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Opinion

Reducing Brain Edema Using Berotralstat, an Inhibitor of Bradykinin, Repurposed as Treatment Adjunct in Glioblastoma

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Abstract: Glioblastomas synthesize, bear receptors for, and respond to bradykinin, triggering migration and proliferation. Since centrifugal migration into uninvolved surrounding brain tissue occurs early in the course of glioblastoma, this attribute defeats local treatment attempts and is the primary reason current treatments almost always fail. Stopping bradykinin-triggered migration would be a step closer to control of this disease. The recent approval and marketing of an oral plasma kallikrein inhibitor, berotralstat (Orladeyo™), and pending FDA approval of a similar drug, sebetralstat, now offers a potential method for reducing local bradykinin production at sites of bradykinin-mediated glioblastoma migration. Both drugs are approved for treating hereditary angioedema. They are ideal for repurposing as a treatment adjunct in glioblastoma. Furthermore, it has been established that peritumoral edema, a common problem during the clinical course of glioblastoma, is generated in large part by locally produced bradykinin via kallikrein action. Both brain edema and the consequent use of corticosteroids both shorten survival in glioblastoma. Therefore, by (i) migration inhibition, (ii) growth inhibition, (iii) edema reduction, and (iv) the potential for less use of corticosteroids, berotralstat may be of service in treatment of glioblastoma, slowing disease progression. This paper recounts the details and past research on bradykinin in glioblastoma and the rationale of treating it with berotralstat.

Keywords: berotralstat; blood–brain barrier; bradykinin; C1 esterase inhibitor; edema; glioblastoma; plasma kallikrein; sebetralstat

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1. Introduction

Since the 1997 article by Weydt et al. showing that bradykinin can play an activating, intracellular, Ca^{++}-releasing role in glioblastoma (GB), there has been interest in blocking this potentially growth-driving element as a GB treatment adjunct [1]. In 2024, 27 years later, Stadnicka et al. demonstrated progressively increasing density of the two bradykinin receptors, B1R and B2R, as glioma malignancy grade increases, Grade 2 < Grade 3 < Grade 4 [2]. This paper will recount data showing that bradykinin signaling is elevated in GB and that several aspects of bradykinin signaling drive GB growth and generate the characteristic peritumoral edema. These data sets result in a conclusion that use of either of two new FDA-approved bradykinin signaling inhibitors—berotralstat, or the related sebetralstat—taken once daily may improve GB prognosis and quality of life. These drugs are approved for treating hereditary angioedema (HAE), a disease of episodic and poorly restrained bradykinin formation.

The recent approval of berotralstat (Orladeyo™, previously designated BCX7353), the first oral inhibitor of plasma kallikrein, opens the way for convenient inhibition of bradykinin during the management of GB [3–5]. Sebetralstat is an oral plasma kallikrein inhibitor similar to berotralstat, was recently approved by the FDA, and will soon be marketed in the USA [6,7]. Berotralstat and sebetralstat have good safety profiles with minor side effects that differ little from placebo [8,9]. The site of action of berotralstat and sebetralstat is diagrammed in Figure 1 [10].

