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Corticosteroid use endpoints in neuro-oncology: Response Assessment in Neuro-Oncology Working Group

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Abstract

Background. Corticosteroids are the mainstay of treatment for peritumor edema but are often associated with significant side effects. Therapies that can reduce corticosteroid use would potentially be of significant benefit to patients. However, currently there are no standardized endpoints evaluating corticosteroid use in neuro-oncology clinical trials.

Methods. The Response Assessment in Neuro-Oncology (RANO) Working Group has developed consensus recommendations for endpoints evaluating corticosteroid use in clinical trials in both adults and children with brain tumors.

Results. Responders are defined as patients with a 50% reduction in total daily corticosteroid dose compared with baseline or reduction of the total daily dose to ≤2 mg of dexamethasone (or equivalent dose of other corticosteroid); baseline dose must be at least 4 mg of dexamethasone daily (or equivalent dose of other corticosteroids) for at least one week. Patients must have stable or improved Neurologic Assessment in Neuro-Oncology (NANO) score or Karnofsky performance status score or Eastern Cooperative Oncology Group (ECOG) (Lansky score for children age <16 y), and an improved score on a relevant clinical outcome assessment tool. These criteria must be sustained for at least 4 weeks after baseline assessment to be considered a *response*, and are confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a sustained response.

Conclusions. This RANO proposal for corticosteroid use endpoints in neuro-oncology clinical trials may need to be refined and will require prospective validation in clinical studies.

Key words

corticosteroids | endpoints | peritumor edema | RANO

Importance of the study

Corticosteroids are the primary treatment for peritumor edema but are associated with significant side effects. Therapies that can reduce corticosteroid use would potentially be of significant benefit to patients. Currently there are no standardized endpoints evaluating corticosteroid use in neuro-oncology clinical trials. The RANO Working Group has developed consensus recommendations for endpoints evaluating corticosteroid use in clinical trials in both adults and children with brain tumors. These proposed endpoints will hopefully provide consistency in evaluating corticosteroid use across clinical trials but may need to be refined and will require prospective validation in clinical studies.

The peritumoral edema associated with brain tumors is an important cause of patient morbidity. Corticosteroids are frequently used to manage symptoms from peritumoral edema, but are associated with undesirable side effects and reduction in both health-related quality of life (HRQoL) and functional status, especially with high doses or prolonged use. Proximal myopathy, weight gain and Cushingoid habitus, mood lability, insomnia, hyperglycemia, and immunosuppression represent common side effects that may be debilitating and are associated with worsened health (Table 1).[1–3]

With few effective new therapies for brain tumors approved by the US Food & Drug Administration (FDA) over the past 30 years,[4,5] there has been an ongoing, urgent need to identify additional treatments that may improve the lives of these patients. While overall survival (OS) has been the primary endpoint in nearly all neuro-oncology trials, there has been increasing realization of the vital role that clinical outcome assessments (COAs) may play in patient-centered drug development. COAs can capture outcomes that are meaningful to patients, such as symptoms, functional capacity, and other aspects of HRQoL.[6–8] Recognizing the negative effects associated with prolonged use of corticosteroids common in many brain tumor patients, there is interest in identifying a relevant clinical trial endpoint related to reduction in the dependency on corticosteroids. In this Response Assessment in Neuro-Oncology (RANO) Corticosteroids Working Group position paper, the committee summarizes key literature on corticosteroid use among brain tumor patients and proposes a new clinical trial endpoint related to corticosteroid use and assessment of clinical benefit.

