RESEARCH ARTICLE

Consensus Recommendations for the Management of Neurosarcoidosis

A Delphi Survey of Experts Across the United States

Giovanna Sophia Manzano,[1,2] James Eaton,[3] Michael Levy,[1] Justin R. Abbatemarco,[4] Allen J. Aksamit,[5] Pria Anand,[6] Denis T. Balaban,[1] Paula Barreras,[7] Robert P. Baughman,[8] Shamik Bhattacharyya,[2] Roberto Bomprezzi,[9] Tracey A. Cho,[10] Bart Chwalisz,[1] Stacey Lynn Clardy,[11] David B. Clifford,[12] Eoin P. Flanagan,[5,13] Jeffrey M. Gelfand,[14] George Kyle Harrold,[1,2] Spencer K. Hutto,[15] Siddharama Pawate,[3] Noellie Rivera Torres,[16] Lama Abdel-Wahed,[10] Steven Richard Dunham,[12] Rajesh Kumar Gupta,[17] Brandon Moss,[4] Carlos A. Pardo,[18] Rohini D. Samudralwar,[16] Nagagopal Venna,[1] Aram Zabeti,[19] and Ilya Kister[20]

Correspondence
Dr. Manzano
gmanzano@partners.org

Neurol Clin Pract. 2025;15:e200429. doi:10.1212/CPJ.0000000000200429

Abstract

Background and Objectives

Neurosarcoidosis poses a diagnostic and management challenge due to its rarity, phenotypic variability, and lack of randomized controlled studies to guide treatment selection. Recommendations for management based on expert opinion are useful in clinical practice and provide a framework for designing prospective studies.

Methods

In this Delphi survey study, specialists with experience in managing patients with neurosarcoidosis were invited to anonymously complete 2 surveys about key elements of evaluation, diagnosis, treatment, monitoring, and long-term management of neurosarcoidosis. Expert consensus recommendations were adopted if >80% threshold of agreement was reached.

Results

Of the 41 invited expert clinicians across the United States, 32 (78%) participated in the study. All round 1 respondents self-identified as neuroimmunologists (except for 1 pulmonologist). Consensus was reached regarding the need to consider neurosarcoidosis phenotype and severity to guide the choice of initial immunosuppression in both the acute (relapse) and maintenance phases. Experts endorsed the use of TNF-α inhibitors as first-line agents in selected phenotypes with poor prognosis. Neuroimaging was recommended to complement clinical surveillance for treatment response.

Discussion

There was agreement on several key issues, most importantly on the need to consider neurosarcoidosis phenotype and severity when deciding initial treatment. No consensus was achieved on the dosing and duration of specific immunosuppressants, nor regarding the management of the peripheral nervous system manifestation of neurosarcoidosis. These topics warrant further investigation.

[1]Department of Neurology, Massachusetts General Hospital, Harvard Medical School; [2]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School; [3]Department of Neurology, Vanderbilt University Medical Center; [4]Department of Neurology, Mellen Center for Multiple Sclerosis, Cleveland Clinic Foundation; [5]Department of Neurology, Mayo Clinic; [6]Department of Neurology, Boston Medical Center; [7]Department of Neurology, Cedars Sinai Medical Center; [8]Department of Medicine, University of Cincinnati Health, OH; [9]Department of Neurology, University of Massachusetts Memorial Health; [10]Department of Neurology, University of Iowa Hospitals; [11]Department of Neurology, University of Utah; [12]Department of Neurology, Washington University; [13]Department of Laboratory Medicine and Pathology, Mayo Clinic; [14]Department of Neurology, Weill Institute for Neurosciences, University of California San Francisco; [15]Department of Neurology, Emory University; [16]Department of Neurology, University of Pennsylvania; [17]Department of Neurology, University of Texas Health Houston; [18]Department of Neurology, The Johns Hopkins University School of Medicine; [19]Department of Neurology, University of Cincinnati Health; and [20]Department of Neurology, New York University Langone Health.

Introduction

Sarcoidosis is a rare multisystem inflammatory disorder. Clinical involvement of the nervous system—termed "neurosarcoidosis"—occurs in 5%–15% of patients with sarcoidosis.[1] More than half of the patients presenting with neurosarcoidosis have no history of systemic sarcoidosis, and 10%–13% of patients with neurosarcoidosis do not have evidence of systemic disease at any point ("isolated neurosarcoidosis").[2] Expert consensus diagnostic criteria by the Neurosarcoidosis Consortium Consensus Group provide a framework for grading diagnostic certainty with respect to available objective data.[3] Diagnosis of neurosarcoidosis is considered "definite," "probable," or "possible" based on recognition of specific clinical-radiologic phenotypes and the presence or absence of pathologic findings confirmatory of sarcoidosis within or outside of the nervous system.[3] This diagnostic framework has been widely accepted by neurosarcoidosis specialists. However, there are no comparable neurologic expert consensus recommendations pertaining to the neurosarcoidosis management and surveillance of treatment response.

