

WHAT'S HOT IN THE TREATMENT OF GIANT CELL ARTERITIS

Valérie Biousse, MD

*Emory University
Atlanta, GA*

LEARNING OBJECTIVES

1. The attendee will be able to recognize GCA patients at high risk for visual loss
 2. The attendee will be able to initiate appropriate therapy based on the patient's characteristics and clinical presentation
 3. The attendee will be able to plan appropriate follow-up based on the expected clinical course of the patient with GCA
- c. Failure to do so should raise the question of an alternative diagnosis.
 - c. Glucocorticosteroid reduction should be considered only in the absence of clinical symptoms, signs and laboratory abnormalities suggestive of active disease
 - d. A number of immunosuppressive agents are effective in preventing GCA relapse.
 - e. Low-dose aspirin should be considered in patients with GCA if no contraindications exist.

CME QUESTIONS

1. Which of the following statements about GCA is FALSE:
 - a. Not all patients with visual loss from GCA have systemic symptoms of GCA.
 - b. GCA patients experiencing episodes of transient monocular visual loss are at very high risk of permanent visual loss when GCA is not promptly treated.
 - c. Most patients with visual loss in the setting of GCA have a central retinal artery occlusion.
 - d. The use of steroids is not supported by randomized clinical trials.
 - e. Cerebral ischemia is uncommon in GCA.
2. Which of the following statement about the visual outcome of GCA patients is FALSE:
 - a. Most patients with visual loss in the setting of GCA recover good visual function with appropriate management.
 - b. High dose intravenous steroids only rarely result in visual improvement in GCA.
 - c. The main goal of steroid treatment in patients with visual loss from GCA is to prevent fellow eye involvement.
 - d. Recurrent visual loss is common when steroids are tapered too quickly.
3. Which of the following statement about the treatment of GCA is FALSE:
 - a. Methotrexate is the most evaluated immunosuppressive agent (other than steroids) in GCA.
 - b. The symptoms of GCA should respond rapidly to high-dose glucocorticosteroid treatment, followed by resolution of the inflammatory response.

KEYWORDS

1. Giant Cell Arteritis
2. Visual Loss
3. Steroids
4. Immunosuppressive Agents

INTRODUCTION

The clinical presentation of giant cell arteritis (GCA) varies greatly and includes numerous clinical subtypes: 1) cranial arteritis with severe ischemic complications, such as visual loss and cerebral ischemia; 2) large vessel arteritis causing subclavian and axillary stenosis, and 3) aortitis leading to aortic dissection, aneurysm, and aortic rupture; 4) a systemic inflammatory syndrome with nonstenosing vasculitis; and "isolated" polymyalgia rheumatica (PMR) with myalgias, fatigue, anorexia, and subclinical systemic vasculitis (1–3). Visual loss is the most dreaded complication of GCA and occurred in 30–60% of patients with GCA before the era of corticosteroid treatment (1). Despite the widespread use of corticosteroids in the modern era, devastating visual loss still occurs in about 20% of patients with GCA (1–4).

Few studies have evaluated treatment protocols by individual GCA subtype, leading to heterogeneous recommendations regarding management and treatment, and most are based on the investigator specialty. Indeed, studies performed by ophthalmologists and by neurologists generally recommend more aggressive treatment measures, sustained for longer periods of time, than studies performed by rheumatologists and population-based studies (5,6). Rheumatologists, for example, often use very low-dose oral prednisone to treat "isolated" PMR and minimize long-term side-effects of

steroids, while neuro-ophthalmologists often use high-dose intravenous methylprednisolone to treat patients with acute visual loss or brain ischemia (2,3).

The treatable nature of GCA and the devastating visual consequences of a delayed diagnosis make identification and treatment of GCA a true medical emergency (2,7–10). Indeed, once a patient has lost vision in one eye, the risk of GCA-related visual loss in the fellow eye is highest within hours to days (5). Delaying steroid treatment not only reduces the chances of visual improvement, but also places the patient at risk for fellow eye involvement, which occurs in more than 50% of patients. Additionally, although the visual outcome of arteritic ischemic optic neuropathy is poor, immediate treatment with steroids might result in some visual improvement (3,7–9).

GCA is considered a prototypical steroid-responsive disease. Patients have fast and profound improvement of constitutional symptoms, such as malaise, anorexia, fevers, and myalgias. Steroids are believed to be vision protective, and headaches and scalp tenderness often respond promptly. However, vascular lesions persist, and disease flares are frequent on tapering of glucocorticoids (1–9). The absence of class A (category 1) clinical trial does not allow for “official guidelines,” but both the European League Against Rheumatism (EULAR) and the British Society of Rheumatology (BSR) have issued recommendations for the optimal treatment of patients with GCA (7–9).

Table 1—Suggested steps in the management of giant cell arteritis (GCA) complicated by ocular or brain ischemia

DIAGNOSIS - Obtain baseline CBC, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and temporal artery biopsy as soon as possible in any patient suspected of having GCA, but do not delay the initiation of treatment while waiting for the biopsy. - Consider non-invasive imaging of the aorta and its branches.
INITIAL TREATMENT - Begin treatment with an induction dose of intravenous methylprednisolone 1g per day for three days for its steroid-sparing effects over the long term and its possible effects on visual recovery in the short-term. - Subsequently begin prednisone 1 mg/kg/day. - For prophylactic bone protection, begin calcium supplementation (1200mg per day) and vitamin D (800IU per day) and obtain a baseline bone density scan. In osteoporotic patients, add a bisphosphonate. - Begin daily low-dose aspirin unless contraindicated. - Educate the patient regarding the natural history of GCA, the planned long-term treatment with corticosteroids and its complications, as well as the risk of visual loss with poor compliance.
INITIAL MONITORING Monitor clinical symptoms very closely (every day during intravenous steroids, then every few days) and platelets, ESR and CRP (at one week, then every month). Question the diagnosis of GCA if improvement of systemic symptoms does not begin to occur within the first few days.
TAPERING AND RELAPSES - When disease control has been achieved (defined as normal ESR and CRP, and no systemic symptoms of GCA), begin to taper prednisone. - Taper prednisone every month, if possible. The taper schedule must be individualized to each patient. Begin by decreasing large doses by 10mg per month initially, then 5mg per month, and then as little as 1mg per month once a prednisone dose of 10–15mg per day has been achieved. Do not use alternate daily dosing. Instruct the patient to seek medical attention immediately upon recurrence of symptoms, particularly visual symptoms. - At each follow-up visit, obtain an ESR and CRP. If both are elevated above normal, increase the prednisone dose to the last level that maintained remission until the ESR and CRP have normalized again. Similarly, increase the prednisone dose when a patient has recurrence of GCA symptoms, even in the absence of elevated ESR and CRP. - Consider Methotrexate or other immunosuppressant (as part of a clinical trial if possible) if recurrent relapses or failure to taper corticosteroids.
FOLLOW-UP Schedule follow-up visits every 2–3 weeks while patient is on more than 40mg per day of prednisone, then every 4–6 weeks until the patient has reached a low maintenance dose; then follow up every 3 months.
DISCONTINUING STEROIDS When a patient has been completely tapered off prednisone, follow the patient clinically and with ESR and CRP for at least one year further to guard against relapse.

CORTICOSTEROIDS

There is universal agreement that glucocorticosteroids are the mainstay of treatment for GCA and should be initiated immediately and aggressively (7–9). The 5 goals of steroid treatment are:

1. Suppress inflammation
2. Prevent further visual loss in the involved eye
3. Prevent visual loss in the fellow eye
4. Suppress disease activity
5. Possibly restore vision

The initial starting dose, route of administration, and duration of therapy are still matters of debate, but depend largely on the patient's potential for visual loss (7–9).

Oral prednisone is the first-line acute therapy for GCA in most cases. The initial starting dose used to control GCA varies widely in the literature—from 20mg per day in a mixed population of patients with either GCA or PMR but with strictly constitutional signs and symptoms (12), to more than 100mg per day in a high-risk neuro-ophthalmic population with recent or impending visual loss (5). Selection bias during enrollment influences the conclusions of these studies; rheumatological reports often combine GCA with PMR (a much milder condition which responds to relatively low doses of prednisone), and neuro-ophthalmic reports often enroll patients with severe visual loss and occult GCA, excluding milder forms of the disease. Although no consensus exists for initial dose of prednisone, the vast majority of patients respond to a dose of 1mg/kg/day, or between 40–60mg per day (2–4). Higher doses of 80–100mg per day are suggested for patients with visual or neurological symptoms of GCA (5,13).

Intravenous pulse methylprednisolone is often proposed as an induction therapy when vision is at risk. Four studies have examined intravenous steroid therapy in GCA, two of which were prospective randomized controlled trials. The study by Chevalet et al. (14) showed no benefit for a single low induction dose of intravenous methylprednisolone 250mg in reducing cumulative steroid dose at one year. However, the study by Mazlumzadeh et al. (15), found that a 3-day course of induction intravenous methylprednisolone at a much higher dose of 15mg/kg (about 1000mg) per day allowed more rapid weaning from prednisone than placebo, and also reduced the cumulative steroid dose at week 78. Interestingly, the benefits of pulse steroid therapy became obvious later in the course of the disease. Only one study, by Chan et al. (16), evaluated intravenous steroids in exclusively “high-risk” patients—those with biopsy-proven GCA and recent or impending visual loss—and found improvement of visual acuity in significantly more patients treated with induction intravenous steroids compared to oral steroids alone. A study by Hayreh et al. (17) did not show any obvious benefit of high-dose intravenous steroids, but the patients were not randomized and the group of patients

treated with intravenous steroids tended to have worse visual loss at presentation, as were those in the Gonzales-Gay et al. study (1).

Following the initiation of corticosteroid treatment, no matter what the route, systemic symptoms of GCA disappear rapidly and dramatically over hours to days in nearly all patients (2–4,7–9,11). Improvement of visual loss is much less striking, and occurs in only 4–34% of affected eyes. Visual improvement, when it occurs, is mild, with persistent and often severe visual field defects (18–22). According to the available literature, there does not seem to be any major difference in terms of visual outcomes based on whether patients receive induction intravenous bolus steroids initially or whether they are treated with oral steroids alone. However, when treatment is initiated within 24 hours of visual loss, 58% of patients have visual improvement, compared to the 6% of patients who improve after a delay in treatment, illustrating the urgency of corticosteroid treatment (1). This trend toward better visual outcomes when steroids are commenced early after visual loss has been documented in other studies (17). Although case reports also suggest occasional dramatic improvement of visual function in rare patients receiving high-dose intravenous methylprednisolone, it is impossible to draw conclusions from isolated cases. Additionally, despite treatment with high-dose corticosteroids, bilateral vision loss or worsening of unilateral vision loss may sometimes occur, usually within the first 5 days of treatment. This has been reported in both patients treated with oral steroids and those treated with high-dose intravenous steroids (23–25).

Tapering of corticosteroids: When systemic and constitutional symptoms of GCA have disappeared, visual symptoms are stable, and the ESR and CRP have reached consistently low levels, then GCA is considered to be controlled. Typically, it takes several weeks of treatment with daily high-dose oral corticosteroids to achieve satisfactory suppression of the inflammatory syndrome. Subsequently, the goal of care becomes the slow tapering of steroids to achieve either a stable maintenance dose or complete withdrawal of the drug.

Because GCA may relapse during the tapering process, necessitating an increase in corticosteroid dose, the tapering process must be individualized to each patient and may take years to accomplish. Indeed, a one- to two-year course is typically required. The daily oral dose can be tapered by 10mg every month at first, followed by 5mg every month, and then by as little as 1mg every month once the dose reaches 10–15mg per day. A prospective study by Hunder et al (26) demonstrated decreased efficacy and increased risk of relapse with alternate-day dosing, and, therefore, corticosteroids should be given daily, and not on alternate days. Close follow-up is indicated during the tapering process, with follow-up visits every two to three weeks until the dose of prednisone reaches 40mg per day, followed by regular visits every four to six weeks thereafter

until the dose of prednisone reaches a low maintenance dose, at which point the patients may be followed approximately every three months.

At each visit, decreases in corticosteroid dose should be undertaken only when symptoms of GCA remain absent and the ESR and CRP remain normal. Because irreversible blindness from ION may occur in the absence of other GCA symptoms (occult GCA), it must be emphasized that symptom monitoring alone is insufficient to guide the tapering of corticosteroids (7–9). If ESR and CRP have both risen, in the absence of an intercurrent illness, the GCA is considered to have “relapsed,” and an immediate increase in the corticosteroid dose to the last effective dose is recommended (7–9). Although a rise in laboratory parameters from normal range into the abnormal range certainly warrants an increase in corticosteroid dose, small rises within the normal range need to be followed carefully with repeat ESR and CRP a few days later to confirm relapse prior to increasing steroids. An isolated increase in ESR without a corresponding rise in CRP may not be an indication to increase the corticosteroid dose, and careful clinical correlation is necessary.

LONG-TERM STEROID-SPARING AGENTS

Because of the morbidity associated with long-term corticosteroid use, efforts have been made to investigate steroid-sparing agents in GCA. For ethical reasons, these agents cannot be directly compared with corticosteroids in a prospective double-blinded fashion. They can, however, be used adjunctively with corticosteroids and compared with corticosteroid treatment alone. Although the search for a safe and effective steroid-sparing agent continues, there is very little persuasive evidence that any of these agents is really helpful, and their use remains debated.

Methotrexate in a single weekly dose similar to that used in rheumatoid arthritis has been evaluated in a few trials either as a concomitant first-line therapy with steroids, or in patients with corticosteroid resistance or dependency. The results have varied, with two studies (27–28) reporting no significant decrease in cumulative steroid dose or in relapse rate at 1 year among patients treated with corticosteroids and methotrexate compared with those treated with corticosteroids and placebo, and one study (29) reporting a significant decrease in cumulative steroid dose and relapse rate at 2 years among patients treated with adjuvant methotrexate compared with placebo. A subsequent meta-analysis (30) of these three studies suggested a benefit for oral methotrexate 7.5 to 15 mg/week over placebo in preventing both first and second relapses of GCA and in reducing the cumulative corticosteroid dose by 48 weeks. No significant differences in adverse events were seen between the 2 groups. A benefit of methotrexate over placebo in preventing GCA relapses began late in the disease course, between weeks 24 and 36, and strengthened as the follow-up period increased. In a prespecified subgroup analysis, a statistically significant benefit was seen in women, but not in men.

The authors concluded that low-dose methotrexate was an effective steroid-sparing agent for use in patients with GCA; however, the latency period of more than 6 months before methotrexate exerts its therapeutic effect remains unexplained. Potential benefits obtained by using methotrexate must be weighed against its possible adverse effects in elderly patients.

Numerous other steroid-sparing agents have been reported as potentially useful in anecdotal cases of GCA, but subsequent studies have not shown any benefit of these agents compared with steroids alone. These include hydroxychloroquine, TNF inhibitors such as infliximab and etanercept, azathioprine, cyclosporine, dapsone and cyclophosphamide. A newer agent, tocilizumab (anti-IL-6 receptor) was reported to induce a rapid clinical and laboratory response in 7 patients with large-vessel GCA (31); however, it is unclear whether tocilizumab can effectively prevent ischemic events in GCA.

In a double-blind, placebo-controlled study (15) employing *glucocorticoid pulse therapy*, patients pulsed at diagnosis had fewer disease flares and discontinued therapy earlier than patients without initial pulse therapy. However, benefits of pulse glucocorticoids were delayed until 12 to 18 months into treatment.

ANTITHROMBOTIC AGENTS

There are a number of arguments to support the use of antithrombotic agents acutely in GCA. Ischemic complications of GCA, including visual loss and strokes, presumably result from local arteritic inflammation of vessel walls. However, the ultimate pathology of ischemia may differ depending on the location. Arteritic ischemic optic neuropathy results from local inflammatory intimal hyperplasia with subsequent vaso-occlusion of the short posterior ciliary arteries. It is not clear whether intracranial ischemic strokes result from distal embolization of thrombi formed in inflamed large arteries or from proximal vessel occlusion. Additionally, arteritic inflammation may involve the coronary arteries and the aorta, increasing the risk of acute myocardial ischemia in GCA patients.

Aspirin has been used as an antiplatelet agent in the prevention of myocardial infarctions and brain ischemia for decades. Weyand et al. (32) demonstrated additional potent anti-inflammatory effects of aspirin in the mouse chimera model of GCA (33,34). However, the clinical effectiveness of aspirin in GCA has only been studied in 2 retrospective reviews. One study of 166 GCA patients treated with prednisone (33) found significantly fewer GCA-related cranial ischemic complications, both at the time of GCA diagnosis and during the follow-up, in patients who were taking aspirin at the time of diagnosis, compared with those not taking aspirin (8% vs 29%; $P = 0.01$). This protective effect of aspirin was seen in spite of the significantly increased prevalence of cerebrovascular risk factors in the aspirin-treated group. The other study

included 143 GCA patients also treated with prednisone (34) and had a similar design but compared patients taking any antithrombotic agent (aspirin, clopidogrel, or warfarin) with those not taking such agents. The authors' multivariate analysis suggested fewer ischemic events in patients taking aspirin (OR = 0.18; $p < 0.0005$) or warfarin (OR = 0.17; $P < .04$), and did not demonstrate an increase in bleeding complications. The authors recommended the use of low-dose aspirin in the treatment of GCA, but did not comment on a role for anticoagulation.

Although *anticoagulation* has sometimes been used in treating GCA patients with ischemic complications worsening on steroids, no prospective trials have verified its utility.

We recommend the use of aspirin 81 or 325 mg as an adjunct to corticosteroids in the treatment of GCA patients, particularly those who present with ischemic complications or have vascular risk factors, unless contraindicated.

STATINS

HMG-CoA reductase inhibitors (statins) are drugs widely used in the treatment of dyslipidemia and prevention of atheromatous cardiovascular disease. In addition to their lipid-lowering effects, statins have also been discovered to have anti-inflammatory and immunomodulatory properties. Because long-term corticosteroid use can be associated with dyslipidemia, many patients being treated for GCA are treated concurrently with statins. In a retrospective study (36), statins were not found to have any corticosteroid-sparing effect and did not improve disease outcome.

ANTIBIOTICS

Because infectious agents such as *Burkholderia pseudomallei* have been linked to GCA, antibiotics such as minocycline and doxycycline have been suggested as a possible adjunctive treatment for GCA (Katz B, personal communication). A clinical trial evaluating antibiotics as an adjuvant treatment (in addition to steroids) for GCA is planned.

CONCLUSION

The treatment of GCA is still centered on glucocorticoids, but other drugs are increasingly available. Better understanding in the pathophysiology of GCA will lead to the use of newer biologic agents for the first-line or second-line treatment of patients with glucocorticoid resistance or dependence (41,42).

Table 2: British Society of Ophthalmology guidelines regarding the initial dose and route of steroids to treat giant cell arteritis (Adapted from Dasgupta B, Borg FA, Hassan N, et al. BSR and BHRP guidelines for the management of giant cell arteritis. *Rheumatology* 2010; 49: 1594–1597).

Uncomplicated GCA (no jaw claudication or visual disturbance)	40–60mg oral prednisone daily (not less than 0.75 mg/kg daily)
Evolving visual loss (recent onset visual symptoms over 6–12 hours) or transient visual loss	Intravenous methylprednisolone 500–1000 mg daily for 3 days before oral steroids
Established visual loss	At least 60 mg prednisolone daily, to protect the contralateral eye

Patients should also receive bone protection with weekly bisphosphonate and calcium/vitamin D supplementation. Proton pump inhibitors for gastrointestinal protection should be considered, especially if low-dose aspirin is also prescribed. The symptoms of GCA should respond rapidly to high-dose glucocorticosteroid treatment, followed by resolution of the inflammatory response. Failure to do so should raise the question of an alternative diagnosis. The initial dose of steroids should be continued for 3–4 weeks and reduced in the absence of any clinical symptoms or any laboratory abnormalities suggestive of ongoing active disease. The steroid tapering should be gradual, provided there is no relapse.