Table 1 Side effects of corticosteroids

Neurologic/Psychiatric	Insomnia
	Mood lability
	Anxiety/depression
	Psychosis
	Increased appetite
	Hiccups
	Tremor
Musculoskeletal	Proximal myopathy
	Osteoporosis
	Arthralgias
	Avascular necrosis
	Decreased growth/height (pediatric patients)
Gastrointestinal	Dyspepsia/gastritis
Hematologic/ Immunologic	Immunosuppression-related infections (oropharyngeal candidiasis, *Pneumocystis jiroveci* pneumonia, etc)
Endocrine	Hyperglycemia
	Weight gain
	Cushingoid habitus
	Adrenal insufficiency (after discontinuation)
Cutaneous or Vascular	Acne
	Striae
	Purpura
	Delayed wound healing
	Peripheral edema
Ocular	Visual blurring
	Cataract formation

Corticosteroid Effects

While corticosteroids represent one of the most common medications used in the management of patients with brain tumors, the precise mechanism of action leading to clinical benefit remains incompletely understood. Steroids were first used to alleviate symptoms in patients with brain tumors in the 1950s,[9] with reliance specifically on dexamethasone beginning in the 1960s,[10] due to its potent glucocorticoid effect and low mineralocorticoid activity, high brain penetration, and long biologic half-life.[11] For these reasons, dexamethasone is widely considered the corticosteroid of choice for patients with brain tumors, which is reflected in consensus guidelines.[2,12]

The reduction of peritumoral edema by corticosteroids appears to be mediated predominantly by a reduction in tumor capillary permeability and cytokine-driven blood–brain barrier breakdown. Corticosteroids diffuse through plasma membranes and bind to cytoplasmic receptors, leading to nuclear localization and DNA binding to glucocorticoid response elements, affecting transcriptional regulation and activating various signaling cascades.[13] Tight junction components including occludin are upregulated within endothelial cells, contributing to decreased

capillary permeability.[14] Corticosteroids repress pro-inflammatory nuclear factor-kappaB, which has the effect of reducing cytokine-driven breakdown of the blood–brain barrier and local leukocyte recruitment, as well as reducing transcription of other cytokines, including interleukins, involved in inflammation.[15] Magnetic resonance imaging (MRI) studies of patients with brain tumors have demonstrated that 2–3 days after dexamethasone administration, there is local reduction in extracellular water content and diffusion on MRI, without a decrease in cerebral perfusion, suggesting that reduced local tissue pressure may alleviate neurologic symptoms.[16,17] Corticosteroids can also reduce tumor enhancement on neuroimaging studies, which can confound accurate response assessment. One study reported that 90% of patients had a measurable reduction in the size of gadolinium-enhancing region after introduction of corticosteroids, which was greater than a 25% reduction in cross-sectional enhancing area in 30% of patients.[18] Similarly, corticosteroids can reduce contrast enhancement on computerized tomography (CT) images and mimic treatment responses.[19]

Side effects of corticosteroids are common, oftentimes serious, and increase in likelihood with prolonged use or higher dosage.[1,3] In one study of primary brain tumor patients, the average duration of dexamethasone use was approximately 5 months, with nearly 20% of patients remaining on dexamethasone until death.[20] Proximal, symmetric myopathy is the most common functionally limiting side effect of protracted corticosteroid exposure impacting quality of life, with incidence ranging widely from 10% to 90%.[21–24] Steroid-related myopathy appears to be mediated by apoptosis of skeletal muscle cells induced by corticosteroids, particularly fluorinated corticosteroids such as dexamethasone.[25] A recent survey conducted by the National Brain Tumor Society among patients and caregivers, in which 50% of patients had high-grade gliomas, found that maintaining the ability to walk and perform physical tasks was one of the top priorities desired for brain tumor treatments,[26] highlighting the potential impact of steroid myopathy. Mood lability, insomnia, and psychiatric manifestations occur in approximately 25% of patients receiving dexamethasone,[23,27] with the incidence of severe symptoms reported at 6%.[27] Weight gain and unpleasant cosmetic changes are frequently noted by patients taking corticosteroids. Cushingoid features were reported by nearly 75% of physicians assessing 200 brain tumor patients taking a mean dexamethasone daily dose of 10 mg for a median of 7 weeks.[23] Elevated serum glucose may occur in at least 50% of patients taking corticosteroids,[20] and is associated with a worse prognosis in high-grade gliomas.[28,29] These side effects are only among the most common, and do not include others, such as immunosuppression-associated infection, arthralgias, avascular necrosis, osteoporosis, dyspepsia, visual symptoms, skin changes, and increased risk of venous thromboembolism. In addition, there may be potential interactions between corticosteroids and anti-epileptic drugs. The Jumpstarting Brain Tumor Drug Development Coalition (JSBTDDC) conducted a workshop with the FDA in 2014 and identified corticosteroid side effects and impact on function as an important COA to address.[8,30]