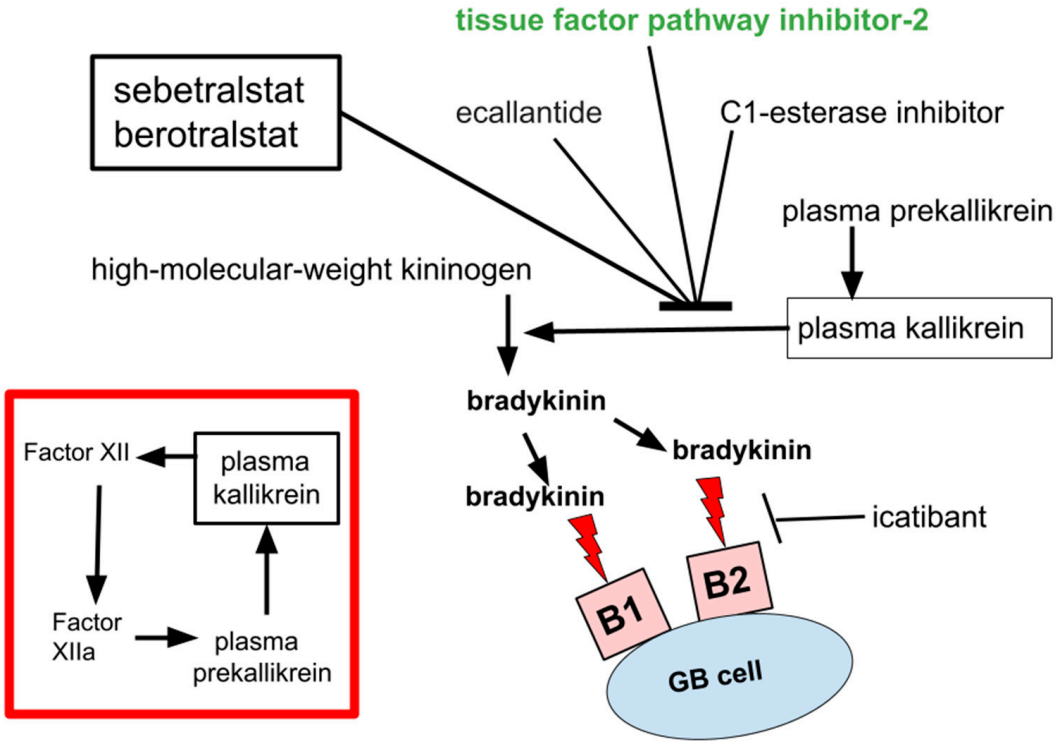

Figure 1. A simplified schematic of the kallikrein–bradykinin system taken from Lima et al. [10] showing locus of action of four FDA/EMA-approved drugs to inhibit bradykinin functions, berotralstat, ecallantide, icatibant, and sebetralstat, all FDA approved to treat HAE. Concentrated human plasma and recombinant C-1 esterase are also FDA approved and marketed for this. The amplifying feedback cycle between coagulation factor XII and prekallikrein is shown in red rectangle. Blue oval represents a glioma cell. Not shown in this schematic is the blood–brain barrier-opening effect of excess bradykinin signaling associated with and common in GB.

Peritumoral brain edema is a common, if not universal, finding during the course of GB and its treatment with irradiation. Dexamethasone or other similar corticosteroids remain the standard treatment for that edema. Although this is frequently effective in controlling GB-related brain edema, long-term survival is unequivocally and proportionately shortened by such use [11,12]. The exact mechanism by which dexamethasone use is inversely proportional to survival is unknown, but the well-known immunosuppression caused by dexamethasone is likely to figure prominently in this. Throughout this paper, the term "dexamethasone" should be understood to refer to dexamethasone and all its congeners (methylprednisolone, prednisone, prednisolone, etc.) that function similarly to dexamethasone and also are in common use to reduce peritumoral edema in GB.

This paper will show how the collected data on bradykinin signaling in GB create much of the associated brain tissue edema, and how berotralstat or sebetralstat have great potential to reduce the need for dexamethasone.

The current standard treatment of GB after maximal feasible resection is chemoirradiation—six weeks of irradiation with daily temozolomide. Median overall survival remains under two years.

2. Bradykinin

Bradykinin is a nine amino acid (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg), 1060 Da peptide inflammation mediator cleaved from a precursor protein, high molecular weight kininogen, by the serine proteinase plasma kallikrein [13]. See the simplified schematic of the plasma kallikrein–bradykinin system, Figure 1. Bradykinin is a locally acting, short half-life inflammation mediator. It is rapidly inactivated by angiotensin-converting enzyme (ACE) and others. Bradykinin signals via one of two receptors, B1R and B2R. B2R tends to

be constitutively expressed and B1R tends to be inducibly expressed, but this distinction is not strict. Amplification of B2R expression can be induced and B1R is constitutively expressed in some cells. Bradykinin acting via either B1R or B2R triggers phospholipase C and Ca^{++} release. Such signaling contributes to inflammation-related vasodilation, blood vessel leakage, and consequent edema [13]. Figure 1 shows the site of action by which selected marketed pharmaceutical agents suppress bradykinin generation.