CME ANSWERS

- c
- a
- d

REFERENCES

- Gonzales-Gay M.A., Blanco R., Rodriguez-Valverde V., et al : Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum* 41:1497–504, 1998.
- Salvarani C., Pipitone N., Versari A., Hunder GG: Clinical features of polymyalgia rheumatica and giant-cell arteritis. *Nat Rev Rheumatol* 24 July 2012, advance online publication.
- Weyand C.M., Goronzy J.J: Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med*. 2003; 139:505–515.
- Ghosh P., Borg F.A., Dasgupta B.: Current understanding and management of giant cell arteritis and polymyalgia rheumatic. *Expert Rev Clin Immunol* 913–928, 2010.
- Hayreh S.S., Zimmerman B.: Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. *Ophthalmologica* 217:239–259, 2003.

6. Pipitone N., Boiardi L., Salvarani C.: Are steroids alone sufficient for the treatment of giant cell arteritis? *Best Pract Res Clin Rheumatol* 19:277–292, 2005.
7. Dasgupta B., Borg F.A., Hassan N., et al: BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology* 49: 1594–1597, 2010.
8. Dashgupta B. on behalf of the Giant Cell Arteritis Guideline Development Group: Concise guidance: diagnosis and management of giant cell arteritis. *Clin Medicine* 10:381–386, 2010.
9. Mukhtar, Guillevin L., Cid M.C., et al” EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 68:318–323, 2009.
10. Ezeonyeji A.N., Borg F.A., Dasgupta B.: Delays in recognition and management of giant cell arteritis: results from a retrospective audit. *Clin Rheumatol* 30: 259–262, 2011.
11. Hayreh S.S., Bioussé V.: Treatment of acute visual loss in giant cell arteritis: Should we prescribe high-dose intravenous steroids or just oral steroids. *J Neuro-Ophthalmol*. In press.
12. Lundberg I., Hedfors E.: Restricted dose and duration of corticosteroid treatment in patients with polymyalgia rheumatica and temporal arteritis. *J Rheumatol* 17:1340–1345, 1990.
13. Rahman W., Rahman F.Z.: Major review—giant cell (temporal) arteritis: an overview and update. *Surv Ophthalmol* 50:415–428, 2005.
14. Chevalet P., Barrier J.H., Pottier P., et al : A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year followup study of 164 patients. *J Rheumatol* 27:1484–1491, 2000.
15. Mazlumzadeh M., Hunder G.G., Easley K.A., et al: Treatment of giant cell arteritis using induction therapy with high-dose corticosteroids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum* 54:3310–3318, 2006.
16. Chan C.C.K., Paine M., O’Day J.: Steroid management in giant cell arteritis. *Br J Ophthalmol* 85:1061–1064, 2001.
17. Hayreh S.S., Zimmerman B., Kardon R.H.: Visual improvement with corticosteroid therapy in giant cell arteritis: report of a large study and review of the literature. *Acta Ophthalmol Scand* 80:353–367, 2002.
18. Aiello P.D., Trautman J.C., McPhee T.J., et al: Visual prognosis in giant cell arteritis. *Ophthalmology* 100: 550–555, 1993.
19. Liu G.T., Glaser J.S., Schatz N.J., et al: Visual morbidity in giant cell arteritis: clinical characteristics and prognosis for vision. *Ophthalmology* 101:1779–1785, 1994.
20. Kupersmith M.J., Langer R., Mitnick H., et al: Visual performance in giant cell arteritis (temporal arteritis) after 1 year of therapy. *Br J Ophthalmol* 83:796–801, 1999.
21. Foroosan R, Deramo VA, Buono LM, et al. Recovery of visual function in patients with biopsy-proven giant cell arteritis. *Ophthalmology*. 2003; 110:539–542.
22. Danesh-Meyer H., Savino P.J., Gamble G.G: Poor prognosis of visual outcome after visual loss from giant cell arteritis. *Ophthalmology* 112:1098–1103, 2005.
23. Cornblath W.T., Eggenberger E.R: Progressive visual loss from giant cell arteritis despite high-dose intravenous methylprednisolone. *Ophthalmology* 104: 854–858, 1997.
24. Loddenkemper T., Sharma P., Katzan I., et al: Risk factors for early visual deterioration in temporal arteritis. *J Neurol Neurosurg Psychiatry* 78:1255–1259, 2007.
25. Hayreh S.S., Zimmerman B: Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. *Ophthalmology* 110:1204–1215, 2003.
26. Hunder G.G., Sheps S.G., Allen G.L., et al: Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann Intern Med* 82:613–618, 1975.
27. Spiera R.F., Hoffman G.S., Cid M.C., Hellmann D.B., et al: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 46:1309–1318, 2002.
28. Jover J.A., Hernández-García C., Morado I.C., et al. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 134:106–114, 2001.
29. Mahr A.D., Jover J.A., Spiera R.F. et al: Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 56:2789–2797, 2007.
30. Salvarani C., Magnani L., Catano M., et al: Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology (Oxford)*;51:151–156, 2012.
31. Adizie T., Christidis D., Dharmapaliah C., et al: Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. *Int J Clin Pract* 66:906–909, 2012.
32. Loock J., Henes J., Köter I., et al: Treatment of refractory giant cell arteritis with cyclophosphamide: a retrospective analysis of 35 patients from three centres. *Clin Exp Rheumatol* 30 (1 Suppl 70):S70–76, 2012.
33. Weyand C.M., Kaiser M., Yang H., et al: Therapeutic effects of acetylsalicylic acid in giant cell arteritis. *Arthritis Rheum* 46:457–466, 2002.
34. Neshet G., Berkun Y., Mates M. et al: Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum* 50:1332–1337, 2004.
35. Lee M.S., Smith S.D., Galor A., et al: Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 54:3306–3309, 2006.
36. Narváez J., Bernad B., Gómez-Vaquero C., et al: Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis. *Clin Exp Rheumatol* 26 (3 Suppl 49):S57–62, 2008.
37. Narváez J., Bernad B., Nolla J.M., et al: Statin therapy does not seem to benefit giant cell arteritis. *Semin Arthritis Rheum* 36:322–327, 2007.
38. Hoffman G.S.: What does the future hold for clinical studies in vasculitis? *Clin Exp Immunol* 64 Suppl 1:35–38, 2011.
39. Catano M, Pipitone N, Magnani L, Boiardi L, Salvarani C. New indications for biological therapies. *Intern Emerg Med*. 2011 Oct;6 Suppl 1:1–9.
40. Salvarani C., Pipitone N.: Treatment of large-vessel vasculitis: where do we stand? *Clin Exp Rheumatol* 29 (1 Suppl 64):S3–5, 2011.
41. Pipitone N., Olivieri I., Salvarani C.: Italian Society of Rheumatology. Recommendations of the Italian Society of Rheumatology for the treatment of the primary large-vessel vasculitis with biological agents. *Clin Exp Rheumatol* 30 (1 Suppl 70):S139–161, 2012.

THERAPY OF NEURO/NEURO-OPHTHALMIC SARCOID

Larry Frohman, MD

*New Jersey Medical School
Newark, NJ*

LEARNING OBJECTIVES

1. To make the reader aware of the various drugs that are available to begin treatment of newly diagnosed neuro/neuro-ophthalmic sarcoid
2. To make the reader aware of the studies that support the choice of therapeutic agents for neuro/neuro-ophthalmic sarcoid
3. To make the reader aware of options and strategies when an initially selected therapy for neuro/neuro-ophthalmic sarcoid fails to control the disease process
4. To introduce some of the side effects of agents used to control sarcoidosis
5. To have the reader consider whether corticosteroids alone are the most appropriate treatment for neuro-ophthalmic sarcoidosis

CME QUESTIONS

1. Which of the following is an appropriate initial therapy for the treatment of neuro-ophthalmic sarcoid with acute optic neuropathy?
 - a. Corticosteroids
 - b. Methotrexate
 - c. Cellsept
 - d. Thalidomide
2. Which of the following is not an appropriate drug to add in a patient with steroid dependent sarcoid optic neuropathy who flares when the prednisone dose is reduced below 20 mg?
 - a. Methotrexate
 - b. Mycophenolate mofetil
 - c. Infliximab
 - d. Etanercept
3. Which of these is a rationale sequence of drugs to try to use in a corticosteroid-resistant case of neurosarcoid?
 - a.
 - i. Chloroquine
 - ii. Hydroxychloroquine
 - iii. Tacrolimus
 - iv. Etanercept

- b.
 - i. Methotrexate
 - ii. Cyclophosphamide
 - iii. Infliximab
 - iv. Thalidomide
 - c.
 - i. Thalidomide
 - ii. Infliximab
 - iii. Leflunomide
 - iv. Cyclosporine
 - d.
 - i. Cladribine
 - ii. Apremilast
 - iii. Hydroxychloroquine
 - iv. Minocycline
4. Which of the following is not an unexpected potential consequence of treatment of rheumatoid arthritis with infliximab?
 - a. Induction of a sarcoid like illness
 - b. Reactivation of latent tuberculosis
 - c. Development of further autoimmune disease
 - d. Increased efficacy of the drug with prolonged usage

KEYWORDS

1. Sarcoid or Sarcoidosis
2. Optic Neuropathy
3. Drug Therapy

1) WHY WE CANNOT ANSWER THE KEY QUESTIONS

What we really want to know about neuro-ophthalmic sarcoid is when we face a newly diagnosed case, what is the optimal treatment to use? And if the patient breaks through this therapy, what should we turn to next? And how long do we have to maintain the patient on therapy? Sadly, we cannot, at this time, answer these key questions with level three evidence for neuro-ophthalmic sarcoid. The incidence of the disease is too rare, and virtually all studies have been single institution studies, for anyone to have approached the number of cases requisite for a proper two armed prospective study. Not only can this not be done for neuro-ophthalmic sarcoid, if one combines neuro-ophthalmic sarcoid with all other forms of neurologic sarcoid, the disease

incidence is still too low for there to have been Level-I evidence generated. Most of what we have to analyze and use to decide how to treat neurologic sarcoid comes from Level III evidence, and largely from a few people's opinions based upon their single institution experience.

Another problem interpreting the literature on the therapy of neurosarcoid is the very definition of neurosarcoid. Some authors consider all facial nerve palsies to be cases of neurosarcoid. But in sarcoid, with its predilection to target the parotid gland, there are many cases where the facial nerve palsy is not a primary manifestation of central nervous system (CNS) sarcoid, but is rather the result of the parotid inflammation causing a secondary compression of the facial nerve with subsequent dysfunction. This does not imply primary CNS involvement. Thus, analyses of various series results in treating CNS sarcoid will find that many of the series include cases of facial nerve palsy as if they were the equivalent of a direct cranial nerve infiltration, such as might occur with the auditory or optic nerve. Since these cases of facial nerve involvement do not really have CNS involvement, the data is skewed, and interpretation of the literature becomes even more complex.

Furthermore, when looking at what some might think may be a single mechanism causing sarcoid optic neuropathy; we see that there are actually several potential pathogenic mechanisms. One can get "spillover" involvement of the papilla from a case of sarcoid uveitis. Should this be counted as CNS sarcoid? One can have an infiltrative optic neuropathy in sarcoid, one can have meningitic involvement of the optic nerve, one can have extrinsic optic nerve compression from an orbital granuloma without intrinsic optic nerve disease, one can have vasculitic infarction of the nerve, and one may have what is felt to be a primary optic neuropathy which is really secondary involvement of the optic nerve from raised intracranial pressure in CNS sarcoidosis. The fact that these cases are usually mixed together in the literature under the label of "sarcoid optic neuropathy", although they may have different mechanisms of action, makes selecting the best agent to use in an individual case based upon the literature difficult. In addition, the literature often has treated the lack of improvement in a chronic case of sarcoid optic neuropathy that begins therapy when the patient is already count fingers with chalk white optic nerves as the same evidence of failure of therapy as an acute case with a healthy disc presenting with 20/50 acuity two days after initial onset of a first bout of optic neuropathy.

The best we can do is to review the literature on neuro-ophthalmic sarcoid (and this is largely pertaining to sarcoid optic neuropathy) where it exists, and to use the data on CNS sarcoid to see what has been successful, and to employ some understanding of the mechanism of disease in CNS sarcoid to allow us to develop a rational strategy of therapy. We will need to foster multicentered studies to use evidence based medicine to answer the key questions.

2) THE NEED TO USE EXTRAPOLATED DATA FROM PULMONARY SARCOID, AND AT BEST, FROM STUDIES OF EXTRAPULMONARY SARCOID

Another caution about interpreting the literature is that since CNS sarcoid is so unusual there are few centers with adequate experience to make meaningful suggestions, what one largely sees in the literature is extrapolation of data from a center's experience in treating all cases of sarcoidosis, which is, of course, comprised largely of pulmonary involvement. From centers with greater experience and volume, one may see the segregation of cases of "extrapulmonary sarcoidosis", and an analysis of therapeutic responses for these cases separately. However, this then lumps together cardiac sarcoid, cutaneous sarcoid, uveitis, and CNS sarcoid, amongst other forms, and assumes that the response of cutaneous sarcoid and CNS sarcoid to therapeutic agents should be comparable. There is a paucity of data specifically on neurosarcoid therapy. Discussion of issues such as the impact of the blood brain barrier upon the selection of an individual agent to treat CNS sarcoid is surprisingly sparse in the literature. One does see statements that a drug does not work for any form of sarcoid, including neurosarcoid based solely upon experience in treating pulmonary sarcoid.

3) GENERAL CONCEPTS

There is no consensus on the need to treat all case of non-CNS sarcoid, or if one treats, what the best agent is. A review of the evidence for treatment or not is found in Baughman¹. This paper also has a discussion of the available medications at its time of publication (2003), and the suggested regimens and side effects of each agent. Another more recent excellent review of the treatment of all forms of sarcoid is found in King².

There is not enough data on neuro-ophthalmic sarcoidosis and specifically on sarcoid optic neuropathy therapy to allow one to make therapeutic recommendations on anything more specific than the treatment of neurosarcoid in general. Yet there is a difference. Although Terushkin³ points out in a 2010 review of the therapy of neurosarcoid that there are asymptomatic cases of neurosarcoid that might not get treated at all, this is not a consensus opinion. This is not generally a consideration for the neuro-ophthalmologist, as we rarely see asymptomatic cases.

Some advocate that different flavors of neurosarcoid require different therapeutic regimens. King says "Optimal treatment for neurosarcoidosis is based on the disease manifestation. Aseptic meningitis and isolated cranial nerve abnormalities, particularly seventh nerve palsy, will frequently resolve spontaneously or with a short course of corticosteroid (CS). Patients with parenchymal disease, spinal cord involvement, and multiple cranial nerve palsies often have a chronic course, requiring prolonged treatment. No randomized trials of therapy for neurosarcoidosis exist, so the optimal therapeutic

regimen remains unknown².” Hoitsma sums up that there is no definitive evidence for a specific therapy by stating that “Considering the morbidity and mortality of neurosarcoidosis, most authors recommend early treatment. However, recommendations about treatment are based on experience rather than evidence”⁴.

Recommendations regarding therapy have evolved over time, not just because of new therapeutic strategies, but also due to a perceived shift in the seriousness of CNS sarcoid and its responsiveness to corticosteroids. In 1985, Stern’s seminal article on neurosarcoid reported 33 patients who had neurologic involvement in sarcoid⁵. He reported that the Johns Hopkins sarcoid patient population had an incidence of neurologic involvement of 5.1%. Optic neuritis was quite rare in his series, only being diagnosed in one of the 33 cases (3%), with the patient’s outcome unreported. In this series, there were 21 patients who were treated with prednisone who had follow-up. Improvement was seen in 19/21 (90.4%). One died, and one had no improvement. No patient required any other therapeutic agent. The article concluded that neurosarcoid was responsive to corticosteroid therapy, and that its prognosis was good.

And yet in 2009, Pawate, reporting on the experience at Vanderbilt, where 25% of their sarcoid patients had neurologic disease, found that sarcoid optic neuropathy (SON) had a poor prognosis, despite their use of several agents not used in Stern’s series.⁶ Which end of the spectrum is correct? Is the difference related to the stage of the case when referred? Is it related to difficult, more sinister cases not being diagnosed at all with only the obvious acute cases being diagnosed? Is it that cases not fully worked up which are being classified as “unknown optic neuropathy” which may have a more deleterious outcome, may not have been captured in some series? Is it related to the differential willingness at different centers to start treatment in presumed sarcoid optic neuropathy without an absolute tissue diagnosis?

When discussing the treatment of patients with sarcoid optic neuropathy, we hear statements such as “Sarcoid is so sensitive to corticosteroids that if you show the patient the bottle their vision gets better,” or “I can easily treat sarcoid optic neuropathy with a local injection of steroids.” We read incorrect generalizations such as “Corticosteroid therapy is dramatically efficient but sometimes several months’ treatment is required.”⁷ I have encountered a patient who has looked at the internet and has insisted that they want to be treated for their SON with steroid eye drops and nothing systemic. Galetta has indeed reported a case of sarcoid optic neuropathy with spontaneous recovery without treatment⁸. Nonetheless, most of these cases need be treated vigorously to try to minimize permanent visual loss. When the patient has an antecedent diagnosis of sarcoid before there is visual loss, the diagnosis is relatively easy. When there is no established diagnosis of sarcoid, diagnosis depends upon

obvious clinical clues, such as an abnormal chest X-ray or angiotensin converting enzyme (ACE) funduscopy or iris lesions that establish the diagnosis. However, in cases without these “calling cards” diagnosis is often not easy, and may be quite delayed. This may explain the dichotomy of opinion about the relative ease of treating sarcoid optic neuropathy, that is, cases that have features that permit prompt diagnosis before structural changes ensue may respond well to therapy with just corticosteroids. These patients are different animals from the otherwise healthy patient with no other ocular disease who has been treated for three years as a case of unknown steroid dependent optic neuritis, or from the healthy patient who presents acutely with no history of sarcoidosis, a normal or non-specific MRI scan, and a normal chest CT. They are also different from the patient with a long history of refractory neurosarcoid who ultimately develops visual loss from optic nerve or chiasmal involvement. Unlike Stern’s original thoughts, there are clearly cases of neuro-ophthalmic sarcoidosis that are resistant to appropriate therapies that are instituted expediently. Thus, the neuro-ophthalmologist needs to understand the full panoply of treatment regimens available for sarcoid optic neuropathy and other forms of CNS sarcoid impacting the visual system.

The basic science of granuloma formation and the theories regarding the etiology of sarcoidosis are well beyond the scope of this paper. For a discussion of the mechanism of disease and the basic science of therapy, the paper by Moller is an excellent resource⁹. To simplify Moller’s description of granuloma formation, in general, the first step in their formation is Granuloma Initiation, which involves the deposition of poorly soluble antigens into tissue. These antigens are then phagocytized by macrophages and dendritic cells. Protein fragments derived from these antigens are then presented on the cell surface, where they are the proteins are analyzed by CD4+ T cells. The second stage of granulomatous inflammation is that of Granuloma Formation and Maintenance. Here, chemokines and cytokines drive the granulomatous inflammatory process. The major T-helper 1 derived cytokine that may enhance granuloma formation is interferon alpha, whereas IL4, IL5, and IL13 are the T-helper 2 derived cytokines that may promote granuloma formation. As the cytokines drive the immune response, tumor necrosis factor (TNF)-alpha expression is enhanced, as are the expression of chemokines and cytokines that are regulators of cell attraction, which promotes the migration of inflammatory cells migrate to the granuloma site⁹.