Corticosteroids and Survival

Dependence on corticosteroids is independently associated with significantly shorter OS in one study; glioma patients undergoing radiotherapy who could discontinue corticosteroids had a median OS of 29 months compared with a median of 5 months in those who were steroid dependent.[31] Patients in the landmark European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) trial[32] who were taking corticosteroids at the start of adjuvant therapy had a 36% higher risk of death compared with those not taking steroids, after adjustment for other prognostic factors.[33] At least 2 studies have reported that baseline steroid use is among the factors most strongly associated with prognosis, in addition to patient age and performance status.[34,35]

It is unclear whether the use of corticosteroids is mechanistically responsible for shorter survival among brain tumor patients, or simply a proxy for a larger or more aggressive tumor, or an unfavorably located tumor that cannot be fully resected. However, there are data suggesting a cytoprotective effect of glucocorticoids in glioma that diminishes the therapeutic efficacy of both radiotherapy and chemotherapy.[29,36–38] Regardless, most brain tumor trials have inclusion criteria requiring a stable or decreasing corticosteroid dose at time of enrollment[6,7,32] to reduce bias in the comparison between arms, and to ensure the baseline brain MRI or CT scans are valid by minimizing any effects of dexamethasone on contrast enhancement or T2/fluid attenuated inversion recovery abnormality.[18,19]

Steroid-Sparing Effects of Recent Clinical Trial Agents

Recent neuro-oncology trials using primary endpoints of OS or progression-free survival (PFS) have provided illustrative secondary data related to corticosteroid use. In a secondary analysis of the BRAIN trial, a phase II randomized, noncomparative trial of bevacizumab with or without irinotecan for adults with recurrent glioblastoma,[39] investigators reported that the majority of patients in each treatment arm using corticosteroids at baseline were able to reduce their dosage during the study.[40] Among patients receiving bevacizumab alone, 30% experienced sustained reduction in corticosteroid dose, defined as ≥50% reduction in corticosteroid dose relative to baseline for ≥50% of the time while on the study drug, while 16% experienced a complete reduction in corticosteroid dose, defined as not using corticosteroids for ≥25% of the time on study drug. Of patients receiving bevacizumab plus irinotecan, 47% had a sustained reduction in corticosteroid dose, and 21% had a complete reduction. While corticosteroid analysis was not a primary endpoint in the BRAIN trial, these data emphasized the potential corticosteroid-sparing effects of bevacizumab. A phase II study among adults with recurrent glioblastoma that assessed the activity of cabozantinib[41] found that among the 76 patients receiving corticosteroids at baseline, there was a trend toward stable or decreasing corticosteroid doses over time—yet, as in the BRAIN trial,

the study did not contain a corresponding COA to determine patient function.