Plasma kallikrein is proteolytically cleaved from plasma prekallikrein. Plasma kallikrein is under tonic inhibition by 104 kDa C1 esterase inhibitor (synonymous with 104 kDa C1 inhibitor), a heavily glycosylated serine protease inhibitor present in human plasma in a relatively large amount, at 0.25 mg/mL. In HAE, the congenital absence of C1 esterase inhibitor or production of a defective C1 esterase inhibitor results in episodic uncontrolled over-activation of the plasma kallikrein/bradykinin system, resulting in intermittent pathologic localized tissue edema and inflammation [14–16]. There are, in addition, rare acquired forms of bradykinin-produced angioedema not resulting from acquired defective or absent C1 esterase inhibitor, but these also tend to respond to pharmacological plasma kallikrein inhibition [17]. In addition to C1 esterase inhibitor, there are other naturally occurring physiologic circulating and tissue-bound inhibitors of plasma kallikrein action.

Coagulation Factor XII and plasma prekallikrein can reciprocally activate each other, forming a potential amplifying feedback loop that would be particularly destructive in GB [15,18,19]. This is schematically depicted within the red rectangle of Figure 1. Localized bradykinin exposure in a rat brain tumor model caused vessel leakage and microthrombi [20]. Microthrombi and related areas of necrosis are typically present in human GB and, as the extent of these increases, prognosis worsens [21–23]. Furthermore, it tends to be those hypoxic, microthrombi-related areas where GB stem cell niches are found [24].

There have been several other FDA/EMA-approved pharmaceutical inhibitors of plasma kallikrein. Concentrated human C1-esterase inhibitor (Haegarda^{TM} or Berinert^{TM}), recombinant C1-esterase inhibitor (Ruconest^{TM}), and the monoclonal anti-C1 esterase antibody lanadelumab (Takhzyro^{TM}) are administered via subcutaneous or i.v. injection. Also available are the short half-life (2 h) plasma kallikrein inhibitor ecallantide or the B2R specific inhibitor icatibant, all diagrammed in Figure 1. These are all available to reduce bradykinin function in HAE and in acquired angioedema. The recent approval and marketing of an oral, long half-life (90 h), small molecule plasma kallikrein inhibitor, berotralstat, has made chronic daily use ideal and feasible in GB to reduce—if not eliminate—the need for dexamethasone.

3. Safety of Bradykinin Inhibition

In recent clinical trials and over long periods of daily administration, low-grade nausea, diarrhea, headache, and gastroesophageal reflux were observed in 10% of patients taking berotralstat for angioedema prophylaxis. Minor asymptomatic hepatic transaminase elevations were occasionally seen [25–27]. The steady state Cmax of berotralstat is 158 ng/mL, with a half-life of 3 to 4 days [4,5,25].

There are no reports of delayed wound healing in patients taking the bradykinin inhibitors or the C1-esterase inhibitors, nor has evidence of clinical immunosuppression been observed [27,28].

4. Pathogenic Contributions of Bradykinin in GB

Since bradykinin exposure stimulates in vitro growth of GB cells and triggers an increase in B1R receptors in GB [29–32], a particularly malignant amplifying feedback loop is thus formed, depicted in Figure 2, where bradykinin agonism at B2R upregulates B2R expression that, in turn, further increases bradykinin signaling, making inhibiting that loop with berotralstat a particularly attractive option in GB. Successively, bradykinin stimulated the influx of calcium, phosphorylation of MEK1, and extracellular signal-regulated kinase (ERK)1/2, which result in translocation and transactivation of nuclear factor-kappaB (NF-κB) in GB cells.