Sarcoidosis is largely a disease process driven by T-helper cell 1. These facts may help guide an overall treatment status for sarcoidosis. Moller defines stages in the inflammatory process and discusses how the available therapies may be of use in the treatment of sarcoid. The first goal is the suppression of the initiation of granuloma formation. In some cases, the initial step in rational treatment, if one believes the inciting antigen

is bacterial, is to kill organisms. One of the proposed mechanisms of sarcoidosis is altered immunity to mycobacterial species or to propionibacterium acnes. A subset of patients with sarcoid are sensitive to doxycycline and minocycline, which are effective against p. acnes; whereas in another group, dapsone and clofazimine (Lamprene, largely an antileprosy agent), which have antimycobacterial properties, may be useful⁹.

Besides the issue of whether to empirically try a course of these anti-bacterials, a second mechanism by which one can suppress the formation of granulomas is by inhibiting T-cell response by interfering with the step of antigen presentation. Hydroxychloroquine and chloroquine are believed to act in sarcoid by interfering with this step⁹.

According to Moller the goal for treatment of the second stage is the suppression of ongoing granulomatous inflammation⁹. Drugs that can be used to inhibit this phase of granuloma formation include:

1. Corticosteroids, whose panoply of effects upon inflammation are beyond the scope of this paper.
2. Azathioprine, which is a purine analog and inhibits B and T cell proliferation, and specifically inhibits cytotoxic T cells, with an overall effect greater upon T than upon B
3. Mycophenolate mofetil, which induces death of activated T-cells
4. Methotrexate, a folate acid analog, which interferes with purine metabolism and polyamine synthesis. At higher doses, such as used in chemotherapy, methotrexate is an antiproliferative agent; at the lower doses used in inflammation, it promotes adenosine release which in turn, amongst other effects, inhibits IL6, IL8 and TNF release.
5. Cyclosporine A, fungal peptide which is a T-cell inhibitor
6. Pentoxifylline-a TNF inhibitor that is a methylxanthine derivative. This drug is a nonselective phosphodiesterase inhibitor- which diminishes TNF production by mononuclear cells
7. Thalidomide- This drug inhibits TNF production, as well as the expression of IL 1,2,4,6,8 amongst other effects
8. Etanercept, a biologic dimer, which binds to TNF and blocks its interaction with cell surface receptors.
9. Infliximab, a biologic monoclonal chimeric, which blocks TNF receptor binding to receptor by blocking TNF

These and other agents shall be discussed in more detail below.

4) INITIAL THERAPY

The current evolution of thought is that all cases of neurosarcoid need be treated, and that unless there is a specific contraindication, the initial therapy is systemic corticosteroids. There is no consensus on what dose to start therapy with, and this is generally tailored to the severity and acuteness at the time of the decision to initiate therapy. For the more severe cases, high dose CS, such as one gram of solumedrol a day for 3-5 days, followed by 1 mg/kg/day of oral prednisone or the equivalent, may

be used. For less acute or severe cases, 0.5-1.0 mg/kg of prednisone daily or equivalent may be used. The duration and course of therapy is completely variable. There is beginning to evolve a new concept that not all cases of CNS sarcoid are equivalent in their response to CS, leading to the question of multidrug therapy as initial therapy for CNS sarcoid. Hoitsma says ""Combination therapy of corticosteroids and alternative immunosuppressive agents immediately at the time of initial diagnosis are recommended in cases with poor prognosis such as intracranial masses and myelopathy."⁴ We do not know if initial multidrug therapy will lead to better outcomes in neuro-ophthalmic sarcoid, just as we do not yet know if some of the newer available agents would make for better initial single drug therapy for neuro-ophthalmic disease.

5) SUBSEQUENT THERAPY

The two reasons that patients with CNS sarcoid require therapy other than single agent CS are

1. Failure for CS to achieve disease remission or stability, and
2. Inability to tolerate the dose of CS requisite to achieving remission or stability.

The main purpose of this paper is to report the evidence we have that will assist us in selecting the next agent to employ. There are a few general points to consider. The first is that many of the agents employed after CS as a single agent take several weeks to begin to achieve significant clinical immunosuppressive effect. Thus, it is not purely the agent's track record regarding efficacy and safety that needs be considered when selecting an agent; the rapidity of response required in the specific case must be considered. In a patient with chiasmal disease who has just gone no light perception in their second eye, methotrexate, which has a good efficacy and safety profile in CNS sarcoid, is simply not rapid enough in onset to make it an appropriate choice in this situation. Nonetheless, if one can induce improvement with a faster acting drug, methotrexate might be a good choice for long term disease suppression.

Several papers have reported what is largely institution-specific experience in treating patients whose neurosarcoid could not be controlled by CS alone. In 1995, Agbogu presented the Johns Hopkins experience with 26 patients who had neurosarcoid that could not be controlled at tolerable doses of CS¹⁰. They used chlorambucil, cyclophosphamide, azathioprine, and methotrexate, as well as radiation therapy in conjunction with CS. They were able to decrease prednisone dosage to 10-20 mg/day in 38% of cases. Their therapy was not wholly benign; not all responded, some flared, and one patient died. Their conclusion in 1995 was that cyclosporine A was the best drug to start patients on for refractory neurosarcoid.¹⁰ In 1997, Lower published the experience gained at the University of Cincinnati's sarcoid clinic regarding treatment of neurosarcoid¹¹. They treated 71 patients with neurosarcoid in a group of 554 sarcoid patient seen in a ten year period (incidence = 12.8%, which may be

high, as it included 24 patients who only had facial nerve palsy). In the group with neurological involvement other than just a facial nerve palsy, they reported that CS led to improvement in 29% so treated, and methotrexate led to improvement in 17/28 (61%), while cyclophosphamide controlled the neurologic process in 9/10 so treated (90%). Although it was notable that their data showed the immunosuppressants had better efficacy than CS, the data did not change the practice pattern that CS are the initial treatment for CNS sarcoid, which persists today.

In 1999, Zajicek presented another large series of 68 patients with neurosarcoid. This series included 26 patients (38%) who had optic nerve disease at presentation. Eighteen (69%) of these were unilateral and 31 % were bilateral. They describe the course of the optic nerve disease as "one of an atypical optic neuritis, often subacute in onset, which might recover following steroids or cause permanent visual impairment. Initial steroid sensitivity was occasionally followed by dependence, with symptoms deteriorating below a certain dosage level." They had 47 neurosarcoid patients with at least 18 months of follow-up. Thirty-four of these received CS therapy alone. Of these, 10 improved or stabilized (29%) and 24 (71%) deteriorated. They tried numerous alternate regimens, including azathioprine and methotrexate as individual agents, as well as a combination of hydroxychloroquine-methotrexate and CS. Of the three that they treated with CYA, one improved. All three treated with high dose IV cyclophosphamide improved. They did not break out the results in the SON cases. They concluded "Although this is the largest single series of patients with neurosarcoidosis yet reported, with the most extensive follow-up details, it remains impossible to identify those patients in whom early aggressive immunotherapy would be beneficial."¹²

In 2000, Ferriby reported a series of 40 patients with neurosarcoid. In 40%, CS alone were not adequate, and the patients required immunosuppressants (azathioprine, methotrexate, cyclosporine A, cyclophosphamide). Only 13/40 (32.5%) had complete recovery. Based upon this, they suggest that if there is not a rapid response to CS, alternate therapy should quickly be begun¹³.

Before abandoning any therapy, it has been suggested that one first consider whether complications of immunosuppression itself might be the source of visual loss rather than the sarcoid itself. Hoitsma says "In case of increasing deterioration after immunosuppressive treatment further diagnostic testing is indicated, including JCV-DNA analysis by PCR."⁴

The individual therapies are detailed below.

6) INDIVIDUAL AGENTS

A. ORAL/SYSTEMIC CORTICOSTEROIDS (CS)

The initial case reports indicated that sarcoid optic neuropathy was a steroid responsive disease. In 1980, Rush reported on one of the earlier cases of SON and said that his

patient showed a dramatic response to CS¹⁴. In the same year, Burde and colleagues also reported a similar case with response to high dose pulsed steroid therapy.¹⁵ An early series on SON by Beardsley reported that of 11 patients with sarcoid optic neuropathy, 6 (55%) responded to CS¹⁶.

When we categorized our cases of neuro-ophthalmic sarcoidosis and examined the response of 15 cases that had other manifestations than SON (most had diplopia), we saw excellent responses to oral CS. In this series, 13/15 (87%) responded just to CS. The two remaining cases were controlled with Cyclosporine A, one in combination with CS. In some cases, the response of neuro-ophthalmic sarcoid to oral CS can be quite swift. One case in this series was a 32 year old woman with two weeks of severe headaches and a sixth nerve palsy from occult CNS sarcoid. When the diagnosis was established, the first 60 mg dose of prednisone made the headache and double vision abate¹⁷.

Vargas argues that anyone with neurosarcoid, both those with a biopsy of CNS tissue, and those with a biopsy confirming sarcoidosis outside the CNS and with CNS disease, should start CS therapy quickly.¹⁸ This group suggests initially employing 40-60 mg of prednisone daily /day (or 0.5-1 mg/kg/day) for 4-6 weeks. They then taper slowly until they get to 0.1-0.25 mg/kg/day which they maintain as long as the patient is symptomatic. If at diagnosis the CNS disease is severe or debilitating, they use a pulse of one gram of solumedrol daily for 3-5 days.

Other routes of administration of CS can be employed. We have used intramuscular depot steroids in one patient with SON who also had major psychiatric illness preventing compliance with either intravenous or oral steroids. Sader reported on a case of SON that required chronic high doses of systemic therapy that was treated with intrathecal corticosteroids.¹⁹

B. CHLOROQUINE (CQ) AND HYDROXYCHLOROQUINE (HCQ)

Chloroquine is a 4 aminoquinolone. The mechanism of action of HCQ is felt to be via the inhibition of antigen processing and presentation³. A randomized trial of CQ for maintenance therapy in patients with biopsy proven pulmonary sarcoid demonstrated statistically better clinical outcomes on those who received CQ maintenance²⁰.

Sharma has reported one center's experience over several decades in using HCQ and CQ to treat 12 patients with neurosarcoid. There is little other evidence in the literature regarding the use of HCQ for either neurologic or neuro-ophthalmic sarcoid. The limitations of this study, which combines data from pre and post- modern neuro-imaging eras, are significant. Two of the author's conclusions were that if one's CNS sarcoid did not respond to CS, one would not respond to CQ, and that if one did respond to CS, but could not tolerate their side effects, that it was likely that one would respond to either

CQ or HCQ. Based upon such a small trial, Sharma's statement that CQ and HCQ are both effective in treating neurosarcoid seems a bit of a hyperbole.²¹

In their review of the literature as of 2003, Baughman and Lower indicated that HCQ was less efficacious than MTX or AZA¹. Rabinowitz reported a case of orbital involvement confirmed by right medial rectus biopsy who could not tolerate 60 mg of prednisone, but responded to 4000 mg daily of HCQ²². Sharma's series included one case of optic neuropathy treated with CQ and CS that was said to be stable.²¹

I have seen cases of neuro-ophthalmic sarcoidosis referred in with new disease activity that has occurred while on HCQ. This includes a case that developed retinal granulomas and optic nerve involvement while on CS and HCQ²³. Between this experience and the scant evidence in the literature supporting efficacy of CQ or HCQ in neurosarcoid, I have not routinely considered it as part of my therapeutic armamentarium for neuro-ophthalmic sarcoid.

Neuro-ophthalmologists are well aware of the potential visual toxicity of HCQ. Suggested methodologies of following patients for early HCQ visual toxicity include OCT of the macula and multifocal electroretinography. Details of the recommended methods of monitoring these patients for early visual changes are changing too rapidly to report here.

Besides visual loss, HCQ may cause , ototoxicity, myopathy, cardiomyopathy, peripheral neuropathy, as well as neuropsychiatric changes.²¹ If one does choose to use it, besides monitoring the patient for complications of therapy, one needs to prescreen the patient for G6PD deficiency, which, if unrecognized, can lead to hemolysis if these drugs are started.³

C. METHOTREXATE (MTX)

Methotrexate's mechanism of action is as a folate metabolism inhibitor. The first reported use of MTX to treat sarcoid was Lacher's 1968 case of a patient who was refractory to the combination of CS and vinblastine²⁴. Baughman has reported the only randomized study of the efficacy of MTX plus prednisone versus placebo plus prednisone. This is one of the very few randomized treatment trials in the sarcoid literature, and is not specific for CNS sarcoid. Although there was no significant reduction in CS dose required to control the disease at 6 months, there was at 12 months, when a 50% reduction in maintenance CS dose was demonstrated when MTX was added²⁵.

Kiltz has stated that the literature generally supports that most use MTX as the drug of choice when CS do not control, or the dose to control sarcoidosis cannot be tolerated.²⁶

In Reed's paper on his experience with sarcoid rhinosinusitis in combining his cases with those in the literature, he found that 28/30 (93%) eventually required starting an immunosuppressive agent , and MTX was the most commonly used agent.²⁷

Lower reported on 28 cases of CNS sarcoid who could not be controlled with acceptable doses of CS alone who were treated with MTX in conjunction with CS. reported that 17/28 (61%) responded to this therapy as opposed to 29% with CS alone.²⁸

In King's review of the treatment of sarcoidosis, he divides the treatment of neurologic sarcoid into two categories: aseptic meningitis/cranial neuropathy or cerebral/spinal cord involvement. They suggest that the former can be started on 40 mg of prednisone as an initial therapy, but that cerebral and spinal cord involvement may need one mg/kg/day of prednisone pulsed intravenously, and may need an immunomodulatory agent at onset. They typically use a dose of 10-15 mg once weekly with folinic acid. The side effects to watch for are nausea, leucopenia, pulmonary injury, fever, headache, stomatitis, and drug rash. Liver toxicity may be seen in 12% of cases with prolonged usage and must be watched for³.

Maust has reported 3 cases of SON who could not tolerate CS therapy that were treated with MTX. Three either stabilized or improved, all had their CS requirements diminish, although one developed a side effect (leucopenia). The average duration of MTX therapy was 29.6 months, with the longest therapy lasting 3 years²⁹.

In our series of refractory cases of sarcoid optic neuropathy, 6 patients were treated with MTX. Four (67%) had a good response (one in conjunction with CS and thalidomide) and two (33%) failed³⁰.

As with most immunosuppressive agents, the onset of peak effect is usually several weeks after the drug is started.. Thus, in starting MTX on a patient who failed another regimen, we typically either repulse the patient with a gram a day of solumedrol daily for three days, or raise them back up to one mg per kg of prednisone for 4-6 weeks.

D. LEFLUNOMIDE (LFL)

Leflunomide is a pyrimidine synthesis inhibitor. The rationale of its use is that it specifically targets proliferating T-cells. The first reported use of LFL for sarcoidosis was by Majithia in 2003³¹. The patient, who had pulmonary, sinus, and cutaneous sarcoid, had failed or not tolerated CS, AZA, MTX, and HCQ. His disease was successfully controlled with LFL. Baughman reported 32 patients who were treated with LFL.³² In 15 of these, it was part of a two drug regimen with MTX. The response rate they reported for LFL alone was 71% (12/17) and for the combination therapy, 13/15 (87%). Amongst the patients, 28 were being treated for eye disease, and 23 (82%) responded to one of the two regimens. They felt it was as effective as was MTX, with a side effect of nausea. They suggest it as an alternative for those who cannot tolerate MTX.

Sahoo reported the Cleveland Clinic experience with LEF. They treated 76 cases, 86% of whom had been on another immunomodulating agent, and 76% were on CS when the LEF was started.. Of the 76 patients, 34% had side effects

(most common were nausea, diarrhea, and bloating), and half of these had to discontinue the drug. Amongst all with non-pulmonary disease, 51% had a good and 32% had a partial response. Eight patients with ocular disease were treated, 5 (62.5%) had a good response, two (25%) had a partial response, and one (12.5%) had no response. Of the three with central nervous system disease, one (33%) had a good response, but 2 (67%) had no response³³.

E. AZATHIOPRINE (AZA)

Azathioprine is a purine analogue which suppresses the immune system by inhibiting DNA synthesis. Prior to employing it, one should consider obtaining an assay for thiopurine methyltransferase deficiency, which predisposes to azathioprine induced bone marrow toxicity. There is not much experience with this agent for CNS sarcoid, or for sarcoid in general. Pacheco reported on 10 cases of severe CS resistant pulmonary sarcoid that were treated with AZA at a dose of 150 mg daily for six months. Seven of ten (70%) showed clinical improvement³⁴. Baughman's study reported that 19/35 (54%) of patients treated with AZA for pulmonary sarcoidosis either went into remission or stabilized³⁵. AZA failed to control both cases of refractory SON in Eleinin's series³⁰.

F. CYCLOPHOSPHAMIDE (CYP)

Cyclophosphamide is a cytotoxic alkylating agent. In 1992, Zuber reported a 46 year old man with bilateral eighth cranial nerve dysfunction with radiculomyelitis from sarcoid who despite CS therapy, progressed to complete flaccid paraplegia. When he progressed despite methylprednisolone by vein and intrathecally, CYP was infused (5 weeks after the paraplegia had begun), and marked improvement was seen two weeks after the first infusion³⁶.

In their 1997 review of their experience treating 71 cases of neurosarcoid, Lower reported that CYP controlled 9/10 cases (90%), which was a statistically significant benefit over CS alone¹¹. Doty identified seven patients who either could not have their neurosarcoid controlled by CS, or could not tolerate the requisite CS dose required for control. They treated these seven with CYP for a mean duration of 5.4 mos. Four of seven (57%) showed symptomatic improvement; all showed improvement in either their MRI scan or CSF findings. The mean prednisone dose in the group was reduced from 42 to 18 mg daily. The complications seen included an opportunistic infection and a catheter infection. One of the seven did relapse after the therapy was completed³⁷. In 2006, Bradley reviewed the experience at the U Cincinnati in treating spinal cord sarcoidosis. Fourteen cases were followed for at least 6 months after starting immunosuppressives as a steroid sparing measure. Of the ten who were started on MTX, 5 (50%) responded. One received AZA and responded. One received AZA and MTX and responded. All 7 who received CYP responded, and the drug was well tolerated³⁸. CYP was one of several drugs that failed to control a very aggressive case of SON in Eleinin's series.³⁰

One of the advantages of CYP is that when given intravenously, it may have a rapid onset of action. However, it is associated with tumor induction and may cause leukemia, lymphoma, and bladder carcinoma, the latter especially if treatment is maintained for more than one year. It also may cause hemorrhagic cystitis. Nonetheless, in selected cases, CYP is a useful drug in severe cases of neurosarcoid, especially those calling for rapid remission¹⁸.

G. CYCLOSPORINE (CYA)

CYA is an inhibitor of IL-2. The rationale for the use of CYA originates in that the inflammation in sarcoid demonstrates activated T-lymphocytes that are secreting IL-2. CYA reduces T cell activation. In 1988, Cunnah reported the treatment of 2 cases of CNS sarcoid with CYA³⁹. The same year, Bielory and colleagues reported successful treatment of a patient with sarcoid uveitis and optic neuritis with CYA⁴⁰. However, in 1992, Stern reported the use of CYA in 6 cases with refractory neurosarcoid. He found that although CYA allowed a reduction in CS dose by 30-58%, 4 patients deteriorated, and one of these died⁴¹. Despite this, they felt it was safe and could be effective for CNS sarcoid.