It is increasingly recognized that the neurosarcoidosis phenotype influences prognosis and treatment response.[4,5] Isolated facial nerve palsy and uncomplicated aseptic meningitis often demonstrate excellent response to glucocorticosteroids and typically do not recur.[5–7] By contrast, neurosarcoidosis optic neuropathy often has a poor long-term prognosis, with 24% showing bilateral visual acuity of ≤20/200 at the last follow-up.[4] In phenotypes with poor long-term prognosis, it is reasonable to opt for treatments that are most likely to reverse disability progression and sustain remission as early as possible. However, the field lacks robust prospective data to guide management because there have been no randomized controlled trials (RCTs) specific to neurosarcoidosis to date.[8]

There are several areas of uncertainty regarding the management of neurosarcoidosis with resultant variability in clinical practice. The use of glucocorticosteroids is well accepted, but optimal dosing and duration are not standardized. Similarly, there is a lack of uniformity in the choice and duration of steroid-sparing agents, such as methotrexate or azathioprine. There is also a lack of standardization in the assessment of treatment response and disease stability and the questions of whether and when immunosuppressants should be tapered after a period of stability or improvement.

Recognizing the rarity of neurosarcoidosis, a paucity of high-level evidence, and the variability of clinical practice, we sought to collate expert consensus using a Delphi survey approach for key aspects of management. The Delphi approach[9] is an accepted study design to gather expert opinion anonymously through iterative rounds until consensus is reached.[8] This approach has been successfully deployed for guideline development in many areas of medicine where high-level evidence is not available, including non-neurologic sarcoidosis.[1,10] We aimed to develop consensus on key questions pertaining to the treatment of neurosarcoidosis and monitoring of treatment response and to identify areas of uncertainty requiring further investigation. The consensus recommendations are intended as a practical reference to aid the clinicians who are treating patients with neurosarcoidosis.

Methods

Delphi Panel Recruitment

Clinicians in the United States with expertise in neurosarcoidosis were identified based on authorship of peer-reviewed publications in the field of neurosarcoidosis or membership in the Neurosarcoidosis Consortium Working Group.[3] As per published literature, 30–50 expert respondents are considered optimal.[9]

Questionnaire Development

The core panel of authors with neuroimmunologic expertise (G.M., J.E.E., M.L., I.K.) designed the study and developed and distributed the initial questionnaires for input from co-authors. All authors reviewed and analyzed the data, developed consensus recommendations, and revised the manuscript. The questionnaires were distributed to the experts through an electronic RedCap survey.[11,12] Responses were independently provided and confidentially recorded in the RedCap database.[11,12] The core authors were also among the invited experts, and their responses were collected before any data review to prevent bias. The anonymity of responses was preserved within the larger expert panel as per Delphi survey methodology.[9] The respondents did not receive any compensation for participation.

Round 1 consisted of questions about the respondents' specialty, years of experience, and estimated number of managed neurosarcoidosis cases, followed by 38 neurosarcoidosis-specific sections, some with multiple subsections, for a total of 124 questions. Five initial questions appertained to the general treatment approach, subsequent sets of 13 questions inquired about management of specific neurosarcoidosis phenotypes, and the last 14 questions were about surveillance of treatment response and treatment discontinuation. Phenotypes were defined as per the Neurosarcoidosis Diagnostic Consortium criteria.[3] Severity was defined by the authors for some phenotypes as follows: myelitis was "mild" if there were sensory symptoms only without functional limitation and "moderate-severe" if there was motor weakness or sensory symptoms with functional limitations with or without bowel/bladder dysfunction. For optic neuritis, "mild" was defined as Snellen chart VA 20/60 or better in 1 or both eyes and "moderate-severe" as Snellen chart VA worse than 20/60 in 1 or both eyes. Pachymeningitis and leptomeningitis were further classified according to the presence or absence of increased intracranial pressure (ICP) and hydrocephalus. Parenchymal brain disease was divided into 2 classes based on the presence or absence of focal deficits and seizures. The other phenotypes, which were not

split into subclasses, were multiple cranial neuropathies, hypothalamic-pituitary involvement, small-fiber neuropathy, large-fiber neuropathies, and myopathies. Respondents were asked to report clinical experience managing each phenotype and could opt out of responding to questions for any neurosarcoidosis phenotype. The full text of the survey can be found in eAppendix 1.

The round 2 questions were developed after the review of responses to round 1 with the intent of achieving consensus from unresolved round 1 topics. Round 2 responses were also collected anonymously. The questionnaire contained 9 questions and was distributed to all respondents who completed round 1. In round 2, only 1 question stem was phenotype specific: whether an induction vs escalation approach is recommended for different neurosarcoidosis phenotypes. An "induction approach" was defined as the administration of an anti-TNF-α steroid-sparing agent (e.g., infliximab) as first-line early in the disease course with glucocorticosteroids. An "escalation approach" was defined as the administration of glucocorticosteroids with or without commonly used oral steroid-sparing agents, such as methotrexate, mycophenolate mofetil, or azathioprine, and then escalating to an anti-TNF-α steroid-sparing agent if there is inadequate response. Other questions queried about the role of a neuroimmunologist in the management of neurosarcoidosis; the influence of concurrent non-neurologic sarcoidosis activity on treatment selection; whether an adjuvant steroid-sparing agent should always be used along with infliximab to prevent anti-infliximab antibody formation; the need for post-treatment MRI scans with gadolinium contrast to assess treatment response; the recommended duration of treatment before discontinuation attempt; and relapse management. The full text of the survey is provided in eAppendix 1.