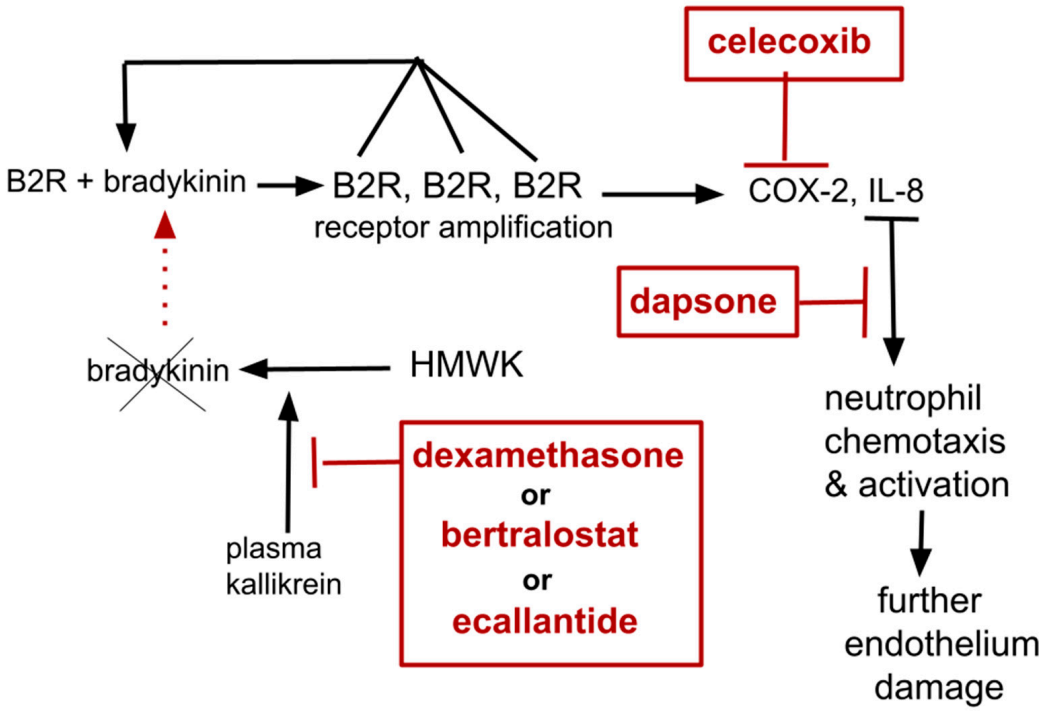

Figure 2. Schematic showing simplified locus of action of how adding celecoxib and/or dapsone has potential to augment berotralstat, lowering edema further. The bradykinin-amplifying feedback loop is depicted, where bradykinin agonism at B2R increases B2R expression, forming an amplifying loop as long as enough bradykinin is present. Bradykinin's T1/2 is <40 s [33]. This means that this amplification cycle is rapidly shut off by berotralstat or any plasma kallikrein inhibitor that would stop bradykinin release. B2R, the bradykinin receptor 2; HMWK, high molecular weight kininogen; the dashed red arrow indicates what would happen if plasma kallikrein were not inhibited.

Human GB cells express components of the kallikrein–bradykinin signaling system. Combined inhibition of B1R and B2R signaling reduced growth in an in vivo murine GL-261 glioma model [29–32]. Inversely, in another murine GB model, bradykinin agonism at B2R stimulated GB growth and accelerated cell migration, particularly at the tumor periphery. Bradykinin signaling at B1R triggered the migration and activation of non-malignant brain microglia [34].

Tissue factor pathway inhibitor-2 (TFPI-2) is a naturally occurring, tissue resident 32 kDa serine protease inhibitor that also functions to tonically inhibit plasma kallikrein action [35–38]. TFPI-2 acts in parallel with soluble, circulating C1 esterase inhibitor, as diagrammed in green at the top of Figure 1. Tellingly, as human glioma malignancy grade increases, the TFPI-2 content of the tumor tissue decreases until, in GB, no tumor tissue TFPI-2 can be seen on immunohistochemistry [38]. Thus, one component of GB pathophysiology can be considered, in part, an acquired, local, partial, HAE-equivalent state.

Bradykinin is a primary link in the creation of blood–brain barrier (BBB) disruption, with its consequent vessel leakage creating the peritumoral edema characteristic of GB [39–41]. BBB leakage is not benign.

- The edema consequent to BBB leakage predisposes that edematous tissue to allow or enhance GB invasion and regrowth [40]. Striking evidence of the importance of restraining bradykinin signaling to the mammalian brain comes from C1 esterase inhibitor knock-down mice, who experience widespread brain edema and generalized cerebral non-malignant glial activation [42].
- GBs' peritumoral edema itself can, and not rarely does, precipitate death by brain herniation.
- Edema clinically requires dexamethasone use to control it, at least today in 2024.

Five articles have reviewed the body of research data assembled over the last two decades showing the central role of bradykinin in generating GB-related leaky BBB and peritumoral edema [39–43]. Bradykinin signaling actually becomes rapidly upregulated after any brain injury, blunt or lacerating. Many different experimental, non-marketed bradykinin signaling inhibitors did reduce brain trauma-generated edema, both in humans and in rodent studies [44–48].

Bradykinin triggers the release of sequestered intracellular Ca^{++} in GB cells in a manner similar to that of platelet-derived growth factor [49,50]. Bradykinin binds to its B2R receptor on GB cells, triggering the intracellular release of, and signaling by, inositol triphosphate.

