have been equally disappointing. In phase 3 trials, both cediranib and enzastaurin failed to improve overall survival in patients with recurrent glioblastoma (148, 149). A recent meta-analysis of 14 clinical trials of VEGF inhibitors confirmed these disappointing findings (150).

Antiangiogenic Therapy Improves Peritumoral Edema

While anti-VEGF therapy does not improve overall survival, clinical trials have consistently shown that the inhibition of VEGF signaling reduces peritumoral edema. A number of studies reported that anti-VEGF therapy reduces corticosteroid requirements (146, 148, 151–153). Radiographically, both bevacizumab and cediranib reduced peritumoral T2 and FLAIR signals (151, 153). Cediranib also reduced tumor mass effect (152). Interestingly, the antiedema effects of anti-VEGF therapy are reversible upon discontinuation of therapy, which can result in a significant rebound of edema (152).

VEGF inhibition is thought to reduce edema by inducing normalization of brain tumor vasculature. In tumor vessel normalization, the dysregulated balance between pro- versus antiangiogenesis is shifted towards antiangiogenesis (154). In support of this hypothesis, bevacizumab treatment reduced the expression of VEGF and reduced tumor vascularity (155).

There are several important caveats to the widespread use of anti-VEGF drugs as antiedema therapies. Firstly, their effects are reversible upon discontinuation and can cause rebound edema. Secondly, tumor progression inevitably occurs with anti-VEGF therapy, and overall survival is unchanged. Progression may be due to nonangiogenic mechanisms of neovascularization, compensatory increases in non-VEGF angiogenesis (156), or heterogeneity in tumor responsiveness (157). Lastly, and most disturbingly, VEGF inhibition has been associated with greatly increased satellite tumor formation, perhaps because VEGF inhibitors worsen hypoxia and thereby promote tumor cell migration (158, 159).

VEGF inhibition has garnered great disappointment due to its poor performance in increasing patient survival. However, given the impressive effects of VEGF inhibition on peritumoral edema and the important role of peritumoral edema in patient morbidity and mortality, these drugs may deserve reconsideration. VEGF inhibitors may be useful as antiedema agents that might best be used in conjunction with other therapies.

CONCLUSION

Cerebral edema is a major cause of morbidity and mortality in patients with neurological and neurosurgical diseases. While our current therapeutic options are limited, we are presently in a period of great potential, with several new antiedema agents being tested in the clinic (**Table 1**). With these new agents, brain edema could be treated prophylactically to prevent the formation of edema, thereby making the terrible consequences of mass effect and increased ICP less common events.

DISCLOSURE STATEMENT

J.M.S. holds a US patent (7,285,574) and is a member of the scientific advisory board of and holds shares in Remedy Pharmaceuticals. W.T.K. and K.N.S. have received grants from Remedy Pharmaceuticals.

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