That CyA was shown to not be an effective steroid sparing agent for *pulmonary sarcoidosis* in a randomized control trial seemed to stop interest in its use in all forms of sarcoid.⁴² This illustrates the general problem in the neurosarcoid literature that as the neurologic form of the disease is quite rare, sometimes statements about its therapy are based upon non-neurologic studies or experience. The fact that CyA is lipid soluble may make it have better efficacy in the CNS than elsewhere. As the penetrance of agents into the central nervous system may be different from their penetrance into the lungs, the response to therapy may be quite different, and thus extrapolating data that comes from pulmonary trials to neurologic/neuro-ophthalmic disease needs be done with caution. There are other reports about its utility in CNS and neuro-ophthalmic disease^{43, 44}. In Eleinin's series presented at NANOS in 2012, it only controlled 2/7 (29%) cases of SON³⁰.

However, although in theory it may be a good drug for targeting CNS sarcoidosis despite its limited efficacy in pulmonary sarcoid, its renal toxicity, and that it is a tumor promoter practically restrict its consideration to the most serious of cases⁹. It may also cause hypertension, and is a difficult agent to keep within a safe therapeutic range.

H. TACROLIMUS (TCL)

Tacrolimus is a macrolide immunosuppressive agent that inhibits T-cell-mediated responses. Katoh has reported the use of topical tacrolimus for the treatment of cutaneous sarcoid that was resistant to local and systemic CS.⁴⁵ Tsuboi reported a patient who had uveitis and cutaneous sarcoidosis. She was treated with oral TCL. The uveitis got somewhat better, and the skin lesions resolved. After the drug was stopped, the skin and eye lesions recurred, but were controlled with methylprednisolone⁴⁶. As tacrolimus

may also produce an optic neuropathy, it may not be the best agent to choose as a second line agent for SON. I am not aware of its use in neurosarcoid.

I. MYCOPHENOLATE MOFETIL(MMF)

MMF is an inhibitor of monophosphate dehydrogenase, a necessary enzyme in purine synthesis, and attenuates B and T cell proliferation. The utility of MMF as a steroid sparing agent for sarcoid was reported by Kouba⁴⁷. Their initial patient had pulmonary and cutaneous sarcoid, and was refractory to multiple agents including MTX, AZA, and HCQ, and would flare when prednisone was tapered below 20-30 mg daily. The patient was treated with HCQ and MMF with good response. They subsequently treated four more cases. None had ocular or neurologic involvement, but all four showed a good response allowing all of their prednisone doses to be tapered to 10 mg daily or less. In a 1998 paper on using MMF as rescue therapy for uveitis, one patient had sarcoid as the cause and had a good response⁴⁸. Bhat treated 7 patients with sarcoid uveitis with MMF. Six of the seven had failed CS therapy. One had been not been controlled with CYA and MTX, one failed on MTX, infliximab (INF) and adalimumab (ADA), and three were not controlled with MTX. All responded and tolerated MMF, with the mean time to control the uveitis 6.7 weeks⁴⁹.

There are a few studies that report on the use of MMF for ocular or neurologic sarcoid. The first reported use for neurosarcoid was by Chaussenot, who, in 2007, reported two younger patients (ages 14 and 27) who were refractory to treatment for their neurosarcoid and were treated with the combination of CS and MMF. They had a rapid clinical response that was paralleled by improvement in their neuroimaging studies⁵⁰.

Androdias had 9 consecutive cases of CNS sarcoid that were treated with either MMF alone or in conjunction with CS. Eight of nine (89%) improved, 6/9 (6%) went into complete remission. Four of these were patients who had failed prednisone and another immunosuppressant, and three (75%) had significant improvement. In those without muscular involvement, where the drug was not useful, the mean prednisone dose was able to be reduced from 59 mg to 6 mg over the mean period of follow up of 21 months. They did not see any significant side effects and concluded that the drug was effective and safe for CNS sarcoid⁵¹.

J. CHLORAMBUCIL (CHL)

In 1980, Kataria reported ten cases of pulmonary sarcoid that were treated with CHL. Two were treated due to diabetes mellitus, one due to steroid psychosis, and the remaining seven due to lack of response to CS. Eight patients (80%) improved. One who initially improved also had bilateral optic atrophy and gallactorrhea, and died from her disease which at autopsy was confirmed as neurosarcoid⁵². Israel reported 31 patients with refractory systemic sarcoidosis who were treated with CHL. Marked improvement was seen in 15/31 (48%) and another 13/31 (42%) showed moderate improvement. However, patients often relapsed with drug withdrawal⁵³.

Shaikh has reported a case of orbital sarcoidosis with proptosis and ophthalmoplegia that responded to CHL and CS⁵⁴. There is little experience with this drug in neuro-ophthalmic sarcoid. Gelwan and colleagues have reported a patient refractory to radiation therapy whose chiasmal sarcoidosis was successfully treated with CHL⁵⁵.

K. ETANERCEPT (ETA)

ETA is an anti-TNF factor agent which acts by blocking the TNF alpha receptor. Unlike other anti-TNF agents, ETA was not found to be useful in the therapy of ocular sarcoidosis^{1,56}. Furthermore, there are several cases reported where sarcoidosis or a sarcoid-like illness developed during the treatment of another disease with ETA.^{57,58,59} Tong's review found 3 such cases out of 165 (2%) treated with anti-TNF agents. Two of these were in patients treated with ETA. The first, treated due to psoriatic arthritis, had both an elevated ACE and a positive biopsy. Another had rheumatoid arthritis, and during their course, had received ADA and ETA. Abnormal chest CT led to a positive biopsy for sarcoid. Their third case had rheumatoid arthritis and was treated with ADA, and an abnormal chest CT led to a positive biopsy, although the ACE was not elevated. They report that this induction of sarcoid can occur with any anti-TNF agent, and in reviewing the literature, found 37 cases. ETA was the agent in 22/37 cases (59.5%), 5/37 had received ADA (13.5%) and 10/37 had been treated with INF (27%). They suggest that because unlike ADA and INF, ETA is a soluble receptor antagonist, that it has a higher chance of inducing sarcoid than do ADA and INF, which are monoclonal antibodies directed against TNF⁵⁹. Cathcart has recently reviewed the cases of patients who developed sarcoidosis while on anti-TNF agents. He identified 34 cases. The average duration of therapy until the onset of the sarcoid was 22 months. The lung and lymph nodes were the typical sites of involvement. In 33/34 cases (97%) drug withdrawal brought remission from sarcoid, with an average of 5-6 months until the sarcoid was quiescent⁵⁸.

Moller further points out that besides the lack of efficacy of ETA for sarcoid, there is a risk for induction of a multiple sclerosis like syndrome, and an even greater risk of lupus and infection with its use⁹. It is not a drug that should be employed for neurosarcoid.

L. ADALIMUMAB (ADA)

Adalimumab is a human monoclonal IgG1 TNF- α antibody. The first use of ADA for sarcoid was reported by Phillips who used it for cutaneous sarcoid. This patient did not respond to CS, MTX, or HCQ⁶⁰. Once ADA was begun in conjunction with CS, the patient healed within about 2 months. Erckens has reported the usefulness of ADA in patients with refractory sarcoid uveitis⁶¹. Marnane reported the first case of the use of ADA in neurosarcoid. This patient had a right facial nerve palsy and bilateral uveitis, and developed right sided weakness while on CS. She did not improve on CS and MTX. HCQ was not tolerated. ADA was added to CS and MTX, and the neurologic illness resolved within 6 months. She was successfully removed from CS and MTX, was maintained on ADA alone for 6 months before it too, was successfully removed.⁶²

As with other drugs in this class, infection, central demyelination, and lymphoma are potential complications of ADA62. If a multiple sclerosis-like syndrome develops, it may include optic neuritis, rendering it difficult to separate out SON from drug induced optic neuritis. Other complications of therapy worsening of congestive heart failure and that ADA itself may induce sarcoidosis. Seve has reported a patient who was on ADA for rheumatoid arthritis who developed a first bout of uveitis that was due to presumed drug-induced sarcoidosis while on ADA. She improved with drug withdrawal and a course of CS⁶³. Marcella described a patient who developed pulmonary and cutaneous sarcoid while on ADA therapy for psoriasis⁶⁴.

M. INFLIXIMAB (INF)

Infliximab is a recombinant chimeric IgG1k monoclonal antibody against TNF alpha. Hostettler reported on the safety and efficacy of long-term INF therapy for steroid resistant sarcoid. They had 16 patients who were treated for at least 12 months. Eleven of these 16 had largely extrapulmonary disease. Six of the 11 (55%) had complete remission, and 4/11 (36%) had a partial response to INF. This response was better than that seen in the largely pulmonary cases. They found that only 1/16 (6%) had to be removed from the therapy for an adverse event⁶⁵.

Sodhi reported four cases of neurosarcoid who progressed while on CYP, who then received INF. One patient had also failed AZA, three had failed MTX. All four subjects showed a rapid clinical and radiologic improvement, and tolerated the drug well. One patient had unilateral optic neuritis with NLP vision. This patient recovered to 20/50 with the first infusion and 20/20 after the third⁶⁶.

Terushkin, citing Stern, points out the potential for INF to yield a quick "rescue" to the neurosarcoid patient in crisis. "In addition, infliximab can also be used to emergently stabilize a severely ill or deteriorating patient if high-dose corticosteroid therapy is unsuccessful³.

A potential additional consideration in selecting agents for neurosarcoid was the observation that amongst such patients treated with prednisone, prednisone with MTX, or anti-TNF agents, the group treated with the anti-TNF agents had statistically significant improvement in their cognition when compared with the other therapeutic regimens.⁶⁷

In 2003, Katz and colleagues reported the successful treatment a case of neuro-ophthalmic sarcoid with INF. Their patient was already NLP in one eye, and the other eye was 20/25 with field loss and asymmetric bilaterally swollen discs. The seeing eye deteriorated despite CS and CYP. The addition of INF led to improvement in her seeing eye. A complication of herpes zoster dermatitis ensued⁶⁸.

In 2004, Carter reported a case of a 41 year old woman who was thought to have a pituitary adenoma, but the surgery revealed non-caseating granulomas with pituitary and chiasmal

involvement, without adenoma. CS, MTX, CYP all failed to control her bilateral field loss. A regimen of MTX and INF led to visual stabilization and improvement in her MRI images⁶⁹.

Salama has reported a case of bilateral SON which was not controlled by immunosuppressives (CS- AZA and CS-MTX). Treatment with INF saw recovery in one eye from NLP to 20/200 over 6 months, although the other eye only gained from NLP to LP⁷⁰.

Santos reported successful treatment of four neurosarcoid cases (three with optic neuropathy) with INF. His first case was said to have "spots before the eyes", with acuities of 6/6 OD and 6/3 OS, yet was said to have normal fields (method of field testing not mentioned) and pale optic discs. The combination of CS-MTX did not halt progression. INF was started. No mention of the visual outcome is given, although it was stated that he stabilized and the MRI improved.. The second case was treated with CS-AZA, and was said to have already been no light perception in the left eye before the treatment with INF, and had a right optic nerve and chiasm that were enhancing on MRI scan. No assessment of visual function of the right eye before or after treatment is given, but the clinical course is said to have stabilized on INF. The third case presented with papilledema, and developed diplopia while on CS. AZA was not tolerated. The combination of CS-MTX did not resolve the papilledema and diplopia. INF was begun and the neurologic symptoms were said to improve.⁷¹

More recently, Pereira reported 3 cases of refractory neurosarcoid treated with INF and reviewed the literature. All three of Pereira's cases responded to the drug. One case had failed just CS, the second failed CS, AZA, and MTX. The third patient, who had bilateral recurrent optic neuropathy and spinal cord disease, had failed on CS, MTX, CP, AZA, CYA, IVIG, and plasma exchange. This patient was already blind before the institution of INF, but his other neurologic symptoms improved as did his MRI scan. The other 20 cases they culled from the literature, (including Santos' four cases), all reported that the neurosarcoid improved on INF. There were 16 cases that reported whether adverse effects had occurred. They were seen in 4/16 (25%). Four of these cases had optic nerve involvement⁷².

With this biologic agent, diminished efficacy may occur with time. Hoitsma states

"Antibody formation is associated with loss of response. Concomitant immunosuppressive treatment may optimize response to infliximab by preventing the formation of antibodies. Finally, anti-TNF therapy can be responsible for auto-immune reactions, including SLE. Whether infections such as PML will occur more frequently is unknown so far." ⁴

Sturfelt has reported a case of neurosarcoid that developed in a patient with rheumatoid arthritis who was being treated with INF⁷³. This patient had papilledema, a sixth nerve palsy, uveitis, and retinal periphlebitis. Removal of the drug, and placement of a ventriculoperitoneal shunt, with the use of CS and MTX led to symptom resolution.

N. RITUXIMAB (RTX)

Rituximab is a chimeric monoclonal antibody that depletes circulating B-cell lymphocytes. The first use of RTX in sarcoid was reported in 2005 by Gottenberg.⁷⁴

Bomprezzi has reported the first treatment of a case of neurosarcoid with RTX. This patient, who had neurologic disease before other manifestations of sarcoid, was refractory to CS, CTX, and MTX, and developed cutaneous nodules while on these treatments. RTX was begun, infused every 6 months, and after two years, the cutaneous lesions had regressed and there was no progression of the neurologic component.⁷⁵

O. CLADRIBINE (CLD)

Cladribine is a purine analog that inhibits the production of DNA via inhibition of adenosine deaminase. There is but one case report on the use of cladribine in sarcoid, and it was a case of refractory involvement of the visual pathways⁷⁶. Tikoo reported a 54 year old man with suprasellar involvement with bilateral visual loss that had been confirmed as neurosarcoidosis by biopsy. When prednisone was tapered, visual loss recurred, and the patient had developed diabetes mellitus. CYA and CYP were tried as steroid sparing agents, and did not control the disease. Recognizing that CLD was a helpful therapy in CNS Langerhans cell histiocytosis, which, like sarcoid, is characterized by histiocytic infiltration, they tried CLD. They employed a dose of 20 mg daily by infusion for 2 days every three weeks with a total of 5 cycles. There was response both clinically and on MRI scan. The patient was initially able to be tapered off of prednisone. Unfortunately, the visual loss recurred within a year of the completion of CLD therapy, but with reinstitution, visual improvement was again achieved.

P. PENTOXIFYLLINE (POF)

Pentoxifylline (POF) is a methylxanthine derivative which inhibits the production of TNF by mononuclear cells⁹. Korber described that at higher doses, POF has anti-inflammatory properties that appear to be mediated by inhibition of TNF-alpha. He specifically showed decreased production of TNF-alpha by alveolar macrophages in patients with sarcoid⁷⁷.

Zabel studied its efficacy in 23 patients with pulmonary sarcoid at a dose of 25 mg/kg/day. Three patients could not tolerate the gastrointestinal side effects at this dosage, two were lost to follow-up. Amongst the 18 followed for six months, 11 (61%) improved and the rest were stable⁷⁸. Three of these patients were on combination therapy with CS; all were able to have their dose tapered with the addition of POF. I am not aware of the use of POF for neurologic or neuro-ophthalmic sarcoidosis.

Q. APREMILAST (APR)

Apremilast is, as is POF, a phosphodiesterase-4 inhibitor. A considerable problem with POF is it is hard for patients to take a dose adequate to receive its anti-inflammatory effects without having too many gastrointestinal side effects to tolerate the drug. APR is a new phosphodiesterase-4 inhibitor with less gastrointestinal side effects. It ultimately diminishes TNF-alpha. The drug has some moderate efficacy for cutaneous sarcoid⁷⁹. I am not aware of its being used in other forms of sarcoidosis.

R. THALIDOMIDE (THL)

Thalidomide blocks release of TNF-alpha. THL is quite effective in cutaneous sarcoidosis. The original thought to use thalidomide for neurosarcoid came from the report of Carlesimo on its successful use in two cases of refractory cutaneous sarcoid⁸⁰. During a study of its effectiveness for skin lesions, patients who had concomitant chest disease did not get better, whereas many who had sinus sarcoidosis did improve⁸¹. Estines felt that THL would suspend cutaneous disease activity, but that the process would recur if the drug was stopped⁸².

The success using THL for cutaneous sarcoid led to Frohman obtaining an IND for its use in neurosarcoid⁸³. THL stabilized our initial case of SON who had failed multiple two and three drug combinations (CS-AZA, CS-CYA, CS-CYA-bromocriptine, CS-CYA-MTX, CS-CYA-AZA, CS-CHL-CYA). In this index patient, who had been blind in one eye for several years, and was wheelchair-bound due to CS side effects, the institution of THL with maintenance CS at the onset of another attack of SON allowed her to regain her vision back to the levels it had been at prior to the most recent optic neuropathy episode, and allowed her steroid doses to be tapered significantly. The effect of THL was dose dependent; at a point where the patient erroneously cut her THL dose by 50%, she had a new flare of optic neuropathy, which recovered when her error was rectified. She remained on the drug for about three years, tolerating the side effects of peripheral neuropathy. In conjunction with other NANOS members, we then tried it in 5 more similar cases. The drug is difficult to use due to its well-known potential for teratogenicity. This makes it difficult for the patient to comply with the treatment regimen requirements, and it may also cause sleepiness and lethargy, and may cause a painful peripheral neuropathy. But it did buy several cases several years of disease control (Frohman, unpublished data).

In 2007, Hammond published a case of neurosarcoid that failed two courses of intravenous CS, but improved clinically and on MRI scan on THL⁸⁴. The following year, Hoyle reported a patient with neurosarcoid who was refractory to high dose CS, AZA, CYP and CYA. The patient was started on THL, and within six months, clinical and radiologic improvement in the neurosarcoid was seen⁸⁵.

Yasui gave THL to a 16 year old and an 8 year old who both had onset of sarcoid before the age of 5. One case had multiple system involvement, including uveitis with papillitis. She had

failed CS, TCL, INF and MTX. THL led to resolution of the bilateral papillitis and marked recovery of vision. The boy had cutaneous involvement, arthritis, and had recently developed papillitis. He had failed CS, MTX, and CYA. He responded to the combination of ETA and THL⁸⁶. THL appears to have reasonable efficacy for CNS sarcoid and specifically for SON, its difficulty in use, side effects, and notoriety limits its use to cases refractory to most other choices.

S. INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIG has been successfully used in a case of sarcoid polyneuropathy that was refractory to CS⁸⁷. I am not aware of its reported use in neuro-ophthalmic sarcoid.

T. TETRACYCLINES (TC)

Minocycline has anti-inflammatory as well as antibacterial properties. Bachelez has reported on the efficacy of minocycline in cutaneous sarcoidosis⁸⁸. Amongst their 12 patients, 10 (83%) improved, with 8 (67%) resolving. One patient progressed, and one stabilized (8% each). Park has reported a 41 year old woman who presented with sarcoid involving the canthal region, the parotids, and the lacrimal glands. She had multiple biopsies that confirmed the diagnosis, and was found to have choroidal granulomas and pulmonary involvement. Multiple medical comorbidities were felt to be a relative contraindication for CS. Minocycline was used as initial therapy. Within months, all lesions, including the choroidal granulomas, had regressed.⁸⁹ Miyazaki has reported a woman with uveitis, cutaneous, pulmonary, and muscular sarcoidosis who refused therapy with CS. Minocycline was given, and over the next several months, the symptoms abated and the ACE level improved, and the drug was stopped. The disease recurred a few months later, and the drug was successfully restarted. In this case, a pre-treatment muscle biopsy was performed, and immunohistochemical stains directed against propionibacterium acnes showed small particles within the granulomas felt to be evidence of the presence of p. acnes.⁹⁰ The patient did not allow repeat biopsy after therapy to determine if these particles had disappeared. Although Marshall has provided evidence that the etiology of sarcoid may be infectious, including his conclusion that a potentially life threatening Jarish-Herxheimer reaction may be seen when sarcoid patients are treated with antibiotics,⁹¹ most authors have not embraced this theory in planning their therapeutic strategies.