Bradykinin signaling at B2R is an important chemotactic signal directing the invasion of GB cells toward blood vessels, consistent with GBs' perivascular migration pattern in humans [34,51,52]. Bradykinin signaling at B1R also triggers GB cell migration [53].

A single case study of a case of GB with severe and intractable peritumoral edema given human C1 esterase inhibitor plasma concentrate experienced marked edema reduction [54].

5. Evidence of Bradykinin Signaling Driving Other Cancers

Bradykinin enhanced in vitro growth and migration in cell lines from prostate cancer [55], colon cancer [56], gastric cancer [57], lung adenocarcinoma [58], melanoma [59], chondrosarcoma [60], small cell lung cancer [61,62], hepatocellular carcinoma [63], and ovarian cancer [64].

Bradykinin acting on B2R as a growth drive as a general phenomenon across the common cancers was reviewed in 2002 and again in 2022 [65,66].

6. Data on BBB Opening for Drug Delivery Using Bradykinin Agonists

One of the many problems in treating GB is the non-leaking, non-peritumoral BBB. Most of the current cancer chemotherapy drugs that would otherwise be useful in treating GB will not cross the BBB sufficiently to achieve effective brain tissue levels a few cm away from the central tumor and its edema. At the time of diagnosis, GB is already a whole-brain disease [67].

To address this limitation, dozens of studies have used bradykinin analogs to temporarily open the BBB prior to administering a variety of cytotoxic drugs [68–71]. This does get drugs through the BBB but it cannot be done on a daily basis and, for reasons outlined in this paper, bradykinin agonism increases GB growth and migration—not a good idea, at least not yet. However, this does bring up a double-edged sword: the leaky BBB that creates peritumoral edema in GB also allows freer entry of the main chemotherapy drug, temozolomide, to brain tissue. Tightening the BBB with dexamethasone does reduce peritumoral edema, but it also thereby restricts temozolomide entry to brain tissue [72]. The relative degree of benefit from reducing dexamethasone use versus potentially lower brain tissue temozolomide levels from tightening the BBB, for now, can only be determined by a controlled clinical study.

7. Discussion

This paper discusses two naturally occurring physiologic inhibitors of plasma kallikrein, 104 kDa C1 esterase inhibitor and 34 kDa tissue factor pathway inhibitor factor-2. There are others, but these two are the major ones.

A hardy cancer like GB will not be defeated by half measures. Bradykinin signaling inhibition with berotralstat can be expected to be only partially effective, warranting the addition of further drugs to stop BBB leakage and consequent brain edema during the course of GB. Since BBB opening is multifactorial, plasma kallikrein inhibition with berotralstat may only reduce the need for use of dexamethasone. Any reduction in dose or frequency of dexamethasone use during the course of GB will improve survival, as discussed in the above text.

Commonly, GB treatment centers will use routine daily dexamethasone in all patients in the perioperative period to limit edema formation. Dexamethasone cannot be tapered

off in about half of these people in the early phase of chemoirradiation [12]. Median overall survival is 23 months in those who have successfully tapered off, and 13 months in those whose edema cannot be controlled without dexamethasone [12].

As we see in treating many conditions, for example hypertension, the physiological systems active in maintaining blood pressure—low, high, or normal range—are multifactorial, and our treatment paths reflect this. We can give (i) a diuretic to reduce fluid overload, (ii) an angiotensin receptor inhibitor (an ARB) to lower angiotensin-2 signaling at angiotensin receptor 1, (iii) a calcium channel blocker to relax arterial walls, and (iv) a beta blocker to reduce heart rate and pump force. It is not usual that all four classes of drug are needed to control hypertension, but it is common that one class is insufficient and two or three classes are used. Just so can we expect when treating the edema of GB.

Other repurposed drugs that lower brain edema and could potentially reinforce berotratstat's edema reduction are discussed below.