Consensus Definition

Consensus for any item was defined a priori as ≥80% of respondent agreement. Only items with <80% agreement on the first survey were incorporated into the second-round survey. We excluded responses for questions with ≤50% respondent participation.

Consensus Statements

Anonymized results were shared with and reviewed by all authors, including both quantitative response outcomes and anonymous comments. Consensus recommendations were then collaboratively formulated with the approval of all coauthors.

Standard Protocol Approvals, Registrations, and Participant Consents

The study design was reviewed with the Institutional Review Board (IRB) of the senior investigator (NYU Langone) and was deemed to be exempt from IRB approval because of the anonymity of the Delphi survey responses and absence of patient data.

Data Availability

Anonymized data can be made available by request from any qualified investigator.

Results

Study Respondents

Forty-one clinicians across the United States with expertise in neurosarcoidosis were invited to participate by electronic survey distribution. Thirty-two experts (78% response rate) from 19 academic institutions participated in round 1. All included experts identify as neuroimmunologists except for 1 pulmonologist. Among the 32 respondents, the distribution of years in practice is as follows: 0–5 years (25%), 5–10 years (25%), 10–20 years (25%), and >20 years (25%). The estimated number of patients with neurosarcoidosis cared for by the respondents is as follows: 1–10 patients with neurosarcoidosis (9.4%), 10–24 patients (12.5%), 25–50 patients (40.6%), and >50 patients (37.5%). Experts who submitted responses to round 1 were invited to complete the round 2 questionnaire.

Round 1

General Approach to Neurosarcoidosis Management

Consensus (≥80%) was reached for 3 of 5 questions regarding the general treatment approach. There was support for consideration of neurosarcoidosis phenotype and its severity when determining the treatment approach. There was support for the use of immunosuppression to treat "possible" neurosarcoidosis syndrome if other causes (infections, malignancies, other neuroimmune conditions) are reasonably excluded (Table 1). A consensus threshold was not reached for the preferred oral steroid-sparing agent for neurosarcoidosis, although a strong majority (76%) favor methotrexate with a target weekly methotrexate dose of 15–25 mg and supplemental folate. The rates of use of other agents—mycophenolate mofetil, azathioprine, rituximab, cyclophosphamide, or IV immunoglobulin—did not meet the consensus threshold (Table 2).

Phenotype-Specific Questions

For acute treatment of neurosarcoidosis, regardless of the phenotype, glucocorticosteroids should be used when not contraindicated. For acute treatment of leptomeningeal disease with associated ICP, IV infliximab with concurrent high-dose glucocorticosteroids is recommended. There was universal consensus that oral prednisone alone is insufficient for the initial treatment of moderate-to-severe myelitis; most favored an IV steroid-sparing agent (i.e., infliximab) in addition to high-dose IV glucocorticosteroids (72.4%) for this phenotype, but consensus was not attained. Similarly, a strong majority (78.3%) favored the use of an anti-TNF-α immunosuppressant (i.e., infliximab) plus high-dose glucocorticosteroids for acute treatment of symptomatic brain parenchymal disease due to neurosarcoidosis (i.e., focal deficits and seizures), and a slightly less majority (70.8%) favored the same approach for acute treatment of

Table 1 Consensus Recommendations

General approach to treatment of patients with neurosarcoidosis	
1	The recommended initial treatment regimen for probable or definite neurosarcoidosis depends on the neurosarcoidosis phenotype and symptom severity (phenotype-dependent: 87.5% [28/32], severity-dependent: 81.3% [26/32]) A stepwise escalation approach is not recommended for all phenotypes
2	It is appropriate to apply treatment strategies for "possible" neurosarcoidosis so long as alternative etiologies have been appropriately excluded (87.5% [28/32]). Careful monitoring and reevaluation for other etiologies before and after empiric treatment initiation are critical. It is especially important to exclude demyelinating disease before treatment with TNF-α inhibitors. There is a FDA boxed warning recommending against use of this class of agents in patients with preexisting demyelinating diseases[31]
3	Glucocorticosteroids should be administered as part of the initial treatment regimen for neurosarcoidosis when treatment is warranted (100% [32/32])
4	The presence of active, systemic sarcoidosis should be considered when determining an induction vs escalation approach to immunosuppressant use for the treatment of neurosarcoidosis (83.3% [20/24])
5	Neurologists with expertise in neuroimmunology should be involved in the management of neurosarcoidosis whenever possible (95.8% [23/24])
6	After acceptable clinical and radiographic treatment response, an attempt to gradually taper off immunosuppressants is reasonable with close surveillance (91.7% [22/24])
Phenotype-specific recommendations	
1	Specific phenotypes warrant an induction approach with high-dose glucocorticosteroids and an anti-TNF-α steroid-sparing agent (e.g., intravenous methylprednisolone and IV infliximab) for acute management. These include the following
a	Moderate-severe myelitis (91.7% [22/24])
b	Pachymeningitis with elevated ICP (91.7% [22/24])
c	Leptomeningitis with elevated ICP (87.5% [21/24])
d	Symptomatic parenchymal brain disease (e.g., focal deficits or seizures) (91.7% [22/24])
e	Moderate-severe optic neuritis (83.3% [20/24])
2	Maintenance immunosuppression for at least 1 y is strongly encouraged for certain phenotypes regardless of initial response to acute treatment
Utilization of neuroimaging to monitor treatment response	
1	If an initial neuroimaging study is abnormal, repeat neuroimaging should be obtained within the first 2–6 mo after initiation of neurosarcoidosis-directed immunosuppression (100% [24/24])
2	Neuroimaging of neurosarcoidosis requires the use of gadolinium contrast if not contraindicated (95.8% [23/24])