In addition, several recent drug trials in glioblastoma, while not meeting primary endpoints related to survival, showed promising effects on secondary endpoints related to corticosteroid use and patient function. A randomized phase III trial evaluating cediranib, lomustine, or the combination of both agents found that mean corticosteroid use decreased by 26% in the cediranib arm (P = 0.01 vs lomustine), decreased by 23% in the combination arm (P = 0.01 vs lomustine monotherapy), and increased by 5% in the lomustine monotherapy arm.[42] In the AVAglio trial of bevacizumab versus placebo for newly diagnosed glioblastoma,[6] among patients receiving corticosteroids at baseline, corticosteroids were discontinued for at least 5 consecutive days among 66% of patients receiving bevacizumab compared with 47% of patients receiving placebo. Among patients not on corticosteroids at baseline, time to initiation of corticosteroids was 12.3 months for bevacizumab versus 3.7 months for placebo (hazard ratio [HR] = 0.71; 95% CI, 0.57–0.88; P = 0.002). Patients who received bevacizumab had a longer time with KPS ≥70 (9.0 vs 6.0 mo for placebo); however, in both this trial and the cediranib trial, it was not clear whether patients with favorable KPS outcomes were the same patients with decreased corticosteroid use. Finally, in the EORTC 26101 trial comparing bevacizumab plus lomustine chemotherapy versus lomustine alone in recurrent glioblastoma found that among the 50% of patients taking corticosteroids at baseline, 23% in the bevacizumab arm were able to stop corticosteroids while on treatment, compared with 12% in the control arm.[43,44]

Steroid-Sparing Therapies

The best-studied medication with an explicit corticosteroid-sparing effect among brain tumor patients, beyond bevacizumab, is corticorelin acetate (Xerecept), a peptide formulation mimicking human corticotropin releasing factor. In vivo data from orthotopic glioma models demonstrated favorable efficacy and toxicity of corticorelin acetate compared with dexamethasone.[45] Corticorelin was evaluated in a randomized, placebo-controlled trial of 200 patients with peritumoral edema from malignant brain tumors, approximately 80% of whom had primary brain tumors.[23] At baseline, patients enrolled in the trial had stable corticosteroid doses of 4–24 mg/day dexamethasone equivalent[46] for more than 30 days and had failed ≥1 taper, experienced ≥1 adverse steroid effect, had KPS ≥50, and had no anticancer treatments planned for a 5-week period. Randomization was to corticorelin (n = 100) versus placebo (n = 100) for 12 weeks. Following randomization, investigators reduced the daily dexamethasone equivalent dose by 50% by study week 2, and maintained that dose if possible until week 5, at which point further reductions could be made using investigator discretion, with the lowest tolerated dose maintained through study week 12.[23] The primary endpoint was the percentage of responders at week 2 who continued to have response at week 5, with responders defined as patients with at least a 50% reduction in dexamethasone equivalent dose from baseline, stable/improved KPS, and stable/improved neurologic examination score.[23] A secondary endpoint was the proportion of patients with improvement in myopathy from baseline to week 12, using the Kendall myopathy score (KMS),[47] a manual test of muscle strength that scores the proximal muscle groups.

Results from the corticorelin trial showed that at enrollment, mean dexamethasone equivalent dose was 9.6 mg daily for a median of 7.1 weeks, with an average of 4 steroid-related adverse effects, including myopathy (90% by self-report, 62% by physician report, and 80% by KMS) and Cushingoid features (74%).[23] The two treatment groups separated numerically early in the study, and the primary endpoint demonstrated a trend toward a higher proportion of corticorelin patients who were responders at weeks 2 and 5 compared with placebo, at 57% versus 46%, respectively (P = 0.12), as well as more patients with improved KMS (61% vs 44%, P = 0.11).[23] At individual timepoints, including at weeks 2, 5, and 8, there were more responders in the corticorelin arm ($P \leq 0.03$ for all timepoints). New Cushingoid appearance was also less frequent in the corticorelin group (2% vs 13%, P = 0.004).[23]

In a pediatric phase I dose escalation trial of corticorelin, patients <18 years of age with CNS tumors and chronically on corticosteroids who had failed prior weaning received escalating doses of corticorelin acetate at 10–60 μg/kg divided twice daily.[48] Attempts at reducing dexamethasone were initiated after 7 days of therapy. No dose-limiting toxicity was observed and a maximum tolerated dose not defined. Remarkably, all 14 evaluable patients were able to reduce dexamethasone, and 4 patients weaned off completely despite disease progression. Additional analysis showed improved HRQoL, improved physical and emotional functioning, and improved sleep/fatigue scores. Despite these promising findings, further development of corticorelin was discontinued by the sponsor.