(1) Dapsone

Ricardio et al. outlined data on a bradykinin-related amplifying feedback loop [73]. In human asthma, bradykinin stimulation of bronchial fibroblasts' B2R receptors results in COX-2, IL-4, IL-13, TNF, IL-6, and IL-8 increases that, in turn, result in the recruitment of neutrophils, their cytokine release, tissue destruction, and an increase in expression of B2R receptors. This is diagrammed in Figure 2. Qin et al. provided evidence that the BBB leakage provoked by bradykinin may act, at least in part, via an intermediary of TNF in a rat glioma model [74]. Regarding specifically IL-8, in 2021, in a review of the physiology of the old antibiotic dapsone as used in GB to decrease growth and peritumoral edema, the IL-8-directed, chemotaxis-inhibiting effect of dapsone figured prominently [75]. IL-8-attracted neutrophils are an important link in an amplifying feedback system with IL-8 and neutrophils [75–78].

Neutrophils migrate along several chemotaxic cytokine (chemokine) gradients, an IL-8 gradient among them. Endothelial cells synthesize IL-8 under a variety of damage or infectious stimuli. That IL-8 attracts neutrophils bearing IL-8 that arrive at the site of damage, degranulate, and release more IL-8, etc. By inhibiting neutrophil migration along an IL-8 gradient, dapsone inhibits that amplifying feedback loop [75–81].

Erythema marginatum skin rash, a common prodrome to a full-fledged HAE attack, increases IL-8 and neutrophilia to amplify an initial smaller bradykinin signal that continues more widely during the full-fledged HAE attack [82–84]. That amplifying loop is depicted in Figure 2 and discussed in the text main body above. Dapsone is effective in reducing IL-8-mediated dermatitis.

(2) Celecoxib

Celecoxib is a COX-2 selective inhibitor marketed to lower pain. The extensive database was recently reviewed supporting high-dose celecoxib use during GB treatment on several grounds [85,86]. COX-2 expression in GB worsens prognosis, as independently confirmed in three independent studies [87–89]. COX-2 expression increased brain edema in CNS meningioma [90]. Celecoxib reduced brain edema in a rat epilepsy model [91]. Microglia isolated from intracranial rat glioblastoma expressed high levels of COX-2 and PGE associated with brain edema. All-COX-2, PGE, and brain edema were reduced by a COX-2 selective inhibitor related to celecoxib (rofecoxib) [92]. Celecoxib also reduced brain edema after intracerebral hemorrhage in a rat model [93].

Celecoxib reduced edema volume in human patients with intracerebral hemorrhage of edema noted on follow-up brain CT scans as compared with the edema volumes in a control group [33].

(3) SEC

SEC is also a repurposed drug regimen to reduce brain edema in GB [40]. SEC uses spironolactone, an antihypertensive potassium-sparing diuretic that also inhibits the mineralocorticoid receptor and clotrimazole, an old antifungal drug that inhibits the

intermediate conductance Ca^{++}-activated K+ channel (KCa3.1). Both the mineralocorticoid receptor and KCa3.1 have been shown to be links in the chain of events creating BBB leakage [40]. In SEC, the B2R-specific receptor ecallantide is also used, as diagrammed in Figure 1, but the data on B1R reviewed here indicate that a dual B1R and B2R inhibitor like berotralstat would be preferable. Spironolactone, clotrimazole, and celecoxib would all be compatible with berotralstat use in reducing GB edema, helping to limit or avoid dexamethasone use.

8. Conclusions

Evidence recounted here has shown that (i) berotralstat is likely to reduce peritumoral edema in GB, (ii) reducing the need for dexamethasone. (iii) Reduction of dexamethasone use has a well-documented effect of lengthening survival in GB. (iv) Bradykinin signaling on GB cells triggers their migration and growth. Our core conclusion is that on all these accounts, the oral plasma kallikrein inhibitors berotralstat or sebetralstat will be of benefit during all phases of GB treatment by lowering bradykinin signaling and its associated growth and migration promotion.

Given the lethality of GB and the fairly well-established pathophysiological role of bradykinin in GB pathophysiology, as reviewed above, the eminently benign side effect profile of berotralstat as a newly available, small molecule inhibitor of bradykinin signaling, a pilot study is being planned to determine if daily oral berotralstat during the chemoirradiation phase of GB treatment will reduce the need for dexamethasone and reduce the incidence of peritumoral edema. The secondary endpoint will determine if berotralstat use delayed progression or prolonged survival.

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Abbreviations

B2R, bradykinin receptor 2; BBB, blood–brain barrier; GB, glioblastoma; HAE, hereditary angioedema; TFPI-2, tissue factor pathway inhibitor-2.

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