7. COMBINATION DRUG THERAPIES

When a patient fails therapy with the first agent they experience after CS, the choice is usually to add another agent with the hope that the combination will allow the tapering of CS. After several single agents fail, with or without CS, the next option is often or to use a combination of agents. Every case needs be individualized. Regimens that work in one case may not work in another, and there are no set rules, and you may need to try combinations, being mindful not to use multiple drugs with additive toxicities. Even so, some cases resist effective therapy.

Guilpain has reported a case of bilateral sarcoid optic neuropathy refractory to the combination of CS, MTX, and INF⁹². We have reported a case that required multiple two drug combination therapies to control sarcoid optic neuropathy in a patient, already blind in one eye, who flared whenever prednisone dosing was less than 60 mg/day. Combinations of CS and CYA as well as CS and AZA did not allow for tolerable steroid dosing. A three drug regimen of CS-CYA-CHL permitted the tapering of the prednisone dose to a tolerable maintenance dose of 10-20 mg/day⁹³.

More recently, Moravan reported on the results of a series treating 7 patients with biopsy proven neurosarcoid who had failed CS therapy. All seven received INF; six also received MMF. Patients were followed both clinically and via MRI scan appearance. All patients reported symptomatic relief by the fourth infusion of INF, and all showed improvement in their MRI scan (either decrease in lesion size or reduction in enhancement). In this small series, the improvement was not affected by the location or distribution of the lesions (dural/leptomeningeal based versus intraparenchymal, cord versus brain; single lesion versus multifocal). They concluded that this combination of MMF-INF therapy was well tolerated and effective for CNS sarcoidosis⁹⁴.

8. RADIATION THERAPY

Gelwan, based upon the successful use of radiation therapy in non-visual cases of neurosarcoid, treated 4 patients with chiasmal and optic nerve involvement with suprasellar sarcoidosis with radiation⁹⁵. All had previously responded to intravenous megadose CS, and flared with steroid taper. They received 4500, 4500, 4800, and 2600 grey of external beam therapy respectively. Although there was a transient improvement, three recurred within 3 months of the radiation, the fourth was lost to follow-up at 8 months. The three who failed were subsequently controlled with AZA, AZA, and CHL respectively. This experience has discouraged the use of radiation therapy in neuro-ophthalmic sarcoid.

Despite this failure, Motta had a single patient who had failed CYA, MTX and CS with neurosarcoidosis involving the hypothalamo-hypophyseal region. This patient received whole brain irradiation with a dose of 26 GY in 13 fractions. The patient received a short course of CS with the radiation, and was followed for 12 months without relapse. Motta culls nine additional cases from the literature. They received anywhere from 20-30 GY. Three of nine (33%) had no response, whereas in the six who had a response, the effect was observed for 3-240 months of follow-up. The authors conclude that radiotherapy is a reasonable therapy to employ in neurosarcoid, but that it should be expected to stop further disease progression, and not to deliver any restitution of function lost. This may make it a less attractive alternative for cases with visual loss, although it can be considered in selected cases.⁹⁶

Ahmad reported a single case with neurosarcoid refractory to CS and CYP, who had a significant improvement with total nodal and craniospinal irradiation. This response allowed the removal of CS for the three years that he was observed⁹⁷.

Stelzer has reported a single case of neurosarcoid that failed CS and responded to 20 GY of fractionated external beam radiotherapy⁹⁸. In 2004, Bruns reported a single case of a patient with pulmonary sarcoidosis felt to be in remission. He developed headaches, nausea, and vomiting. The MRI showed a mass preoperatively felt to be a glioma; the pathology revealed sarcoidosis. There was no other activity of sarcoidosis found. After an initial response, the neurologic component became refractory to CS. He was treated with 20 GY of fractionated whole brain irradiation, and showed clinical and radiologic stabilization⁹⁹. Because of concerns about an evanescent treatment effect, radiation, for the most part, is reserved for selected cases of failure of medical therapy.

9. SUMMARY

There are only a few studies that report treatment outcomes in series of cases of neuro-ophthalmic sarcoidosis. Koczman has reported the Iowa experience with this disease, which may be a little bit distinct from other United States centers in that 70 % of their patient population was Caucasian. They found that 5/20 (25%) of their cases required therapy beyond CS to control their neuro-ophthalmic disease.

In 2010, Terushkin published a treatment strategy for neurosarcoid. They looked at their cases as having either severe or mild to moderate neurologic impairment. When CS fail to control a patient with severe disease, they suggest either MMF or intravenous INF. They point out that MMF takes 2-3 months to have maximal effect, so they suggest INF in cases that require a more rapid onset of therapeutic benefit. CYP is an alternative rapidly acting agent to use if the patient cannot access INF therapy or is not a good candidate. For mild to moderate neurologic disease, they propose MMF, MTX, AZA, or HCQ. They also suggest consideration of radiation therapy. They feel asymptomatic cases of neurosarcoid may be treated with either CS or HCQ.³

In general, we recommend a similar approach for the treatment of neuro-ophthalmic sarcoid as do Baughman, Weiss, and Golnik,¹⁰⁰ who use their experience gained at the University of Cincinnati's sarcoidosis center to suggest CS be used as the initial therapy for all cases of neurosarcoid. They use either intravenous CS or high dose oral CS as first therapy, and try to taper the dose after about 4-6 weeks. If the patient either then flares or does not tolerate the requisite dose of CS, they choose to add either MMF, AZA, or MTX as their second agent. Once on the second agent, they attempt to taper the patients off of CS. If they cannot, they add another agent- their preference is an anti-TNF therapy, or intravenous pulse CYP. They do not discuss what they would choose if these agents would fail. We further

agree with their statement that "While some have reported a poor outcome for optic neuropathy associated with neurosarcoidosis, others have found that early, aggressive therapy was associated with a favorable outcome."

What we have done (FIGURES 1-3) for neuro-ophthalmic sarcoid is to start patients with acute severe disease (i.e., acute SON) on one gram of solumedrol daily for 3-5 days, followed by about 0.5 to 1 mg/kg of oral prednisone. Less acute cases are started on 0.5 to 1.0 mg/kg of oral prednisone. Decisions about when to taper are determined by the clinical course. If there is an adequate response, we typically begin a steroid taper after about a month, but at a rate that would lead to removal from steroids, if no relapse, over six months. If the patient had a dramatic response to CS, but flared with the initial taper, rather than start a second agent immediately, we sometimes initiate a repulse followed by slower taper of CS over a year. More often, however, in the patient who either flares on CS taper, or cannot tolerate the dose of CS that is requisite to control their disease, we start a second agent. As do Baughman et al, when the clinical situation requires an acute response, we would use CYP or INF. However, we find that in many requiring rapid onset of therapy, a re-bolus with 3-5 days of intravenous CS imparts enough of a therapeutic effect that a second agent with slower time until full efficacy is reached may be used as the oral CS dose after initial bolus is restarted at 0.5-1.0 mg/kg. In this case, as we would do in a CS failure who did not need acute onset of therapeutic effect, we typically select MTX, as it is relatively well tolerated by the patients, and is easy for them to comply with. We also find MMF well tolerated by most, but its relative cost and the increased risk, as is the case for several immunomodulatory agents, including rituximab, of progressive multifocal leukoencephalopathy¹⁰¹, make us generally reserve it for patients who do not tolerate or get benefit from MTX. Patients who fail MTX and MMF may be offered AZA, or CYA. When the patient is on a two drug combination that is controlling their disease, we try to taper the CS over 3-6 months, depending upon how long the patient has been on CS. If removal from CS is successful, we would generally maintain the patient on the single immunosuppressant for 6-12 months, and after that point, if the clinical disease and MRI are quiescent, then we would try to taper and remove it over about 6 months. In the patient who flares with CS taper while on an immunosuppressant, or flares after the CS are withdrawn and they are on immunosuppressant alone, either at a steady dose or with taper, the flare tells us that the immunosuppressant was not adequate to completely suppress disease activity. The option then is to repulse with steroids and begin the process again, knowing that the patient may require long term maintenance on immunosuppressive, or, to restart the process with a new steroid bolus, but trying a different immunosuppressive agent.

If CS and MTX or AZA, MMF, and CYA all fail, before INF was available, we would have tried a 3 drug combination, such as CS-CYA-MTX, trying to select drugs with different non-additive toxicities. Since INF has become available,

we would try CS-INF, mindful that INF, as it can cause sarcoidosis, could theoretically worsen the process. Furthermore, due to the question of tachyphylaxis, consideration should be given to using it concomitantly with an immunosuppressive such as MTX.

If we could not control a patient with a CS-INF, we would try various three drug combinations, which might include INF. If this failed, options include agents that work in systemic sarcoid but where there is less experience in neurosarcoid, such as THL, RTX, PFO, CHL, or CLD.

Future areas of investigation include:

1. As there are no two-armed blinded studies in the treatment of neuro-ophthalmic sarcoid, organizing a network study to compare perhaps CS alone versus CS-MTX or CS-INF at initiation of therapy for SON would be quite helpful.
2. Whether the apparent anatomic location of the lesion causing sarcoid optic neuropathy prognosticates outcome and perhaps calls for different treatment schema. Our experience is that the lesions that are restricted to the papilla or more distal intraorbital optic nerve are more steroid responsive and may have a better outcome. We also suspect that the cases with intracranial involvement have a worse outcome. Perhaps the latter should always be started on a two drug regimen at initial therapy? To answer this would require a registry and a retrospective look at pooled data.
3. Should all patients receive a course of HCQ at time of diagnosis of neuro-sarcoid to potentially interfere with antigen presentation and thus granuloma formation?
4. Is there a role for starting all patients on TC at time of diagnosis, as it is well tolerated and there may be a subpopulation of sarcoid patients who experience a dramatic response to this drug?

Unfortunately, for many reasons, such studies will be quite difficult to organize. It may continue to be that, as Pawate wrote in 2009, that "the low prevalence of the disease makes clinical trials difficult and therapeutic decisions are likely to be made from careful reporting from case studies."⁶

CME ANSWERS

1. a
2. d
3. b
4. d

REFERENCES

1. Baughman RP. Lower EE. du Bois RM. Sarcoidosis. *Lancet*. 361(9363):1111-8, 2003.
2. King CS. Kelly W. Treatment of sarcoidosis. *Disease-A-Month*. 55(11):704-18, 2009
3. Terushkin V, Stern BJ, Judson MA, Hagiwara M, Pramanik B, Sanchez M, Prystowsky S. Neurosarcoidosis: presentations and management. *Neurologist*. 16(1):2-15, 2010.
4. Hoitsma E. Drent M. Sharma OP. A pragmatic approach to diagnosing and treating neurosarcoidosis in the 21st century. *Curr Opin Pulm Med*. 16(5):472-9, 2010
5. Stern BJ. Krumholz A. Johns C. Scott P. Nissim J. Sarcoidosis and its neurological manifestations. *Archives of Neurology*. 42(9):909-17, 1985.
6. Pawate S. Moses H. Sriram S. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. *Qjm*. 102(7):449-60, 2009.
7. Brindeau C. Glacet-Bernard A. Roualdes B. Abd Alsamad I. Oubraham H. Meyrignac C. Soubrane G. Sarcoid optic neuropathy *Journal Francais d Ophthalmologie*. 22(10):1072-5, 1999.
8. Galetta S. Schatz NJ. Glaser JS. Acute sarcoid optic neuropathy with spontaneous recovery. *Journal of Clinical Neuro-Ophthalmology*. 9(1):27-32, 1989.
9. Moller DR. Treatment of sarcoidosis — from a basic science point of view. *Journal of Internal Medicine*. 253(1):31-40, 2003.
10. Agbogu BN. Stern BJ. Sewell C. Yang G. Therapeutic considerations in patients with refractory neurosarcoidosis. *Archives of Neurology*. 52(9):875-9, 1995.
11. Lower EE. Broderick JP. Brott TG. Baughman RP. Diagnosis and management of neurological sarcoidosis. *Archives of Internal Medicine*. 157(16):1864-8, 1997.
12. Zajicek JP. Scolding NJ. Foster O. Rovaris M. Evanson J. Moseley IF. Scadding JW. Thompson EJ. Chamoun V. Miller DH. McDonald WI. Mitchell D. Central nervous system sarcoidosis—diagnosis and management. *Qjm*. 92(2):103-17, 1999.
13. Ferriby D. de Seze J. Stojkovic T. Hachulla E. Wallaert B. Blond S. Destee A. Hatron PY. Decoulx M. Vermersch P. [Clinical manifestations and therapeutic approach in neurosarcoidosis]. *Revue Neurologique*. 156(11):965-75, 2000.
14. Rush JA. Retrobulbar optic neuropathy in sarcoidosis. *Annals of Ophthalmology*. 12(4):390-4, 1980.
15. Burde RM. Keltner JL. Gittinger JW. Miller NR. Optic neuritis—etiology? *Survey of Ophthalmology*. 24(5):307-14, 1980.
16. Beardsley TL. Brown SV. Sydnor CF. Grimson BS. Klintworth GK. Eleven cases of sarcoidosis of the optic nerve. *American Journal of Ophthalmology*. 97(1):62-77, 1984.
17. Frohman L, Grigorian R, Bielory L. Neuro-ophthalmic manifestations of sarcoidosis: clinical spectrum, evaluation, and management. *J Neuro-ophthalmol* 21:132-137, 2001.
18. Vargas DL. Stern BJ. Neurosarcoidosis: diagnosis and management. *Seminars in Respiratory & Critical Care Medicine*. 31(4):419-27, 2010.
19. Sader A. Gramer E. Korner U. Sarcoidosis of the optic nerve. *Klinische Monatsblätter für Augenheilkunde*. 206(2):128-33, 1995.
20. Baltzan M, Mehta S, Kirkham TH, Cosio MG. Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med*. 160(1):192-7, 1999.
21. Sharma OP. Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement. *Archives of Neurology*. 55(9):1248-54, 1998.
22. Rabinowitz MP. Murchison AP. Orbital sarcoidosis treated with hydroxychloroquine. *Orbit*. 30(1):13-5, 2011.
23. Frohman, LP, Grigorian R, Slamovits T. Evolution of Sarcoid Granulomas of the Retina. *Am J Ophthalmol* 131:661-2, 2001.

24. Lacher MJ. Spontaneous remission or response to methotrexate in sarcoidosis. *Annals of Internal Medicine*. 69(6):1247-8, 1968
25. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. *Sarcoidosis Vasc Diffuse Lung Dis*. 2000;17:60–66.
26. Kiltz U, Braun J. Use of methotrexate in patients with sarcoidosis. *Clinical & Experimental Rheumatology*. 28(5 Suppl 61):S183-5, 2010.
27. Reed J, deShazo RD, Houle TT, Stringer S, Wright L, Moak JS 3rd. Clinical features of sarcoid rhinosinusitis. *American Journal of Medicine*. 123(9):856-62, 2010.
28. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med*. 155:846-851, 1995.
29. H.A. Maust, R. Foroozan, R.C. Sergott et al. Use of methotrexate in sarcoid-associated optic neuropathy. *Ophthalmology*, 110:559–563, 2003.
30. Eleinen, Rania A, Vasudev, Deepta, Turbin, Roger, and Frohman, Larry. Analysis of Therapeutic Agents and Their Effectiveness in Sarcoid Optic Neuropathy. Poster at NANOS 2012 Annual Meeting, San Antonio, TX.
31. Majithia V, Sanders S, Harisdangkul V, Wilson JG. Successful treatment of sarcoidosis with leflunomide. *Rheumatology*. 42(5):700-2, 2003.
32. Baughman RP, Lower EE. Leflunomide for chronic sarcoidosis. *Sarcoidosis Vasculitis & Diffuse Lung Diseases*. 21(1):43-8, 2004.
33. Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG, Lazar CA, Chapman JT, Culver DA. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. *European Respiratory Journal*. 38(5):1145-50, 2011.
34. Pacheco Y, Marechal C, Marechal F, Biot N, Perrin Fayolle M. Azathioprine treatment of chronic pulmonary sarcoidosis. *Sarcoidosis*. 2(2):107-13, 1985.
35. Baughman RP, Lower EE. Alternatives to corticosteroids in the treatment of sarcoidosis. *Sarcoidosis*. 14: 121–130, 1997.
36. Zuber M, Defer G, Cesaro P, Degos JD. Efficacy of cyclophosphamide in sarcoid radiculomyelitis. *Journal of Neurology, Neurosurgery & Psychiatry*. 55(2):166-7, 1992 .
37. Doty JD, Mazur JE, Judson MA. Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. *Chest*. 124(5):2023-6, 2003.
38. Bradley DA, Lower EE, Baughman RP. Diagnosis and management of spinal cord sarcoidosis. *Sarcoidosis Vasculitis & Diffuse Lung Diseases*. 23(1):58-65, 2006.
39. Cunnah D, Chew S, Wass J. Cyclosporin for central nervous system sarcoidosis. *American Journal of Medicine*. 85(4):580-1, 1988.
40. Bielory, L, Holland, C, Gascon, P, and Frohman, L. Uveitis, Cutaneous, and Neurosarcoid: Treatment with Low-Dose Cyclosporine A. *Transplantation Proceedings*: 20(3): June, 1988.
41. Stern BJ, Schonfeld SA, Sewell C, Krumholz A, Scott P, Belendiuk G. The treatment of neurosarcoidosis with cyclosporine. *Archives of Neurology*. 49(10):1065-72, 1992.
42. Wyser CP, van Schalkwyk EM, Alheit B, Bardin PG, Joubert JR. Treatment of progressive pulmonary sarcoidosis with cyclosporin A. A randomized controlled trial. *American Journal of Respiratory & Critical Care Medicine*. 156(5):1371-6, 1997.
43. Koczman JJ, Rouleau J, Gaunt M, Kardon RH, Wall M, Lee AG. Neuro-ophthalmic sarcoidosis: the University of Iowa experience. *Seminars in Ophthalmology*. 23(3):157-68, 2008
44. Bielory L and Frohman, LP. Low Dose Cyclosporine A Therapy of Granulomatous Optic Neuropathy and Orbitopathy. *Ophthalmol* 98:1732-1736, 1991.
45. Katoh N, Mihara H, Yasuno H. Cutaneous sarcoidosis successfully treated with topical tacrolimus. *British Journal of Dermatology*. 147(1):154-6, 2002.
46. Tsuboi H, Yonemoto K, Katsuoka K. A 14-year-old girl with lichenoid sarcoidosis successfully treated with tacrolimus. *Journal of Dermatology*. 33(5):344-8, 2006.
47. Kouba DJ, Mimouni D, Rencic A, Nousari HC. Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *British Journal of Dermatology*. 148(1):147-8, 2003.
48. Kilmartin DJ, Forrester JV, Dick AD. Rescue therapy with mycophenolate mofetil in refractory uveitis. *Lancet* 352: 35–6, 1998.
49. Bhat P, Cervantes-Castaneda RA, Doctor PP, Anzaar F, Foster CS. Mycophenolate mofetil therapy for sarcoidosis-associated uveitis. *Ocular Immunology & Inflammation*. 17(3):185-90, 2009.
50. Chausseuot A, Bourg V, Chanalet S, et al. Neurosarcoidosis treated with mycophenolate mofetil: two cases. *Rev Neurol*. 163:471-475, 2007.
51. Androdias G, Maillet D, Marignier R, Pinede L, Confavreux C, Broussolle C, Vukusic S, Seve P. Mycophenolate mofetil may be effective in CNS sarcoidosis but not in sarcoid myopathy. *Neurology*. 76(13):1168-72, 2011.
52. Kataria YP. Chlorambucil in sarcoidosis. *Chest*. 78(1):36-43, 1980.
53. Israel HL, McComb BL. Chlorambucil treatment of sarcoidosis. *Sarcoidosis*. 8(1):35-41, 1991.
54. Shaikh ZA, Bakshi R, Greenberg SJ, Fine EJ, Shatla A, Lincoff NS. Orbital involvement as the initial manifestation of sarcoidosis: magnetic resonance imaging findings. *Journal of Neuroimaging*. 10(3):180-3, 2000.
55. Gelwan Mark, Kellen, Rodney I, Burde, Ronald M, and Kupersmith, Mark J. Sarcoidosis of the anterior visual pathway: successes and failures. *Journal of Neurology, Neurosurgery, and Psychiatry*. 51:1473-1480, 1988.
56. Baughman RP, Lower EE, Bradley DA, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest*. 128(2):1062-47, 2005.
57. Skoie IM, Wildhagen K, Omdal R. Development of sarcoidosis following etanercept treatment: a report of three cases. *Rheumatology International*. 32(4):1049-53, 2012.
58. Cathcart S, Sami N, Elewski B. Sarcoidosis as an adverse effect of tumor necrosis factor inhibitors. *Journal of Drugs in Dermatology: JDD*. 11(5):609-12, 2012.
59. Tong D, Manolios N, Howe G, Spencer D. New onset sarcoid-like granulomatosis developing during anti-TNF therapy: an under-recognised complication. *Internal Medicine Journal*. 42(1):89-94, 2012.
60. Philips MA, Lynch J, Azmi FH. Ulcerative cutaneous sarcoidosis responding to adalimumab. *Journal of the American Academy of Dermatology*. 53(5):917, 2005.
61. Erckens RJ, Mostard RL, Wijnen PA, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Archive for Clinical & Experimental Ophthalmology*. 250(5):713-20, 2012.
62. Marnane M, Lynch T, Scott J, Stack J, Kelly PJ. Steroid-unresponsive neurosarcoidosis successfully treated with adalimumab. *Journal of Neurology*. 256(1):139-40, 2009.
63. Seve P, Varron L, Broussolle C, Denis P, Kodjikian L. Sarcoid-related uveitis occurring during adalimumab therapy. *Ocular Immunology & Inflammation*. 20(1):59-60, 2012.
64. Marcella S, Welsh B, Foley P. Development of sarcoidosis during adalimumab therapy for chronic plaque psoriasis. *Australasian Journal of Dermatology*. 52(3):e8-11, 2011.
65. Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. *Respiration*. 83(3):218-24, 2012.
66. Sodhi M, Pearson K, White ES, Culver DA. Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis. *Respiratory Medicine*. 103(2):268-73, 2009.

67. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. *Respiration*. 80(3):212-9, 2010.
68. Katz JM, Bruno MK, Winterkorn JM, Nealon N. The pathogenesis and treatment of optic disc swelling in neurosarcoidosis: a unique therapeutic response to infliximab. *Archives of Neurology*. 60(3):426-30, 2003.
69. Refractory neurosarcoidosis: a dramatic response to infliximab. Carter JD, Valeriano J, Vasey FB, Bognar B. *American Journal of Medicine*. 117(4):277-9, 2004.
70. Salama B, Gicquel JJ, Lenoble P, Dighiero PL. Optic neuropathy in refractory neurosarcoidosis treated with TNF-alpha antagonist. *Canadian Journal of Ophthalmology*. 41(6):766-8, 2006.
71. Santos E, Shaunak S, Renowden S, Scolding NJ. Treatment of refractory neurosarcoidosis with Infliximab. *Journal of Neurology, Neurosurgery & Psychiatry*. 81(3):241-6, 2010.
72. Pereira J, Anderson NE, McAuley D, Bergin P, Kilfoyle D, Fink J. Medically refractory neurosarcoidosis treated with infliximab. *Internal Medicine Journal*. 41(4):354-7, 2011.
73. Sturfelt G, Christensson B, Bynke G, Saxne T. Neurosarcoidosis in a patient with rheumatoid arthritis during treatment with infliximab. *Journal of Rheumatology*. 34(11):2313-4, 2007.
74. Gottenberg J, Guillevin L, Lambotte O, et al. Tolerance and short-term efficacy of rituximab in 43 patients with systemic autoimmune diseases. *Ann Rheum Dis*;64:913-920, 2005.
75. Bompreszi R, Pati S, Chansakul C, Vollmer T. A case of neurosarcoidosis successfully treated with rituximab. *Neurology*. 75(6):568-70, 2010.
76. Tikoo RK, Kupersmith MJ, Finlay JL. Treatment of refractory neurosarcoidosis with cladribine. *New England Journal of Medicine*. 350(17):1798-9, 2004.
77. Korber M, Kamp S, Kothe H, Braun J, Dalhoff K. Pentoxifylline inhibits secretion of O2- and TNF-alpha by alveolar macrophages in patients with sarcoidosis. *Immunitat und Infektion*. 23(3):107-10, 1995.
78. Zabel P, Entzian P, Dalhoff K, Schlaak M. Pentoxifylline in treatment of sarcoidosis. *American Journal of Respiratory & Critical Care Medicine*. 155(5):1665-9, 1997.
79. Baughman RP, Judson MA, Ingledue R, Craft NL, Lower EE. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. *Archives of Dermatology*. 148(2):262-4, 2012.
80. Carlesimo M, Giustini S, Rossi A, Bonaccorsi P, Calvieri S. Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. *Journal of the American Academy of Dermatology*. 32(5 Pt 2):866-9, 1995.
81. Baughman RP, Judson MA, Teirstein AS, Moller DR, Lower EE. Thalidomide for chronic sarcoidosis. *Chest*. 122(1):227-32, 2002.
82. Estines O, Revuz J, Wolkenstein P, Bressieux JM, Roujeau JC, Cosnes A. Sarcoidosis: thalidomide treatment in ten patients. *Annales de Dermatologie et de Venereologie*. 128(5):611-3, 2001.
83. Frohman, LP- Federal Drug Administration, Compassionate Use of Thalidomide for Neurosarcoid (Celgene), 1998, IND 55,321.
84. Hammond ER, Kaplin AI, Kerr DA. Thalidomide for acute treatment of neurosarcoidosis. *Spinal Cord*. 45:802-803, 2007.
85. Hoyle JC, Newton HB, Katz S. Prognosis of refractory neurosarcoidosis altered by thalidomide: a case report. *J Med Case Rep*.; 2:27, 2008.
86. Yasui K, Yashiro M, Tsuge M, Manki A, Takemoto K, Yamamoto M, Morishima T. Thalidomide dramatically improves the symptoms of early-onset sarcoidosis/Blau syndrome: its possible action and mechanism. *Arthritis & Rheumatism*. 62(1):250-7, 2010.
87. Heaney D, Geddes JF, Nagendren K, Swash M. Sarcoid polyneuropathy responsive to intravenous immunoglobulin. *Muscle & Nerve*. 29(3):447-50, 2004.
88. Bachelez H, Senet P, Cadranet J, Kaoukhov A, and Dubertret L. The use of tetracyclines for the treatment of sarcoidosis. *Arch Dermatol*, 137: 69-73, 2001.
89. Park DJ, Woog JJ, Pulido JS, Cameron JD. Minocycline for the treatment of ocular and ocular adnexal sarcoidosis. *Archives of Ophthalmology*. 125(5):705-9, 2007.
90. Miyazaki E, Ando M, Fukami T, Nureki S, Eishi Y, Kumamoto T. Minocycline for the treatment of sarcoidosis: is the mechanism of action immunomodulating or antimicrobial effect?. *Clinical Rheumatology*. 27(9):1195-7, 2008.
91. Marshall TG, Marshall FE. Sarcoidosis succumbs to antibiotics—implications for autoimmune disease. *Autoimmunity Reviews*. 3(4):295-300, 2004.
92. Guilpain P, Andreu MA, Cassoux N, Le Thi Huong-Boutin D, Jaeger-Bizet F, Nasica X, Chapelon-Abrie C, Wechsler B, Lehoang P, Piette JC. *Revue de Medecine Interne*. 25(10):755-8, 2004.
93. Lama P and Frohman L. Annual review of systemic disease—1997—II. *Journal of Neuro-Ophthalmology*. 18(2):127-42, 1998.
94. Moravan M and Segal BM. Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil. *Neurology*. 72(4):337-40, 2009.
95. Gelwan Mark J, Kellen Rodney, Burde Ronald M., and Kupersmith, Mark J. Sarcoidosis of the anterior visual pathway: successes and failures. *Journal of Neurology, Neurosurgery, and Psychiatry*. 51:1473-1480, 1988.
96. Motta M, Alongi F, Bolognesi A, et al. Remission of refractory neurosarcoidosis treated with brain radiotherapy: a case report and a literature review. *Neurologist*. 14:120-124, 2008.
97. Ahmad K, Kim YH, Spitzer AR, Gupta A, Han IH, Herskovic A, Sakr WA. Total nodal radiation in progressive sarcoidosis. Case report.. *American Journal of Clinical Oncology*. 15(4):311-3, 1992.
98. Stelzer KJ, Thomas CR Jr, Berger MS, Spence AM, Shaw CM, Griffin TW. Radiation therapy for sarcoid of the thalamus/posterior third ventricle: case report. *Neurosurgery*. 36(6):1188-91, 1995.
99. Bruns F, Pruemer B, Haverkamp U, Fischebeck AR. Neurosarcoidosis: an unusual indication for radiotherapy. *British Journal of Radiology*. 77(921):777-9, 2004.
100. Baughman RP, Weiss KL, Golnik KC. Neuro-ophthalmic sarcoidosis. *Eye and Brain*. 4:13-25, 2012.
101. Berger, Joseph R. Progressive Multifocal Leukoencephalopathy and Newer Biological Agents. *Drug Saf*. 33(11) 969-983, 2010.

TREATMENT OF NEUROMYELITIS OPTICA

Jeffrey L. Bennett, MD, PhD

*University of Colorado Denver
Aurora, CO*

LEARNING OBJECTIVES

1. Enumerate the clinical and laboratory features that distinguish neuromyelitis optica from multiple sclerosis
2. List therapies beneficial for the acute and chronic treatment of neuromyelitis optica
3. Elaborate on novel treatment strategies for neuromyelitis optica

CME QUESTIONS

1. Clinical feature that may distinguish optic neuritis due to neuromyelitis optica include all of the following except:
 - a. Severe depression of the visual field
 - b. Involvement of the optic chiasm on MRI
 - c. Optic disc edema
 - d. Increased post-inflammatory optic atrophy
2. Treatment of optic neuritis in neuromyelitis optica may be optimized by the combination of the following agents:
 - a. Intravenous methylprednisolone and intravenous immunoglobulin
 - b. Plasma exchange and intravenous immunoglobulin
 - c. Intravenous methylprednisolone and rituximab
 - d. Intravenous methylprednisolone and plasma exchange
3. Potential future treatment strategies in NMO include all of the following except:
 - a. Inhibit IL-17 signaling
 - b. Inhibit TNF- α signaling
 - c. Block aquaporin-4 autoantibody binding
 - d. Block IL-6 signaling

KEYWORDS

1. Neuromyelitis Optica
2. Optic Neuritis
3. Plasma Exchange
4. Aquaporin-4
5. Complement-Mediated Cytotoxicity

INTRODUCTION

Neuromyelitis optica (NMO) is an inflammatory disorder of the central nervous system (CNS) that primarily affects the optic nerves and spinal cord. Recent research has indicated that NMO is a distinct disorder from multiple sclerosis, where CNS injury is driven by an autoimmune antibody response against aquaporin-4 (AQP4) localized on astrocyte foot processes. Due to significant risk for permanent neurologic impairment, rapid diagnosis and appropriate therapy are essential. This presentation will examine current treatment paradigms in NMO and address novel directions for future therapy.

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system (CNS) that commonly presents with optic neuritis or transverse myelitis.¹ Initially considered a variant of multiple sclerosis (MS), NMO is now clearly recognized to be a separate disorder with distinct clinical, radiographic, pathologic and serologic characteristics. Since chronic treatment of NMO and MS are mutually exclusive, accurate diagnosis is imperative. Within five years of diagnosis, more than 50% of NMO patients develop severe visual impairment;²⁻⁴ therefore, for the neuro-ophthalmologist, early diagnosis and aggressive treatment of NMO-related optic neuritis is critical for the preservation of visual function.

NMO: AN AUTOIMMUNE RESPONSE AGAINST ASTROCYTES

NMO is specifically associated with an immune response against aquaporin-4 (AQP4), a water-selective channel expressed on the foot processes of CNS astrocytes.^{5,6} Approximately 70% of affected individuals produce serum autoantibodies (NMO-IgG) against AQP4 (AQP4-IgG).⁷ Clinical, histological, animal, and slice culture data have provided evidence that NMO-IgG is pathogenic. AQP4 autoantibodies are not observed in other disorders and correlate with disease activity.^{8,9} Therapies designed to reduce humoral immune activity (B cell depletion and plasma exchange) ameliorate disease.^{10,11} CNS NMO lesions demonstrate early astrocyte loss, perivascular deposition of IgG and activated complement, and secondary myelinolysis.^{12,13} This NMO-specific pathology can be reproduced in animal models and slice cultures using patient sera or patient-derived, recombinant AQP4 antibodies.¹⁴⁻¹⁷ It is thought that NMO-IgG binding to CNS AQP4 initiates complement activation and cell-

mediated astrocyte destruction, immune cell recruitment, inflammatory cytokine release, myelinolysis, and neuronal injury (Figure 1).

NMO: DIAGNOSIS

Modern criteria for the diagnosis of NMO require a clinical history of optic neuritis and transverse myelitis accompanied by at least two of three supportive criteria (brain MRI not diagnostic of MS; spinal MRI with contiguous lesion ≥ 3 segments; AQP4-IgG seropositivity).¹⁸ In NMO, the clinical presentations of optic neuritis and transverse myelitis may be simultaneous or sequential, although the frequency of AQP4-IgG seropositivity is significantly lower in individuals with simultaneous onset.¹⁹ AQP4-IgG seropositive patients with limited (isolated optic neuritis, longitudinally extensive transverse myelitis, recurrent optic neuritis or transverse myelitis) or atypical (protracted nausea and vomiting, brainstem presentations, encephalopathy) presentations are termed NMO spectrum disease.^{1,20} Given the relatively high risk for clinical relapse²¹ and disability^{22,23} in AQP4-IgG seropositive individuals, prompt treatment is recommended for NMO spectrum disorders.

The prevalence of NMO varies considerably across studies (3–57 per million population).²⁴ In North America, Australia, and Europe, NMO patients represent a small fraction (1–2%) of Caucasians with inflammatory white matter disease; however, in Asia and the West Indies, the percentage rises to almost 50% in some regions.¹ Features of optic neuritis that should prompt consideration for testing for NMO-IgG include severe vision loss ($< 20/200$), severe visual field depression, poor visual recovery, posterior nerve involvement, or involvement of the optic chiasm.^{25–27} Additional consideration should also be given to individuals with a significant extent of anterior visual pathway injury²⁸ or severe and diffuse RNFL loss in the peripapillary region.^{29–31} The presence of a longitudinally extensive spinal cord lesion in a patient with transverse myelitis should always prompt serologic testing for NMO-IgG. Due to rare reported cases of AQP4-IgG restricted to the cerebrospinal fluid (CSF),³² in instances of high clinical suspicion and a negative serum AQP4-IgG titer, AQP4-IgG testing should also be performed on CSF. Additional CSF findings suggestive of NMO include a pleocytosis greater than 50 cells/ml, a high percentage of polymorphonuclear cells, or the presence of eosinophils.³³ The presence of oligoclonal bands should raise concern for MS.

NMO TREATMENT

The treatment of NMO encompasses both the management of acute attacks and the prevention of future exacerbations. The goal of acute therapy is to minimize irreversible damage and accelerate recovery. The goal of preventative therapy is to lower the frequency and severity of future exacerbations. Since disease progression is uncommon outside of clinical relapse in NMO, the prevention of future exacerbations should prevent progression of disability in affected individuals.³⁴

The treatment of acute optic neuritis or transverse myelitis associated with NMO is similar to that administered for other acute inflammatory demyelinating injuries: intravenous methylprednisolone (IVMP) and plasma exchange (PLEX). IVMP is generally administered at a daily dose of 1000 mg for 3–5 days. The role of a steroid taper (prednisone, methylprednisolone, or dexamethasone) has not been investigated. Nonetheless, many practitioners will taper steroid treatment over several months when recovery is incomplete or to bridge the interval between the exacerbation and the onset of preventative therapy. Similar to that observed in the treatment of severe demyelinating attacks,³⁵ PLEX has shown significant benefit in the treatment of both optic neuritis and transverse myelitis associated with NMO.^{11,36,37} Typically, five cycles are administered daily or every other day. PLEX may be administered concurrently with IVMP or delivered in cases that fail to respond to IVMP alone. Since published series have failed to define clinical or temporal criteria for response to IVMP, the institution of PLEX is left to the clinician's judgment. A recent study comparing IVMP to IVMP+PLEX in cases of optic neuritis associated with NMO demonstrated significant improvements in high contrast acuity, visual fields, and temporal RNFL thickness with the institution of PLEX.³⁸ Interestingly, low contrast letter scores (Sloan 0.25%) and color vision (Farnsworth-Munsell 100 Hue) did not show improvement. The study was not designed to investigate the timing of PLEX institution; however, the results suggest that the lack of rapid visual improvement following IVMP therapy for NMO acute optic neuritis should prompt rapid initiation of PLEX. A similar study in NMO-mediated transverse myelitis has shown an increased rate of improvement and a lower residual disability in AQP4-IgG seropositive and seronegative NMO patients.³⁷ Although PLEX appears beneficial for the treatment of acute NMO exacerbations, there are no reports of efficacious treatment of acute NMO relapses with intravenous immunoglobulin (IVIG). Given the failure of IVIG to improve the outcome of steroid resistant idiopathic optic neuritis,^{39,40} the substitution of IVIG for PLEX in cases of optic neuritis associated with NMO is not recommended. For acute exacerbations resistant to IVMP and PLEX, clinical response has been reported with the use of intravenous cyclophosphamide in cases of idiopathic transverse myelitis.⁴¹ Interestingly, a recent case series has reported lack of efficacy in the preventative use of pulse cyclophosphamide in NMO.⁴²

There are no prospective trials that have evaluated the efficacy of treatments for preventative therapy in NMO. As a result, the selection of a preventative therapy must balance the best available retrospective data on clinical efficacy with established short- and long-term side effects and risks. In addition, consideration should be given to factors such as age, sex, comorbid conditions, functional status, and response to prior therapies. Predictors of a higher risk of visual disability in NMO patients include male gender, Afro-Caribbean ethnicity, young age at onset, and optic neuritis at initial presentation; whereas, predictors of motor disability are older age at onset and Asian ethnicity.⁴³ Since several

studies have reported poor efficacy or worsening disease following treatment with approved MS therapies such as beta-interferon,^{44–46} natalizumab,^{47, 48} and fingolimod,⁴⁹ it is important that these medications be avoided for NMO preventative therapy and that a diagnosis of NMO is excluded in atypical cases of demyelinating disease.

There is data in the literature supporting the utility of azathioprine, mycophenolate mofetil, methotrexate, rituximab, prednisone, and mitoxantrone for the off-label treatment of NMO.^{10, 50–59} Due to the rare incidence of NMO, the studies are hampered by limited enrolment, short duration, and retrospective design. The mechanism, efficacy, and side effects for each medication are reviewed in Table 1. Routine infusion of IVIG has recently been shown to be safe and effective in a small cohort of NMO and NMO spectrum patients.⁶⁰ If confirmed, IVIG infusion may be an alternative immunomodulatory therapy for disease prevention.