Other agents have also been investigated for their ability to reduce peritumoral cerebral edema and corticosteroid requirements. Based on small prior reports[49] postulating an anti-inflammatory effect of the frankincense extract *Boswellia serrata* (BS), a randomized study of BS was conducted among 44 brain tumor patients receiving radiotherapy to at least 60% of the brain,[50] with a primary endpoint of reduction in edema volume on MRI between baseline and immediately post-radiotherapy. The trial showed a >75% reduction in edema volume in 60% versus 26% of patients receiving BS versus placebo, respectively (P = 0.023). While BS was well tolerated, there was no significant impact observed between groups in HRQoL or neurocognitive function, and no statistical difference in dexamethasone dose between groups. In addition, a retrospective study examined glioblastoma patients who were taking angiotensin-II inhibitors for hypertension,[51] to explore whether their use may reduce need for corticosteroids, given putative anti–vascular endothelial growth factor properties ascribed to angiotensin-II inhibitors. Among 87 glioblastoma patients, 18 were taking angiotensin-II inhibitors at the time of radiotherapy, and these patients required only half the corticosteroid use per day during radiotherapy compared with the rest of the cohort, on multivariable analysis (P = 0.005). Other anti-hypertensives

also had a steroid-sparing effect, but not to the same degree as angiotensin-II inhibitors. Finally, cyclooxygenase-2 (COX-2) inhibitors have also been associated with reduced peritumoral edema in at least one in vivo study with a rat brain tumor model,[52] and COX-2 inhibitors such as celecoxib are sometimes used clinically for steroid sparing,[53] though without strong supporting data.

Response Assessment and Endpoint Development

The trials outlined above highlight some of the key issues relevant to the development of a clinical trial endpoint related to corticosteroid reduction. The results from a 2014 JSBTDDC survey of adult patients with brain tumors (n = 839) and their caregivers (n = 985) emphasized that the development of a trial endpoint related to corticosteroid use must also contain a COA component, rather than focusing on only corticosteroid dose change.[8,26,30] When asked to rank the most important goals of future brain tumor treatments aside from prolonging survival, both brain tumor patients and their caregivers independently rated "reduction in the need for corticosteroids" as less important than alleviation from the neurologic symptoms or conditions listed on the survey, some of which are possibly corticosteroid related, such as maintenance of ability to walk and performance of basic physical tasks.[26] For example, in the corticorelin trial discussed previously, the study design incorporated a primary endpoint related to both corticosteroid dose reduction and patient function, including KPS and neurologic function score.

The goal of incorporating COAs into clinical trials is to determine whether a drug/intervention can be shown to provide a clinically meaningful benefit to patients, such as how a patient feels, functions, or survives. A recently developed clinician-reported outcome measurement instrument that provides a standardized method for reported neurologic exam findings is the Neurologic Assessment in Neuro-Oncology (NANO) scale.[54] This potentially allows rapid and reliable assessment of 8 relevant neurologic domains based on direct observation/testing during routine office visits, and demonstrated a >90% interobserver agreement rate in a prospective multinational study, with kappa statistic ranging from 0.35 to 0.83 (fair to almost perfect agreement).[54] However, direct comparison to KPS has not yet been reported. Most valuable to patients may be not only preservation of neurologic function, but improvement in specific functional domains as corticosteroids are reduced. For example, given the high priority brain tumor patients place on maintaining mobility,[26] an explicit measure of steroid-related myopathy such as the KMS scale could be integrated as part of a combined endpoint that incorporated both objective corticosteroid dose changes along with improvements in KMS. Other COAs that could be incorporated into a combined endpoint with corticosteroid reduction include patient-reported outcome assessments of neurologic symptoms and HRQoL, such as the MD Anderson Symptom Inventory Brain Tumor (MDASI-BT) module[55] or the EORTC 30-item Core Quality of Life Questionnaire (QLQ-C30).[56] Another potential patient-reported outcome measure is the Dexamethasone Symptom Questionnaire–Chronic (DSQ-C), which is intended to report the incidence and severity of side effects over one prior week and explore changes over time when used longitudinally in patients receiving corticosteroids.[57] It consists of items about 17 symptoms and toxicities associated with corticosteroid use over time. In one study, the total cumulative steroid dose (steroid dose per day × duration of steroid use in days), after adjusting for age, KPS, and patient type, predicted the total DSQ-C score and was associated with increased odds of experiencing increased appetite, hiccups, roundness of face, depression, and difficulty rising up from a sitting position.[57] In another study, DSQ-C administration appeared feasible over the course of serial assessments, and with reasonable agreement between patients and caregiver proxies.[58] Ongoing research will be required to support the adequacy of the DSQ-C in both the adult and pediatric brain tumor populations longitudinally, as well as what defines a meaningful change between scores over the course of serial examinations.