Abbreviation: ICP = increased intracranial pressure.
All consensus recommendations met the specified Delphi survey criterion of ≥80% agreement among participating expert respondents.

neurosarcoidosis pachymeningitis with associated increased ICP or hydrocephalus, although in both phenotypes, we did not reach the consensus threshold. Consensus was also not reached for the specific regimens of oral vs IV steroids nor the choice of steroid-sparing agents (if any) for acute management of the other phenotypes in the acute setting.

Phenotype and severity affect the choice of maintenance (preventative) immunosuppression. Infliximab or adalimumab is recommended for use as maintenance immunosuppressants for moderate-severe neurosarcoidosis myelitis. There is near-consensus agreement that infliximab or adalimumab should be used as maintenance treatment of symptomatic pachymeningitis with associated hydrocephalus (79.2%), symptomatic brain parenchymal neurosarcoidosis (78.3%), and leptomeningitis with associated ICP or hydrocephalus (73.9%). There is a lack of consensus regarding the duration of maintenance immunosuppression in the abovementioned phenotypes. Maintenance immunosuppressants should also be used for the treatment of mild myelitis or moderate-severe optic neuritis, although opinions vary regarding which immunosuppressant.

Consensus opinion supports the use of repeat neuroimaging in 2–6 months after treatment initiation to assess treatment response for the following phenotypes: pachymeningitis, brain parenchymal disease, leptomeningitis, myelitis of any severity, hypothalamic/pituitary involvement, other cranial neuropathies, and optic neuritis of any severity. Owing to ≤50% respondent participation for questions pertaining to small-fiber neuropathy and other polyneuropathies and myopathies, these phenotypes were not included in the final analyses (Table 2).

Round 2

Of the 32 round 1 respondents, 24 (75%) completed the round 2 questionnaire. A comparison of the detailed responses from round 1 participants who then did or did not participate in round 2 did not reveal any differences in

Table 2 Key Areas in Which Consensus Has Not Been Reached

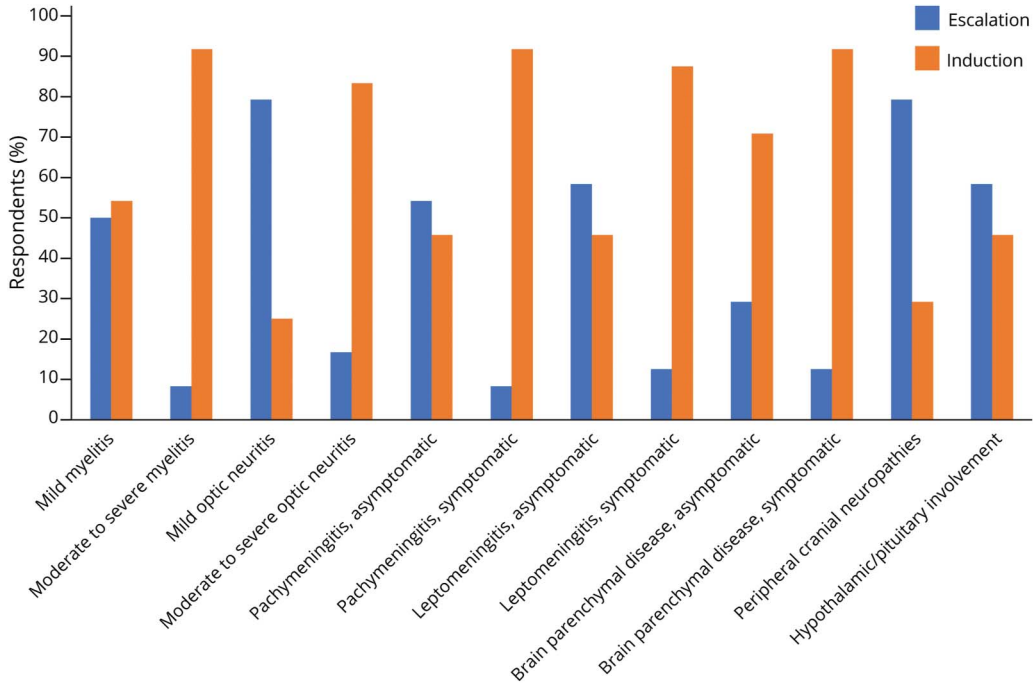
1	Standardization of glucocorticosteroid dosing for different phenotypes
2	Standardization of choice and dosing of steroid-sparing treatments for different phenotypes
3	Optimization of prescribing practices to minimize formation of anti-TNF-α inhibitor antibodies (i.e., use of concurrent oral immunosuppressant)
4	Duration of use of steroid-sparing immunosuppressants after clinical stability/remission
5	Management of peripheral neurosarcoidosis phenotypes, including small-fiber neuropathy, polyneuropathies, and myopathies