Novel therapies for NMO have been proposed that target specific components and processes involved in disease pathogenesis (see asterisks, Figure 1). These include agents to modulate the pathologic immune response, block AQP4-IgG binding, and inhibit the downstream consequences of antibody effector function. Improved understanding of NMO immune pathology has highlighted the potential involvement of the Th17 pathway in immune activation.⁶¹ Additional investigations have indicated that AQP4-specific, IL-6 responsive peripheral blood plasmablasts may be a disease relevant target.⁶² The use of biologic therapies such as an IL-6 receptor inhibitor, an anti-IL-17 monoclonal antibody (mAb), or and anti-CD19 mAb may warrant consideration. Indeed, a single NMO patient treated with 6 monthly infusions of the anti-IL-6 receptor mAb, tocilizumab, had only a single minor relapse following failure of azathioprine treatment.⁶³

Because binding of AQP4-IgG to astrocyte foot processes is likely the initiating event in NMO pathogenesis, competitive inhibitors of pathogenic antibody binding offer a unique non-immunosuppressive strategy for preventative therapy. We have collaborated on two strategies to inhibit AQP4-IgG binding to CNS targets. The first is a non-pathogenic antibody engineered from a recombinant monoclonal NMO antibody derived from a clonally expanded plasmablast isolated from the CSF of an NMO patient (aquaporumab). The second is a small molecule drug identified through high-throughput screening of inhibitors of AQP4-IgG binding. In proof-of-concept studies, we have shown that both aquaporumab and small-molecule

inhibitors prevent binding of AQP4-IgG to target cells and substantially diminished disease pathology.^{64, 65} The challenge in employing blocker treatment will be to maintain therapeutic concentrations in the CNS to inhibit AQP4-IgG binding.

Additional therapeutic approaches have been suggested to block the consequences of AQP4-IgG mediated effector function (Figure 1). The deposition of activated complement is a major feature of NMO lesions.¹² Complement consumption is increased in NMO patients,⁶⁶ and the level of complement activation by AQP4-IgG is increased in NMO patients with severe attacks.⁶⁷ An open-label trial (NCT00904826) of the complement inhibitor eculizumab in refractory neuromyelitis optica has recently been completed, and the results are due to be released. The high cost (US\$400000 per patient per year) of the drug and risk of meningococcal meningitis may limit its routine use in NMO. Neutrophils and eosinophils are a significant component of the inflammatory infiltrate in NMO lesions.¹² Through antibody dependent cell-mediated cytotoxicity, these granulocytes may contribute to local CNS injury through phagocytosis or release of toxic mediators. Neutrophils and purified neutrophil elastase exacerbate NMO lesions in both an animal model⁶⁸ and ex-vivo spinal cord model.¹⁷ Sivelestat, a potent neutrophil elastase inhibitor, reduced lesion formation in the animal and tissue models and may be useful as a corticosteroid-sparing agent to treat acute NMO exacerbations.

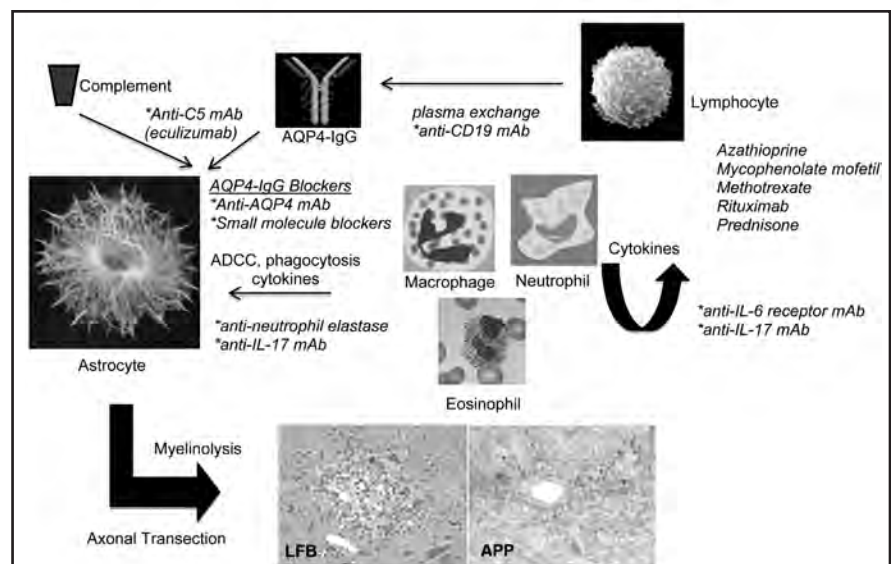


Figure 1. NMO Pathogenesis and Therapeutic Targets. T and B cells interact in lymph node germinal centers to produce AQP4-specific memory B cells and migratory plasmablasts. AQP4-IgG, produced by plasmablasts and tissue resident plasma cells, gains access to the CNS and binds to AQP4 on astrocyte foot processes activating complement and resulting in deposition of membrane attack complexes. Cytokines, such as IL-17 and GM-CSF, recruit neutrophils, macrophages, and eosinophils resulting in antibody dependent cell-mediated cytotoxicity (ADCC) and phagocytosis, furthering astrocyte injury. Astrocyte destruction leads to oligodendrocyte myelinolysis and axonal degeneration. Current NMO therapies are displayed in italics. Theoretical or developmental treatments are asterisked.

Table 1. Preventative Therapies for Treatment of NMO

Drug	Mechanism	Side Effects	Efficacy	References
Azathioprine	inhibits de novo purine synthesis; limits B and T cell proliferation	nausea, hepatotoxicity, leukopenia, diarrhea, hair loss, bone marrow suppression, fatigue; check thiopurine methyltransferase activity to avoid drug toxicity	Reduced ARR On therapy: 0.4–0.52 Reduced EDSS	50–52
Mycophenolate	hinders de novo synthesis of guanosine nucleotides; limits B and T cell proliferation	leukopenia, headache, hair loss, diarrhea, skin malignancy, lymphoma, PML	Reduced ARR On therapy: 0.2 Reduced EDSS	53
Methotrexate	inhibitor of dihydrofolate reductase and purine and thymidine synthesis	leukopenia, stomatitis, nausea, infection	Reduced or stable EDSS	54
Rituximab	anti-CD20 mAb that depletes B cells from pre-B through memory lineages	infusion reactions, infections, PML	Reduced ARR On therapy: 0–0.3 Reduced EDSS	52, 55–56
Corticosteroids	binds to glucocorticoid receptor, induce gene expression, and modulate immune function	insomnia, mood changes, weight gain, glaucoma, osteoporosis, diabetes, hypertension, and growth impairment in children	Reduced ARR On therapy: 0.49	57
Mitoxantrone	intercalates DNA and inhibits topoisomerase, limits B and T cell proliferation	cardiotoxicity, leukemia, hepatotoxicity, leukopenia	Reduced ARR On therapy: 0.7 Reduced EDSS	58–59

Abbreviations: ARR—annualized relapse rate; EDSS—expanded disability status scale; PML—progressive multifocal leukoencephalopathy; mAb—monoclonal antibody.

CME ANSWERS

- c
- d
- b

REFERENCES

- Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. *Lancet neurology* 2007;6:805–815.
- Bizzoco E, Lolli F, Repice AM, et al. Prevalence of neuromyelitis optica spectrum disorder and phenotype distribution. *J Neurol* 2009;256:1891–1898.
- Collongues N, Marignier R, Zéphir H, et al. Neuromyelitis optica in France: a multicenter study of 125 patients. *Neurology* 2010;74:736–742.
- Merle H, Olindo S, Bonnan M, et al. Natural history of the visual impairment of relapsing neuromyelitis optica. *Ophthalmology* 2007;114:810–815.
- Lennon VA, Kryzer TJ, Pittock SJ, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 2005;202:473–477.
- Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;364:2106–2112.
- Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology* 2012;78:665–671.
- Kalluri SR, Illes Z, Srivastava R, et al. Quantification and functional characterization of antibodies to native aquaporin 4 in neuromyelitis optica. *Arch Neurol* 2010;67:1201–1208.
- Lennon V, Wingerchuk D, Kryzer T, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004;364:2106–2112.
- Cree BA, Lamb S, Morgan K, et al. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* 2005;64:1270–1272.
- Watanabe S, Nakashima I, Misu T, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. *Mult Scler* 2007;13:128–132.
- Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* 2002;125:1450–1461.
- Parratt JDE, Prineas JW. Neuromyelitis optica: a demyelinating disease characterized by acute destruction and regeneration of perivascular astrocytes. *Mult Scler* 2010;16:1156–1172.
- Bennett J, Lam C, Kalluri S, et al. Intrathecal pathogenic anti-aquaporin-4 antibodies in early neuromyelitis optica. *Ann Neurol* 2009;66:617–629.

15. Bradl M, Misu T, Takahashi T, et al. Neuromyelitis optica: pathogenicity of patient immunoglobulin in vivo. *Ann Neurol* 2009;66:630–643.
16. Saadoun S, Waters P, Bell BA, et al. Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. *Brain* 2010;133:349–361.
17. Zhang H, Bennett JL, Verkman AS. Ex vivo spinal cord slice model of neuromyelitis optica reveals novel immunopathogenic mechanisms. *Ann Neurol* 2011;70:943–954.
18. Wingerchuk D, Lennon V, Pittock S, et al. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485–1489.
19. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients. *J Neuroinflammation* 2012;9:14.
20. Takahashi T, Miyazawa I, Misu T, et al. Intractable hiccup and nausea in neuromyelitis optica with anti-aquaporin-4 antibody: a herald of acute exacerbations. *J Neurol Neurosurg Psychiatr* 2008;79:1075–1078.
21. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 2006;59:566–569.
22. Akman-Demir G, Tuzun E, Waters P, et al. Prognostic implications of aquaporin-4 antibody status in neuromyelitis optica patients. *J Neurol* 2011;258:464–470.
23. Jarius S, Frederikson J, Waters P, et al. Frequency and prognostic impact of antibodies to aquaporin-4 in patients with optic neuritis. *J Neurol Sci* 2010;298:158–162.
24. Cossburn M, Tackley G, Baker K, et al. The prevalence of neuromyelitis optica in South East Wales. *Eur J Neurol* 2012;19:655–659.
25. Fernandes DB, Ramos Rde I, Falcochio C, et al. Comparison of visual acuity and automated perimetry findings in patients with neuromyelitis optica or multiple sclerosis after single or multiple attacks of optic neuritis. *J Neuroophthalmol* 2012;32:102–106.
26. Khanna S, Sharma A, Huecker J, et al. Magnetic resonance imaging of optic neuritis in patients with neuromyelitis optica versus multiple sclerosis. *J Neuroophthalmol* 2012;32:216–220.
27. Costa C, Arrambide G, Tintore M, et al. Value of NMO-IgG determination at the time of presentation as CIS. *Neurology* 2012;78:1608–1611.
28. Storoni M, Davagnanam I, Radon M, Plant G. The use of magnetic resonance imaging to distinguish between NMO spectrum and MS related optic neuritis based on the appearance of the visual pathways. North American Neuro-Ophthalmologic Society Meeting Abstract 2012
29. Green AJ, Cree BAC. Distinctive retinal nerve fibre layer and vascular changes in neuromyelitis optica following optic neuritis. *J Neurol Neurosurg Psychiatr* 2009;80:1002–1005.
30. Naismith RT, Tutlam NT, Xu J, et al. Optical coherence tomography differs in neuromyelitis optica compared with multiple sclerosis. *Neurology* 2009;72:1077–1082.
31. Ratchford JN, Quigg ME, Conger A, et al. Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies. *Neurology* 2009;73:302–308.
32. Klawiter EC, Alvarez E, Xu J, et al. NMO-IgG detected in CSF in seronegative neuromyelitis optica. *Neurology* 2009;72:1101–1103.
33. Jarius S, Paul F, Franciotta D, et al. Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: results from 211 lumbar punctures. *J Neurol Sci* 2011;306:82–90.
34. Wingerchuk DM, Pittock SJ, Lucchinetti CF, et al. A secondary progressive clinical course is uncommon in neuromyelitis optica. *Neurology* 2007;68:603–605.
35. Keegan M, Pineda AA, McClelland RL, et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology* 2002;58:143–146.
36. Bonnan M, Cabre P. Plasma exchange in severe attacks of neuromyelitis optica. *Mult Scler Int* 2012;2012:1–9.
37. Bonnan M, Valentino R, Olindo S, et al. Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. *Mult Scler* 2009;15:487–492.
38. Merle H, Olindo S, Jeannin S, et al. Treatment of optic neuritis by plasma exchange (add-on) in neuromyelitis optica. *Arch Ophthalmol* 2012;130:858–862.
39. Roed HG, Langkilde A, Sellebjerg F, et al. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. *Neurology* 2005;64:804–810.
40. Noseworthy JH, O'Brien PC, Petterson TM, et al. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* 2001;56:1514–1522.
41. Greenberg BM, Thomas KP, Krishnan C, et al. Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. *Neurology* 2007;68:1614–1617.
42. Bichuetti DB, Oliveira EM, Boulos Fde C, Gabbai AA. Lack of response to pulse cyclophosphamide in neuromyelitis optica: evaluation of 7 patients. *Arch Neurol* 2012;69:938–939.
43. Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain* 2012;135:1834–1849.
44. Palace J, Leite MI, Nairne A, Vincent A. Interferon Beta treatment in neuromyelitis optica: increase in relapses and aquaporin 4 antibody titers. *Arch Neurol* 2010;67:1016–1017.
45. Papeix C, Vidal J-S, de Seze J, et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. *Mult Scler* 2007;13:256–259.
46. Shimizu J, Hatanaka Y, Hasegawa M, et al. IFNβ-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum. *Neurology* 2010;75:1423–1427.
47. Barnett M, Prineas J, Buckland M, et al. Massive astrocyte destruction in neuromyelitis optica despite natalizumab therapy. *Mult Scler* 2012;18:108–112.
48. Kleiter I, Hellwig K, Berthele A, et al. Failure of natalizumab to prevent relapses in neuromyelitis optica. *Arch Neurol* 2012;69:239–245.
49. Min JH, Kim BJ, Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. *Mult Scler* 2012;18:113–115.
50. Costanzi C, Matiello M, Lucchinetti CF, et al. Azathioprine: Tolerability, efficacy, and predictors of benefit in neuromyelitis optica. *Neurology* 2011;77:659–666.
51. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* 1998;51:1219–1220.
52. McKeon A, Lennon VA, Lotze T, et al. CNS aquaporin-4 autoimmunity in children. *Neurology* 2008;71:93–100.
53. Jacob A, Matiello M, Weinshenker BG, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. *Arch Neurol* 2009;66:1128–1133.
54. Minagar A. Treatment of Devic's disease with methotrexate and prednisone. *Int J MS Care* 2000;2:39–43.
55. Jacob A, Weinshenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol* 2008;65:1443–1448.
56. Kim S-H, Kim W, Li XF, et al. Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years. *Arch Neurol* 2011; 68:1412–1420.

57. Watanabe S, Misu T, Miyazawa I, et al. Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis. *Mult Scler* 2007;13:968–974.
58. Kim S-H, Kim W, Park MS, et al. Efficacy and Safety of Mitoxantrone in Patients With Highly Relapsing Neuromyelitis Optica. *Arch Neurol* 2010; 68:473–479.
59. Weinstock-Guttman B, Ramanathan M, Lincoff N, et al. Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). *Arch Neurol* 2006;63:957–963.
60. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. *Neurologia* 2012;epub ahead of print.
61. Wang HH, Dai YQ, Qiu W, et al. Interleukin-17-secreting T cells in neuromyelitis optica and multiple sclerosis during relapse. *J Clin Neurosci* 2011;18:1313–1317.
62. Chihara N, Aranami T, Sato W, et al. Interleukin 6 signaling promotes anti-aquaporin 4 autoantibody production from plasmablasts in neuromyelitis optica. *Proc Natl Acad Sci U S A* 2011;108:3701–3706.
63. Araki M, Aranami T, Matsuoka T, et al. Clinical improvement in a patient with neuromyelitis optica following therapy with the anti-IL-6 receptor monoclonal antibody tocilizumab. *Mod Rheumatol* 2012;epub ahead of print.
64. Tradtrantip L, Zhang H, Anderson MO, et al. Small-molecule inhibitors of NMO-IgG binding to aquaporin-4 reduce astrocyte cytotoxicity in neuromyelitis optica. *FASEB J* 2012;26:2197–2208.
65. Tradtrantip L, Zhang H, Saadoun S, et al. Anti-aquaporin-4 monoclonal antibody blocker therapy for neuromyelitis optica. *Ann Neurol* 2012;71:314–322.
66. Tüzün E, Kürtüncü M, Türkoğlu R, et al. Enhanced complement consumption in neuromyelitis optica and Behçets disease patients. *J Neuroimmunol* 2011;233:211–215.
67. Hinson SR, McKeon A, Fryer JP, et al. Prediction of neuromyelitis optica attack severity by quantitation of complement-mediated injury to aquaporin-4-expressing cells. *Arch Neurol* 2009;66:1164–1167.
68. Saadoun S, Waters P, MacDonald C, et al. Neutrophil protease inhibition reduces neuromyelitis optica-immunoglobulin G-induced damage in mouse brain. *Ann Neurol* 2012;71:323–333.

SHOULD I RECOMMEND STEM CELL THERAPY TO MY PATIENTS WITH VISION LOSS?

Y. Joyce Liao, M.D. Ph.D.

*Department of Ophthalmology, Stanford University School of Medicine
Stanford, CA*

LEARNING OBJECTIVES

1. List the key issues in stem cell therapy to treat vision loss
2. List the current stem cell clinical trials relevant to neuro-ophthalmic conditions
3. Recount the political and financial issues regarding stem cell research
4. Devise an approach as to what to tell your patients

CME QUESTIONS

1. Which of the following is an obstacle in retinal ganglion cell and optic nerve regeneration?
 - A. The inhibitory effects of CNS myelin and the glial scar
 - B. The absence of appropriate trophic factors
 - C. The immune response to injury, ischemia
 - D. Activation of cell death pathways
 - E. All of the above
2. Which *one* of the following types of stem cells is currently most likely to treat vision loss in patients?
 - A. Induced pluripotent stem cells (iPSCs)
 - B. Stem cell harvested from patient's ciliary epithelium
 - C. Human embryonic stem cells
3. Are there currently stem cell clinical trials offered for treatment of neuro-ophthalmic conditions?
 - A. No
 - B. Yes
4. Which of the following states have major stem cell funding initiatives?
 - A. California
 - B. New Jersey
 - C. New York
 - D. All of the above

KEYWORDS

1. Retinal Ganglion Cells
2. Optic Nerve Regeneration
3. Neuroprotection
4. Cell Replacement
5. Neurotrophic Factors
6. Human Embryonic Stem Cells (hESC)
7. Induced Pluripotent Stem Cells (iPSC)
8. Proposition 71: The California Stem Cell Research and Cures Act
9. International Society for Stem Cell Research (ISSCR)

INTRODUCTION

This review will provide a summary of key issues in optic nerve regeneration and the use of stem cell transplantation to treat vision loss with special emphasis on optic neuropathies. It will also delineate current clinical trials to treat vision loss, political and financial issues regarding stem cell research, and important take-home lessons when discussing the possibility of stem cell therapy with patients.