The FDA has provided ongoing guidance to investigators and industry[59,60] on the development of clinical trial endpoints in oncology related to patient-centered outcomes. There is an emphasis on the use of well-defined and reliable COA tools and enrollment criteria related to the COA domains (such as myopathy, neurologic function scores, or global quality of life scores) in addition to capture of the use of concomitant medications (such as corticosteroids). Of equal importance are responder definitions, as outlined succinctly in a study published by authors from the FDA and elsewhere on the analogous topic of pain palliation measurement in cancer clinical trials.[61] Brain tumor treatment strategies that may improve aspects of patient function and reduce corticosteroid requirements are conceptually similar to treatment strategies in other cancers that may improve pain control and reduce pain medication dependency, independent of effects on OS. The authors suggest a potential approach to defining responders that could be translated to neuro-oncology, specifically that a responder would be defined as a patient: (i) with a stable or decreasing corticosteroid dose during the clinical trial, in conjunction with (ii) decreased symptom burden or increased neurologic functionality that was plausibly related. Importantly, these 2 changes need to happen in the same patient to thus be classified as a responder. This differs from the trials cited above which described corticosteroid reductions or KPS, without reporting which patients also had functional/symptomatic improvement.

In the setting of a paucity of new therapies approved for brain tumors in the past few decades, stakeholders in the neuro-oncology community met in Bethesda, Maryland in October 2014 to discuss patient-centric outcomes that are important to patients beyond survival.[8] These stakeholders included members of academia, pharmaceutical companies, the FDA, brain tumor cooperative groups, and importantly, patients. While OS or PFS has traditionally been the endpoint used to evaluate and approve new therapies for brain tumors, the meeting provided a forum to hear from various constituencies and weigh the possibility of other clinical trial endpoints that could lead to approval of new therapies that improve the lives of brain tumor patients

without an explicit goal of extending survival. Regulatory requirements for new drug approval include demonstration of treatment benefit, and while evidence of a clinical benefit is often a survival effect in cancer clinical trials, a positive impact on how a patient feels or functions on a daily basis is also considered clinically beneficial, and evidence of such effects would support regulatory approval.[59,60] Therefore, while most trials of new therapies could continue to test primarily for survival gains as well as examine ancillary patient-function and corticosteroid benefits, other new therapies could be tested explicitly for patient-function and corticosteroid benefits without a presumption of increased survival.

Inclusion of Corticosteroid Use Endpoints in Brain Tumor Clinical Trials

Based on the FDA guidance "Cancer Drug and Biological Products—Clinical Data in Marketing Applications" and recommended best clinical practices, almost all clinical trials include the collection of relevant concomitant medications during investigation of an experimental cancer therapy.[62] Such collection certainly applies to corticosteroid use in ongoing trials for the reasons highlighted above and in fact, the use of dexamethasone in brain tumor trials has been cited by the FDA as a concomitant medication of particular interest based on its extensive impact on the disease.[62] Corticosteroid dose is recorded regularly at the time of MRI assessment, since both the RANO[63] and Macdonald[64] criteria require corticosteroid dose in order to fully evaluate imaging response, and this provides valuable information about the corticosteroid dose across multiple fixed timepoints. Importantly, however, corticosteroid doses are often changed between MRI timepoints in response to neurologic symptoms or toxicities, and such changes may not be accurately captured if dosing is queried only at the time of on-study MRI. A handful of recent studies have assessed corticosteroid dose as an endpoint, but have used non-uniform approaches to assess corticosteroid use.[41,43]