responses. For example, all respondents who did not complete round 2 endorsed the use of anti-TNF-α inhibitors early in the disease course of moderate-severe myelitis and other phenotypes. We did not inquire why several participants did not complete round 2, but this is neither uncommon nor unexpected in Delphi surveys. Reassuringly, those who did not complete round 2 recorded responses to round 1 that were congruent to the consensus opinion of round 2 respondents; thus, it is unlikely that the omission of their responses introduced an important bias.

Consensus was reached for the recommendation of an induction immunosuppressive approach as a first-line, acute treatment of the following phenotypes: moderate-severe myelitis, symptomatic pachymeningitis with increased ICP or hydrocephalus, symptomatic brain parenchymal disease with focal deficits or seizures, symptomatic leptomeningitis with increased ICP or hydrocephalus, and moderate-severe optic neuritis. Near-consensus recommendations for an escalation immunosuppressive approach are present for acute treatment of neurosarcoidosis presenting as mild optic neuritis (79.2%) and peripheral cranial neuropathies (79.2%). There is lack of consensus for escalation vs induction immunosuppressive approach for initial management of mild myelitis, pachymeningitis without increased ICP or hydrocephalus (induction favored by 70.8%), leptomeningitis without increased ICP or hydrocephalus, brain parenchymal disease without associated focal deficits or seizures (induction favored by 69.6%), and hypothalamic-pituitary involvement. The responses for these phenotypes are shown in the Figure.

The involvement of a neurologist with expertise in neurosarcoidosis, whenever possible, is supported because of the complexity of both diagnosis and management of neurosarcoidosis. In the presence of active, concurrent systemic sarcoidosis, a multidisciplinary team approach is advised because extraneural manifestations are critical to consider when determining a treatment approach. Surveillance of treatment response should include repeat MRI of the affected part of the neuraxis within 2–6 months after treatment

Figure Recommendation of Escalation vs Induction Treatment Approach by Phenotype and Severity of Neurosarcoidosis



All 24 round 2 respondents participated.

initiation if the initial neuroimaging is abnormal. All MR imaging in neurosarcoidosis should include gadolinium contrast unless contraindicated.

Once an acceptable treatment response in neurosarcoidosis is attained, clinically and radiographically, it is reasonable to attempt to taper off immunosuppression. How best to taper was not agreed on, but there was consensus that an attempt to taper glucocorticosteroid within a year from treatment start should be made—with close surveillance for disease recurrence—to avoid risks of toxicities from prolonged exposure (87.5%). Consensus was not achieved regarding the rate of decrease of glucocorticosteroids. It is acknowledged that successful discontinuation of immunosuppression is not always achievable in practice. Should relapse occur, a strong majority support the use of an induction approach on treatment restart (79.2%).

There was a lack of unanimity as to whether a steroid-sparing agent such as methotrexate must always be used concurrently with infliximab to reduce anti-infliximab antibody formation[13]: 47.8% were in favor of use, 39.1% were opposed, and 13% were unable to answer.

A summary of consensus recommendations and key areas where consensus was not obtained is provided in Tables 1 and 2.

Discussion

Experience with neurosarcoidosis is limited even among experts, as evidenced by only one-third of the respondents reporting care of >50 patients with neurosarcoidosis. The rarity and notable heterogeneity of neurosarcoidosis have contributed to a lack of standardization of care, furthered by the absence of RCTs. Our study aimed to formulate consensus recommendations regarding key aspects of the management of neurosarcoidosis by broadly surveying experts in the field.

Consensus was achieved in several areas. It is important to note that experts support the idea that an initial treatment approach should depend on the neurosarcoidosis phenotype and severity. This reflects a shift from the traditional, stepwise "escalation" approach[14,15]—described in the 2021 European Respiratory Society (ERS) recommendations—to a phenotype/severity-specific approach in which consideration of an anti-TNF-α inhibitor plus corticosteroids as first-line therapy for selected phenotypes and severity is endorsed. The 2021 ERS systemic sarcoidosis treatment guidelines include a section on neurosarcoidosis management based on expert opinion but did not include neurologists among its authors.[14] The ERS guidelines advocate for glucocorticosteroids first, followed by oral steroid-sparing agents and, finally, infusible therapies if there is an inadequate response.[14] However, nearly 70% of patients with neurosarcoidosis require treatment escalation,[2] and therefore, most patients treated with an escalation strategy will be at risk of irreversible neurologic damage if the pathologic process is inadequately controlled early. Prolonged glucocorticosteroid use is also associated with a substantial risk of toxicities, particularly at the doses and duration needed to treat neurosarcoidosis.[16] A uniform escalation approach for all neurosarcoidosis presentations fails to consider that treatment responsivity and prognosis vary by clinical phenotype.