Since corticosteroids are taken orally and dose is modified by patients, caregivers, or other health care providers, accurate monitoring in the setting of a clinical trial can be challenging. In the similar paradigm of assessing the efficacy of an anticancer therapy based on reduction in the use of analgesics while maintaining pain control, a strategy has been to have patients complete a daily drug diary documenting all daily doses of analgesic. The diary is then reviewed with a study team member at fixed intervals (ie, weekly, monthly). Variations on this approach were applied to assess analgesic use in cancer patients as part of a composite endpoint demonstrating patient benefit of gemcitabine for pancreatic cancer[65] and mitoxantrone/prednisone for hormone-resistant prostate cancer.[66] For both trials, patient-completed medication diaries were a key element of the data presented to support the ultimate approval of these agents for the respective conditions. Paper and pen diaries are still used, yet there is increasing interest in moving to electronic data capture given that several studies have demonstrated noncompliance and erroneous data entering with nonsupervised paper diaries.[67,68] Electronic diaries are increasingly available on platforms accessible to most patients, including smartphones and tablets as well as study-specific devices. However, the optimal format, device, and system for data transfer and storage of patient-entered electronic data have not yet been determined and are a topic under active discussion at the FDA. Although issues of optimizing "e-diaries" for studies moving forward are not yet resolved, it is clear that if corticosteroid use is going to be an endpoint in brain tumor trials, trials must include standardized procedures for collecting daily corticosteroid dosing via structured diaries and study case report forms. Further, the corticosteroid dosing data must be collected concurrently with COA data about symptoms and function to ensure complete and uniform data collection that supports preplanned analyses inclusive of corticosteroid use endpoints. In general, collection methods for concomitant medications and COA data must be prospective, prespecified, systematic, and conducted with efforts to minimize missing or incomplete data to allow for adequate interpretation.

Response Definition

The proposed approach by the RANO Corticosteroids Working Group is to define a patient as a responder during a clinical trial if she/he meets *all* the following criteria during the trial (Table 2):

1. Fifty percent reduction in total daily corticosteroid dose compared with baseline *OR* reduction of total daily dose to ≤2 mg of dexamethasone (or equivalent dose of other corticosteroid); to assess response in patients on steroids, baseline dose must be at least 4 mg of dexamethasone daily (or equivalent dose of another corticosteroid) for 1 week or more.
2. Stable or improved NANO score (preferred), KPS, or Eastern Cooperative Oncology Group (ECOG) performance status.
3. Improved score on a relevant COA tool, preferably DSQ-C (once the threshold for meaningful change has been established), or possibly MDASI-BT (Brain Tumor module; preferred use of overall symptom burden or symptom interference score) or EORTC QLQ-C30/QLQ-BN (Brain Neoplasm module) 20 (preferred use of global health status/QoL subscale), with improvement defined according to that tool's threshold for meaningful change.
4. Criteria 1–3 above sustained for at least 4 weeks after baseline assessment to be considered a *response*, and are confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a *sustained response*.

For criteria 1 and 4, "baseline" is defined as the average daily dose over the week before the study started. It is recommended that corticosteroid dosing be recorded at each clinical evaluation, including any dosing changes related to any clinical event at any point during the trial. The lowest effective dose for a minimum time period required

Table 2 Criteria for determining response related to corticosteroids during a clinical trial (must meet all criteria)

Adult patients	1. 50% reduction in total daily corticosteroid dose compared with baseline* *OR* reduction of total daily dose to ≤2 mg of dexamethasone (or equivalent dose of other corticosteroid); baseline dose must be at least 4 mg of dexamethasone daily (or equivalent dose of other corticosteroid)
	2. Stable or improved NANO score (preferred) or KPS or ECOG performance status
	3. Improved score on a relevant COA tool, preferably DSQ-C (once the threshold for meaningful change has been established), or possibly MDASI-BT (preferred use of overall symptom burden or symptom interference score) or EORTC QLQ-C30/QLQ-BN20 (preferred use of global health status/QOL subscale), with improvement defined according to that tool's threshold for meaningful change
	4. Criteria 1–3 sustained for at least 4 weeks after baseline assessment to be considered a *response*, and are confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a *sustained response*
Pediatric patients	1. 50% reduction in total daily corticosteroid dose compared with baseline *OR* reduction of total daily dose to ≤ physiologic replacement doses of a corticosteroid (eg, 0.75 mg/m^2/day for dexamethasone); baseline dose must be at least 1 mg/m^2/day of dexamethasone (or equivalent dose of other corticosteroid)
	2. Stable or improved performance score (KPS or ECOG performance status for age ≥16 y or Lansky for age <16 y)
	3. Criteria 1–2 are met at least 4 weeks after baseline assessment to be considered a *response*, and confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a *sustained response*

* 'Baseline' is defined as the average daily dose over the week before the study started.
** Different trials could employ different COA tools according to specific study hypotheses, as long as the COA tool is suitable for the particular clinical context and the threshold for meaningful change has been established.

to achieve clinical goals should be prescribed among patients on trial, and the dose monitored and adjusted if appropriate at each clinical evaluation. Dosing should generally be administered as a single daily dose given in the morning, if possible. Prior to enrolling a patient on a clinical trial, it is recommended that any preexisting comorbid conditions that may increase the risk of corticosteroid-associated adverse events be assessed and treated, if possible.

For criterion 3, different trials could employ different COA tools according to specific study hypotheses, as long as the COA tool is suitable for the particular clinical context and the threshold for meaningful change has been established.

There are several caveats when applying the above response definition to the pediatric population. Currently, the NANO score applies to adult patients only, therefore Lansky KPS or ECOG would be used for overall assessment. Additionally, there is a lack of well-defined and reliable pediatric COA tools in the pediatric neuro-oncology population, given the heterogeneity in developmental abilities and requirements for age-defined instruments. However, tools such as the Patient-Reported Outcomes Measurement Information System (PROMIS)[69] are increasingly being incorporated as part of pediatric evaluations,[70–74] and several pediatric instruments are under development. Their use in assessing response in pediatric patients is encouraged although not required at present.

For pediatric patients, therefore, response is defined as (Table 2):

1. Fifty percent reduction in total daily corticosteroid dose compared with baseline *OR* reduction of total daily dose to less than or equal to the physiologic replacement doses of a corticosteroid (eg, 0.75 mg/m^2/day for dexamethasone); to assess response in patients on steroids, baseline dose must be at least 1 mg/m^2/day of dexamethasone (or equivalent dose of another corticosteroid) for 1 week or more.
2. Stable or improved performance score (KPS or ECOG performance status for age ≥16 y or Lansky for age <16 y).
3. Criteria 1–2 are met at least 4 weeks after baseline assessment to be considered a *response*, and confirmed 4 weeks after that (ie, 8 wk after baseline assessment) to be considered a *sustained response*.

Conclusion

This working paper from the RANO corticosteroid subcommittee outlines adverse side effects experienced by most brain tumor patients who require corticosteroids, and summarizes prior trials using corticosteroid-reducing agents. The RANO Working Group recommends incorporation of a new endpoint into neuro-oncology clinical trials related to corticosteroid use and symptom burden/functional outcome. The committee proposes a corticosteroid response definition that incorporates both reduction in corticosteroid dose and improvement on a COA scale, with maintenance of neurologic function, sustained for at least 4 weeks. Implementation into future trials will allow validation of these response criteria, with a goal of developing novel therapies that improve patient quality of life.

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