An alternative to an escalation approach is an "induction approach," whereby high-dose IV methylprednisolone daily for 3–5 days followed by an oral prednisone taper is combined with an anti-TNF-α inhibitor (usually with infliximab), early in the treatment course. Such an approach has been supported by individual experts for the management of severe, disabling neurosarcoidosis phenotypes where the first-level and second-level agents—per the ERS escalation framework—are unlikely to halt or reverse disease progression.[17–19] Several observational studies document the clinical effectiveness of infliximab in forestalling permanent neurologic disability in neurosarcoidosis, including cases in which oral steroid-sparing immunosuppressants were not effective.[17–20] There is also emerging literature regarding the use of another TNF-α inhibitor, adalimumab.[21,22] Consensus recommendations developed in our study support a phenotype severity-based approach and endorse the use of steroid-sparing agents, such as infliximab, as first-line in combination with glucocorticosteroids in phenotypes with potential for significant long-term morbidity (Table 1).

Similar shifts to inductive approaches are emerging in several rheumatologic and neuroimmunologic areas. Thus, current treatment recommendations for eosinophilic granulomatosis with polyangiitis incorporate the degree of end-organ involvement, with first-line cyclophosphamide recommended for severe end-organ dysfunction.[23] A similar shift has occurred in multiple sclerosis: the use of high-efficacy disease-modifying therapies upfront has been shown to forestall long-term disability.[24] Unlike multiple sclerosis, neurosarcoidosis is not known to have a progressive neurodegenerative phase, but both conditions share the imperative to prevent early irreversible neurologic injury.

Prompt initiation of glucocorticosteroids in neurosarcoidosis is recommended for all phenotypes. However, in severe neurosarcoidosis phenotypes, glucocorticosteroid monotherapy is often insufficient. It is acknowledged that neurosarcoidosis severity is not universally defined at present; however, for purposes of this study and its resultant consensus recommendations, severity was defined according to the degree of functional impairment and related consequences as detailed in the methodology of this article. Anti-TNF-α inhibitor therapies, specifically infliximab, were strongly favored as the steroid-sparing agent of choice in the induction approach. Several retrospective series support its early use in neurosarcoidosis.[18,19] One retrospective study found an inverse relationship between time to infliximab initiation and favorable treatment response.[18] In addition, early

infliximab use was shown in a meta-analysis to correlate with more rapid successful tapering or cessation of corticosteroid use in neurosarcoidosis.[19] This finding aligns with the consensus recommendation to initiate anti-TNF-α inhibition early in the disease course of phenotypes associated with the potential for severe neurologic dysfunction. In systemic, nonneurologic sarcoidosis, RCTs have found infliximab to be efficacious for the reduction of disease morbidity.[25,26] The dosing regimen with which infliximab should be used to treat neurosarcoidosis has not been queried in our study, but consensus recommendations in pulmonary sarcoidosis suggest infliximab 5 mg/kg at weeks 0, 2, and 6 for induction, followed by maintenance dosing of 5 mg/kg every 4–6 weeks.[27]

Before starting TNF-α inhibitors, it is critical to ensure that the patient does not have a demyelinating disorder. There are reports that infliximab increases the risk of demyelinating and nondemyelinating CNS complications in patients with rheumatologic conditions.[28,29] A large, nested-cohort study of anti-TNF-α agents in a rheumatologic patient population was associated with a three-fold increased risk of inflammatory CNS events.[29] It is important to note that patients with preexisting systemic sarcoidosis or neurosarcoidosis were not included in this study. To the authors' knowledge, worsening of neurosarcoidosis after TNF-alpha inhibition has not been reported; whereas, there exist reports of de novo emergence of granulomatous disorders with this therapy.[30]

Close clinical and radiologic surveillance is recommended for possible, probable, and definite neurosarcoidosis. Arguably, there may be a need for closer surveillance of patients with "possible neurosarcoidosis" because of the risk of misdiagnosis. The consensus recommendations endorse the utilization of MRI with gadolinium to monitor treatment response. Disease recurrence should lead to consideration of treatment escalation. Regardless of the neurosarcoidosis phenotype or severity, an attempt to deescalate immunosuppression after disease stability or remission is reasonable, although not always achievable in practice. There is an obvious need for prospective, randomized, controlled trials to ascertain the optimal duration of use of immunosuppressants in different neurosarcoidosis phenotypes.

One limitation of this study is the recruitment of experts from academic institutions across the United States only. This potentially restricts the generalizability of recommended practices to other locales. Nonetheless, the inclusion of experts from 19 major academic institutions is expected to provide an adequate representation of clinical practice within the United States and permit reliable consensus thresholds to support the recommendations for the US population. Other limitations included the lack of consensus on optimal management for several phenotypes and the specific dosing and duration of oral immunosuppressants. This lack of agreement reflects the heterogeneity in clinical practice and the need for prospective comparative phenotype-specific studies of anti-TNF-α inhibitors and conventional steroid-sparing agents. Of special interest is the question of long-term use of methotrexate to prevent relapses, as advocated by some specialists. Finally, several particularly rare neurosarcoidosis phenotypes, such as peripheral neuropathies, had low rates of response preventing consensus formulation. We also acknowledge that some questions relevant to neurosarcoidosis management were not included in the surveys; e.g., we did not inquire about the need to test for coexistent common variable immunodeficiency in patients with sarcoidosis.

This Delphi survey study effectively achieved consensus on several key areas of neurosarcoidosis management among practicing experts and identified areas needing further investigation. The immunosuppressive regimen used to treat neurosarcoidosis should be guided by the presenting phenotype and its severity. Several severe phenotypes warrant the consideration of anti-TNF-α inhibitors early in the disease course. These recommendations should not supersede clinical judgment, and the risks and benefits of any intervention need to be assessed for each patient. In the absence of high-level evidence at present, these consensus recommendations can guide practicing clinicians in the formulation of a treatment and surveillance plan for the patients with this rare condition.

TAKE-HOME POINTS

- The Delphi survey model can be used to attain consensus and provide guidelines for the management of neurosarcoidosis, a condition that otherwise lacks robust, prospective data to guide treatment decisions.
- The approach to treatment of neurosarcoidosis should consider the presenting phenotype, its severity, and any concurrent systemic manifestations of sarcoidosis.
- An induction treatment approach, using glucocorticosteroids plus a steroid-sparing agent as first-line treatment of an acute event of neurosarcoidosis, may be appropriate for certain severe phenotypes.
- Clinical reevaluations and imaging surveillance are complementary in assessing both treatment response and persistence of disease remission.
- Cautious weaning of glucocorticosteroids should be considered after disease stability is attained in neurosarcoidosis; the current recommendation is to consider this within 1 year after treatment initiation.

Author Contributions

G.S. Manzano: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J. Eaton: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Levy: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. J.R. Abbatemarco: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A.J. Aksamit: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P. Anand: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D.T. Balaban: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P. Barreras: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R.P. Baughman: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Bhattacharyya: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Bomprezzi: drafting/revision of the manuscript for content, including medical writing for content. T.A. Cho: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B. Chwalisz: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S.L. Clardy: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D.B. Clifford: drafting/revision of the manuscript for content, including medical writing for content. E.P. Flanagan: drafting/revision of the manuscript for content, including medical writing for content. J.M. Gelfand: drafting/revision of the manuscript for content, including medical writing for content. G.K. Harrold: drafting/revision of the manuscript for content, including medical writing for content. S.K. Hutto: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Pawate: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N. Rivera Torres: drafting/revision of the manuscript for content, including medical writing for content. L. Abdel-Wahed: drafting/revision of the manuscript for content, including medical writing for content. S.R. Dunham: drafting/revision of the manuscript for content, including medical writing for content. R.K. Gupta: drafting/revision of the manuscript for content, including medical writing for content. B. Moss: drafting/revision of the manuscript for content, including medical writing for content. C.A. Pardo: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R.D. Samudralwar: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N. Venna: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Zabeti: drafting/revision of the manuscript for content, including medical writing for content. I. Kister: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

C.A. Pardo received funding from NIH R01NS123712 for sarcoidosis research. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology: Clinical Practice* May 14, 2024. Accepted in final form November 6, 2024. Submitted and externally peer-reviewed. The handling editor was Deputy Editor Kathryn Kvam, MD.

References

1. Drent M, Crouser ED, Grunewald J. Challenges of sarcoidosis and its management. *N Engl J Med*. 2021;385(11):1018-1032. doi:10.1056/NEJMra2101555
2. Fritz D, van de Beek D, Brouwer MC. Clinical features, treatment and outcome in neurosarcoidosis: systematic review and meta-analysis. *BMC Neurol*. 2016;16(1):220. doi:10.1186/s12883-016-0741-x
3. Stern BJ, Royal W III, Gelfand JM, et al. Definition and consensus diagnostic criteria for neurosarcoidosis: from the neurosarcoidosis consortium consensus Group. *JAMA Neurol*. 2018;75(12):1546-1553. doi:10.1001/jamaneurol.2018.2295
4. Webb LM, Chen JJ, Aksamit AJ, et al. A multi-center case series of sarcoid optic neuropathy. *J Neurol Sci*. 2021;420:117282. doi:10.1016/j.jns.2020.117282
5. Nwebube CO, Bou GA, Castilho AJ, Hutto SK. Facial nerve palsy in neurosarcoidosis: clinical course, neuroinflammatory accompaniments, ancillary investigations, and response to treatment. *J Neurol*. 2022;269(10):5328-5336. doi:10.1007/s00415-022-11189-6
6. Lacomis D. Neurosarcoidosis. *Curr Neuropharmacol*. 2011;9(3):429-436. doi:10.2174/157015911796557975
7. Bekkour I, Courtin E, Dulau-Metras C, Duffau P, Kremer L, Mathey G. Defining the course of neurosarcoidosis according to presentation at onset and disease modifying treatment: a cohort study of 84 patients. *Ther Adv Neurol Disord*. 2023;16:17562864231205954. doi:10.1177/17562864231205954
8. Obi ON, Saketkoo LA, Russell AM, Baughman RP. Sarcoidosis: updates on therapeutic drug trials and novel treatment approaches. *Front Med*. 2022;9:991783. doi:10.3389/fmed.2022.991783
9. Nasa P, Jain R, Juneja D. Delphi methodology in healthcare research: how to decide its appropriateness. *World J Methodol*. 2021;11(4):116-129. doi:10.5662/wjm.v11.i4.116
10. Rahaghi FF, Baughman RP, Saketkoo LA, et al. Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis. *Eur Respir Rev*. 2020;29(155):190146. doi:10.1183/16000617.0146-2019
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
12. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi. 10.1016/j.jbi.2019.103208
13. Fousekis FS, Papamichael K, Kourtis G, et al. The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease. *Ann Gastroenterol*. 2022;35(1):1-7. doi:10.20524/aog.2021.0682
14. Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J*. 2021;58(6):2004079. doi:10.1183/13993003.04079-2020
15. Cheng RK, Kittleson MM, Beavers CJ, et al. Diagnosis and management of cardiac sarcoidosis: a scientific statement from the American Heart Association. *Circulation*. 2024;149(21):e1197-e1216. doi:10.1161/CIR.0000000000001240
16. Lackey E, Shen J, Veal K, et al. Steroid-induced weight gain in the treatment of neurosarcoidosis. *Mult Scler Relat Disord*. 2023;71:104587. doi:10.1016/j.msard.2023.104587
17. Fritz D, Timmermans WMC, van Laar JAM, et al. Infliximab treatment in pathology-confirmed neurosarcoidosis. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(5):e847. doi:10.1212/NXI.0000000000000847

18. Gelfand JM, Bradshaw MJ, Stern BJ, et al. Infliximab for the treatment of CNS sarcoidosis: a multi-institutional series. *Neurology*. 2017;89(20):2092-2100. doi: 10.1212/WNL.0000000000004644
19. Chaiyanarm S, Satiraphan P, Apiraksattaykul N, et al. Infliximab in neurosarcoidosis: a systematic review and meta-analysis. *Ann Clin Transl Neurol*. 2024;11(2):466-476. doi:10.1002/acn3.51968
20. Voortman M, Drent M, Baughman RP. Management of neurosarcoidosis: a clinical challenge. *Curr Opin Neurol*. 2019;32(3):475-483. doi:10.1097/WCO.0000000000000684
21. Hutto SK, Kyle K, Cavanagh JJ, Reda H, Venna N. Adalimumab for CNS sarcoidosis: single-center experience and literature review. *J Neurol*. 2022;269(4):2064-2072. doi: 10.1007/s00415-021-10793-2
22. Sugita M, Lopez AL, Shen J, Lackey E. Neurosarcoidosis treated with adalimumab: a case series (P8-14.014). *Neurology*. 2024;102(17_supplment_1):2659. doi: 10.1212/WNL.0000000000204659
23. Emmi G, Bettiol A, Gelain E, et al. Evidence-based guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. *Nat Rev Rheumatol*. 2023;19(6):378-393. doi:10.1038/s41584-023-00958-w
24. Giovannoni G. Do we have equipoise when it comes to how we treat active multiple sclerosis? *Lancet Neurol*. 2019;18(10):909-911. doi:10.1016/S1474-4422(19)30227-3
25. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med*. 2006;174(7): 795-802. doi:10.1164/rccm.200603-402OC
26. Judson MA, Baughman RP, Costabel U, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J*. 2008;31(6):1189-1196. doi: 10.1183/09031936.00051907
27. Drent M, Cremers JP, Jansen TL, Baughman RP. Practical eminence and experience-based recommendations for use of TNF-α inhibitors in sarcoidosis. *Sarcoidosis Vascu Diffuse Lung Dis*. 2014;31(2):91-107.
28. Bewley AP, Maleki S. Systemic sarcoidosis reactions as a result of tumour necrosis factor-alpha treatment for patients with psoriasis. *Clin Exp Dermatol*. 2021;46(8): 1548-1550. doi:10.1111/ced.14751
29. Kunchok A, Aksamit AJ, Davis JM, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol*. 2020;77(8):937-946. doi:10.1001/jamaneurol.2020.1162
30. Miedema J, Nunes H. Drug-induced sarcoidosis-like reactions. *Curr Opin Pulm Med*. 2021;27(5):439-447. doi:doi:10.1097/MCP.0000000000000800
31. Kucharz EJ, Kotulska-Kucharz A. Tumor necrosis factor alpha inhibitors and demyelinating disease: what is behind it? *Reumatologia*. 2021;59(2):65-67. doi:10.5114/reum.2021.105438

How to cite this article: Manzano GS, Eaton J, Levy M, Abbatemarco JR, et al. Consensus recommendations for the management of neurosarcoidosis: a Delphi survey of experts across the United States. *Neurol Clin Pract*. 2025;15(2):e200429. doi: 10.1212/CPJ.0000000000200429