KEY ISSUES IN OPTIC NEUROPATHY AND REGENERATIVE THERAPY

LIMITATION OF ENDOGENOUS REPAIR MECHANISMS

The axons of the retinal ganglion cells form the optic nerve, which connects the eye and the brain. This pathway is gradually thinned as part of normal aging, and optic nerve atrophy and retinal ganglion cell loss are accelerated in both hereditary and acquired conditions. Retinal ganglion cells can be injured at the level of the cell body, axon, or dendrites. Axonal damage and retrograde degeneration are responsible for the most common types of optic neuropathies including glaucoma, ischemic optic neuropathies, and traumatic optic neuropathy. Damaged axons show transient sprouting following optic nerve injury without long-distance regeneration, and retinal ganglion cells begin to die a few days after their axons are injured. The retinal ganglion cell and its axon

have long been used to study central nervous system regeneration. Many studies have shown that there are endogenous healing mechanisms and capacity for optic nerve regeneration in mammals (Lebrun-Julien, 2008; Dahlmann-Noor, 2010; Fischer, 2012). However, there are many factors limiting optic nerve regeneration, including the inhibitory effects of myelin and the glial scar, absence or inhibition of neurotrophic factors, immune responses to injury, insufficient intrinsic ability for axonal regrowth, and activation of cell death pathways. While inhibition of transcription factors like KLF4 (Moore, 2009), deletion of PTEN or SOCS (Park, 2008; Sun, 2011), or use of multiple manipulations (de Lima, 2012) have been shown to increase optic nerve regeneration in animals, translation of these interesting findings to human therapy is difficult. Endogenous optic nerve regeneration can potentially be enhanced in patients via treatment with exogenous neurotrophic factors (e.g. BDNF, CNTF, GDNF) or peptidomimetic ligands, blocking cell death cues, or inhibition of myelin inhibitory cues (e.g. Nogo receptor).

PURPOSE OF STEM CELL TRANSPLANTATION

The limitation of endogenous repair mechanisms in the mammalian central nervous system means injury and disease typically lead to irreversible neuronal loss and functional impact. This observation has led to the current fervent, international race for regenerative therapy. Stem cells can either provide neurotrophic factors to enhance the survival of the injured retinal neurons (**neuroprotection**) or replace the neurons that are lost (**cell replacement**), although treatment using either approach is difficult in the adult eye. Decades of research have shown that the survival of transplanted cells in the adult central nervous system is possible, and there are ongoing clinical trials testing the safety and possible benefits of regenerative therapy (see below; Tibbetts, 2012; Schmeer, 2012; Ong, 2012; Singh, 2012).

COMPLEXITY OF THE VISUAL PATHWAY AND DISTANT TARGETS

Regenerative therapy to restore vision is complex because of the necessity to reconstruct precise retinotopic representation of the visual space. Binocularity and stereopsis require lining up of the visual field representation in both eyes, although restoration of vision in one eye is sufficient to significantly improve function. Both neuroprotective and cell replacement therapies have to work in an injured environment, which is different from that occurring during development or in the healthy, adult eye, although some types of injury have been associated with greater capability for regeneration and increased efficacy of stem cell transplantation. Also, both therapies are ideally administered soon after injury, prior to trans-synaptic degeneration, when the pre- or post-synaptic neurons may be lost. The majority of research on cell replacement therapy for the posterior segment has focused on photoreceptor or retinal pigment epithelium regeneration. This strong preference is based on the proximity and therefore the greater likelihood

of reconstituting a circuit where the pre- and post-synaptic neurons are nearby. In contrast, the successful establishment of retino-geniculate pathway involves extending axons to targets far away. Because of this distance, successful regeneration requires overcoming another hurdle—the need to myelinate the retinal ganglion cell axons in order to achieve saltatory conduction for efficient signal transduction.

SOURCE OF STEM CELLS FOR VISION RESTORATION

Possible sources of stem cells for vision restoration include three major types: embryonic stem cells, adult stem cells, and induced pluripotent stem cells (Dahlmann-Noor, 2010; Stern, 2011; Boucherie, 2011; Schmeer, 2012). Right now, the most promising source of stem cells for vision restoration is **human embryonic stem cells (hESCs)**, which are **pluripotent**, or capable of generating any type of cells, and derived from cells early in development, specifically blastocysts leftover from infertility treatments that would otherwise be destroyed. Embryonic stem cells are grown and stored in large numbers and can generate many different types of neurons. Embryonic stem cells have been shown to generate all types of retinal neurons and retinal pigment epithelium. Yoshiki Sasai's group from RIKEN, Japan, has even generated three-dimensional eye cup in vitro containing all layers of the retina and retinal pigment epithelium from human embryonic stem cells (Nakano, 2012). Human embryonic stem cell derived precursor cells are the primary type of stem cells being transplanted in current retinal cell replacement trials (see below; Tibbetts, 2012). However, since discovery of the human embryonic stem cells (Thomson, 1998), there have been significant controversies and political debates due to the association with potential destruction of fetuses and abortions (see below).

Human adult stem cells are also promising for treatment of vision and are isolated from adult tissue. Unlike pluripotent stem cells, which are capable of making any kind of cell, adult stem cells can only make limited types of cells related to their origin. The most significant benefit of adult stem cell is the possibility of autologous transplantation, therefore avoiding the use of life-long immunosuppressive medications. Adult retinal stem cells have been found in the human ciliary epithelium (Lebrun-Julien, 2012) and appear to preferentially generate retinal ganglion cells or glia if injected early during retinal development (Canola, 2007). Retinal progenitors isolated at the appropriate developmental time for photoreceptor generation lead to successful generation of photoreceptors in the transplanted adult mouse eye (MacLaren, 2006). Adult stem cells have also been isolated from the corneal limbus and have been successfully transplanted onto the cornea for treatment of severe ocular surface disease (Bayliss, 2011; O'Callaghan, 2011). Because adult retinal stem cells are very rare, the most common sources of adult stem cells are blood, bone marrow, or abdominal fat. Such adult stem cells are routinely used in bone marrow transplantation, which is the most successful type of stem cell transplantation

so far. There are many ongoing clinical trials using autologous mesenchymal or hematopoietic stem cells to treat retinal diseases (see below; Tibbetts, 2012). Although the potential for these cells to generate neurons is questionable, these cells may be a good source of neurotrophic factors to promote retinal neuronal survival.

Induced pluripotent stem cells (iPSCs) are typically derived from fibroblasts grown from a skin biopsy and have been shown to form retinal progenitors (Boucherie, 2011; Schmeer, 2012; Stern, 2011). There is one report of human blood T-cell-derived iPSCs that form optic vesicle-like structure (Phillips, 2012). Since they are not derived from embryos, the iPSCs are not as controversial as embryonic stem cells. The ability to generate iPSCs from patients means there is increased chance of survival after transplantation and relatively decreased risk of rejection. However, treatment of hereditary diseases using iPSCs is limited since the same mutation is also present in the skin fibroblasts. This fact has been advantageous for the biggest use of iPSC so far, which is the generation of an in vitro system to study hereditary diseases. Generation of retinal neurons from iPSCs requires trans-differentiation because the fibroblasts need to be converted to neurons, either by inducing the fibroblasts to de-differentiate first or directly converting them to neurons. This process is more difficult, heterogeneous, and inconsistent compared to the generation of retinal neurons from embryonic stem cells. Because cellular history is important, ideally iPSCs generated to treat retinal diseases should be derived from retinal cells, but human retinal cells are not readily available. iPSCs may have higher rate of mutation and may be more likely to form tumors. Although the potential use of iPSCs in human cell replacement therapy to treat vision loss is not clear, there is reportedly an upcoming clinical trial involving iPSCs in the treatment of retinopathy from Japan.

STEM CELL CLINICAL TRIALS RELEVANT TO NEURO-OPHTHALMOLOGISTS

The world's first clinical trial using human embryonic stem cell (Geron) was for the treatment of spinal cord injury using human embryonic stem cell-derived oligodendrocytes, which received FDA approval in January 2009. The world's first human embryonic stem cell trial for the treatment of vision loss started in 2011 for dry macular degeneration and Stargardt's macular dystrophy (Advanced Cell Technology), and these trials are ongoing. In addition to these trials, many stem cell trials can be found in ClinicalTrials.gov, a website sponsored by the US National Institute of Health that records all important clinical trials in the world. In November 2012, a search of the word "stem cell" yields 4285 hits, of which 392 are relevant to vision, 71 are for treatment of stroke, 39 are related to retinal diseases, and 32 are for treatment of multiple sclerosis. The actual numbers may be smaller since careful examination of the retinal and multiple sclerosis lists yielded smaller numbers of relevant clinical trials (e.g. 17 pending, recruiting, or completed trials for multiple sclerosis). There are currently no clinical trials for the treatment of glaucoma, ischemic optic neuropathies, mitochondrial optic neuropathies, or traumatic optic neuropathy, although there are anecdotal reports of stem cell transplantation for these conditions in the literature.

NEUROMYELITIS OPTICA AND MULTIPLE SCLEROSIS

There are 3 stem cell trials for the treatment of **neuromyelitis optica**. The University of Calgary (NCT01339455, 10 patients) is currently enrolling patients and treating them with autologous hematopoietic stem cells. The primary outcome is proportion relapse-free at three years, and secondary outcome measures include relapse counts at 5 years, disability, optical coherence tomography retinal nerve fiber layer analysis,

Types of Stem Cells	Source	Retinal Neurons Made	Current Use
human embryonic stem cells (hESCs)	human embryos*	retinal ganglion cells photoreceptors retinal pigment epithelium	generation of retinal pigment epithelium and photoreceptor precursors in many clinical trials
human adult stem cells	ciliary epithelium	retinal ganglion cells photoreceptors retinal pigment epithelium	limited due to rarity of adult stem cells
induced pluripotent stem cells (iPSCs)	skin biopsy (blood)	retinal pigment epithelium retinal neural progenitors** photoreceptors**	no current clinical trial but one pending from Japan

*hESCs are derived from embryos that are leftover from infertility treatments that would otherwise be destroyed.

**There are several published reports of photoreceptor and retinal neural progenitors generated from skin-derived iPSCs, but this process is more heterogenous and less consistent compared to generation of retinal neurons from hESCs.

hospitalizations, survival, and other functional measures over 5 years. Northwestern University (NCT00787722, 10 patients) also has a study using autologous hematopoietic stem cell. The Northwestern study uses a 25-foot walk and 9-hole peg test at pre-transplantation, 6 months, 12 months, and then yearly for 5 years as primary outcome measures and quality of life exams as secondary outcome measures. A third study from Shenzhen Beike Bio-Technology (NCT01364246, 20 patients) uses umbilical cord mesenchymal stem cells. The Beike study uses Expanded Disability Status Scale (EDSS) at one year as primary endpoint and secondary outcome measures include MRI, visual evoked potential, brainstem auditory evoked potential, and somatosensory evoked potential.

Most of the stem cell trials for treatment of **multiple sclerosis** also utilize autologous hematopoietic stem cells. There is a completed phase 2 clinical trial from the National Institute of Neurological Disorders and Stroke (NINDS) involving 34 patients from 2002-2011, and there is no result available. A study that is already closed from University of Cambridge recruited 10 patients with multiple sclerosis and treated them with intravenous bone marrow derived mesenchymal stem cells. Primary outcome includes the number of adverse events. Secondary outcome measures include visual acuity, color vision, visual evoked potential, optical coherence tomography, MRI, and functional disability scales. No study results are available. There is an active open label randomized trial sponsored by Northwestern University (NCT00273364, 110 patients) in collaboration with Rush University, University of Sao Paulo, and Uppsala University to recruit 110 patients with multiple sclerosis who failed interferon A therapy. They compare patients treated with autologous hematopoietic stem cells vs. standard therapy with one conventional drug. Their primary endpoint includes Expanded Disability Status Scale (EDSS), and the secondary endpoints include number of relapses, MRI, survival, and functional measures. It has no visual function measures. There are also trials from many institutions including the Cleveland Clinic (24 patients); Northwestern (20 patients, completed); Texas Oncology Cancer Center (50 patients); Fred Hutchinson Cancer Research Center (35 patients); Baylor College of Medicine (10 patients); Ottawa Hospital Research Institute, Ottawa, Canada (24 patients); Imperial College London, England (13 patients); Royan Institute in Tehran, Iran (30 patients); and Instituto de Salud Carlos III from Barcelona, Spain (16 patients).

OUTER RETINAL AND RETINAL CONDITIONS

Of the 19 clinical trials that involve outer retinal or retinal conditions, there are several trials for **dry age-related macular degeneration** (NCT01344993, 12 patients) or **Stargardt's macular dystrophy** (NCT01469832, 12 patients; NCT01345006, 12 patients) sponsored by Advanced Cell Technology using sub-retinal transplantation of human embryonic stem cell-derived retinal pigment epithelial cells. Preliminary report from the very small number of patients at four-months showed no evidence of rejection or tumor

formation. There was subjective improvement of visual acuity and visually guided behavior in some patients (Schwartz, 2012). There is also a trial for dry macular degeneration involving embryonic stem cell-derived retinal pigment epithelial cells from CHA Bio & Diostech (NCT01674829, 12 patients). For treatment of patients with **wet age-related macular degeneration** and recent, rapid vision decline, there is a trial from Pfizer at University College, London (NCT01691261, 10 patients, not yet open) using human embryonic stem cell-derived retinal pigment epithelium. There are trials for **retinitis pigmentosa** from University of Sao Paulo (NCT01560715, 50 patients; NCT01068561 5 patients completed; both with intravitreal injection) and from Mahidol University in Thailand (NCT01531348, 10 patients, intravitreal injection) using autologous bone marrow-derived stem cells. One open label single arm study from University of Sao Paulo (NCT01518842, 30 patients) uses intravitreally injected autologous bone marrow-derived stem cells to treat patients with **ischemic retinopathy** who have best corrected visual acuity worse than 20/200. There are also several trials for autologous bone marrow or hematopoietic stem cell transplantation following chemotherapy for treatment of pediatric solid tumors including **retinoblastoma**.

OTHER IMPORTANT STUDIES INVOLVING STEM CELLS

There is also growing interest to bank patient specimens for research and possible future stem cell therapy. The National Eye Institute has an ongoing study to collect hair, skin, and blood samples from 350 patients with retinal diseases including Best Vitelliform Dystrophy (Best disease), Late-Onset Retinal Degeneration (L-ORD), and Age-Related Macular Degeneration (AMD) (NCT01432847). A group from M.D. Anderson Cancer Center has an ongoing observational trial recruiting patients to donate and store umbilical cord blood for transplantation (NCT01728545). They state that cord blood will be made available to patients through the National Marrow Donor Program (NMDP) for patients from MD Anderson and other institutions that need bone marrow transplantation but do not have a donor according to established bone marrow transplant donor criteria. Japan, South Korea, and other countries also have substantial efforts to bank stem cells (see below). While the US efforts have focused on using banked stem cells for research purposes, Japan aims to bank stem cells for generation of induced pluripotent stem cells for future treatment.

STEM CELL TRANSPLANTATION: A POLITICAL HOT POTATO

Historically, stem cell research in the US was not federally funded due to a ban placed on embryonic research by the 1995 Dickey-Wicker Amendment signed by President Bill Clinton. This amendment prohibits the use of federal funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. The link between human embryonic stem cell research and the fiercely active pro-life vs. pro-choice politics, which has continued despite the 1973 Roe vs. Wade ruling to legalize abortion, set up the stage for political duels regarding stem cell research in the US.

After the first isolation of human embryonic stem cells in 1998 (Thomson, 1998), President George H. W. Bush limited the use of federal funding for human embryonic stem cell research to the existing 78 lines in 2001. However, many approved lines were later found to be contaminated or contain genetic mutations. The only way to overcome this obstacle is to generate more human embryonic cell lines. After the passage of the Stem Cell Research Enhancement Act in the Senate in 2006 in support of stem cell research, President George W. Bush used his presidential veto power in 2006 and 2007 to maintain restrictions on stem cell research.

In March 2009, President Barack Obama issued an executive order overturning a Bush administration policy that for eight years restricted the use of federal funds for human embryonic stem cell research to a limited number of lines created before August 9, 2001. With this, the United States joined over 35 nations permitting research on embryonic stem cells. The executive order also authorized the National Institutes of Health (NIH) to establish new policy and procedures under which federal funds could be used for stem cell research. In July 2009, the NIH issued guidelines that outlined their new policy (stemcells.nih.gov/policy/2009guidelines.htm). These guidelines still limit human embryonic stem cell research, including the creation of stem cell lines using federal funds.

2009 NIH Guidelines on Stem Cell Research
(stemcells.nih.gov/policy/2009guidelines)

“Although hESCs are derived from embryos, such stem cells are not themselves human embryos.... hESCs should have been derived from human embryos:

1. *that were created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose;*
2. *that were donated by individuals who sought reproductive treatment (hereafter referred to as “donor(s)”) and who gave voluntary written consent for the human embryos to be used for research purposes”*

Federal government further clarify the criteria that NIH funding could not be used for certain embryonic stem cell research:

- *Research in which hESCs or iPSCs are introduced into non-human primate blastocysts.*
- *Research involving the breeding of animals where the introduction of hESCs or iPSCs may contribute to the germ line.*
- *NIH funding of the derivation of stem cells from human embryos is prohibited by the annual appropriations ban on funding of human embryo research..., otherwise known as the Dickey Amendment.*
- *Research using hESCs derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not eligible for NIH funding.*

On August 23, 2010, Chief Judge Royce C. Lamberth of Federal District Court for the District of Columbia issued an order blocking all federally funded stem cell research, citing it violated a ban on federal money being used to destroy embryos based on his interpretation of the 1995 Dickey-Wicker Amendment. The unexpected decision not only overturned President Obama’s 2009 Executive Order, it even halted research on lines approved during the Bush administration. In May 2011, a federal appeals panel voted 2 to 1 to overturn Judge Lambert’s ruling, although this was just the beginning of the battle. On August 24, 2012, a three-judge panel of the US Court of Appeals upheld the previous court’s decision, citing that embryonic stem cell research does not involve destruction of human embryos.

This decision occurred following the Texas Medical Board’s controversial ruling in April 2012 that allow any physician to perform stem cell procedures as long as they receive approval from an institutional review board and the patients sign a consent form. The FDA and the International Society for Stem Cell Research did not comment on this ruling, while many believe this means stem cell therapy can be conducted in Texas without the rigorous oversight of the FDA, which is typically required for clinical trials involving investigational treatments.

STEM CELL TRANSPLANTATION: SHOW ME THE MONEY

FEDERAL FUNDING FOR STEM CELL RESEARCH

In the last 8 years, the National Institute of Health has committed millions to more than one billion research dollars annually to support stem cell research.

Derived from www.report.nih.gov/categorical_spending.aspx:

Research/ Disease Areas (in \$ millions)	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012 Estimated	FY 2013 Estimate
Stem Cell Research	\$938	\$1,231	\$1,286	\$1,179	\$1,185	\$1,182

There have been millions of dollars per year allocated to support both human and animal stem cell research, and several fold more dollars have been spent on *non-embryonic* stem cell research.

NIH Stem Cell Research Funding, FY 2002–2011

FY 2002–FY 2011 (Dollars in millions)				
Year	Human Stem Cells		Non-Human Stem Cells	
	Embryonic	Non-Embryonic	Embryonic	Non-Embryonic
2002	\$10.1	\$170.9	\$71.5	\$134.1
2003	\$20.3	\$190.7	\$113.5	\$192.1
2004	\$24.3	\$203.2	\$89.3	\$235.7
2005	\$39.6	\$199.4	\$97.1	\$273.2
2006	\$37.8	\$206.1	\$110.4	\$288.7
2007	\$42.1	\$203.5	\$105.9	\$305.9
2008	\$88.1	\$297.2	\$149.7	\$497.4
2009 (Non-ARRA)	\$119.9	\$339.3	\$148.1	\$550.2
2009 (ARRA)	\$22.7	\$57.9	\$29.1	\$88.1
2010 (Non-ARRA)	\$125.5	\$340.8	\$175.3	\$569.6
2010 (ARRA)	\$39.7	\$73.6	\$19.6	\$74.2
2011	\$123.0	\$394.6	\$164.6	\$619.9

STATE, PRIVATE, AND INTERNATIONAL FUNDING FOR STEM CELL RESEARCH

Following the ban on federal government funds for stem cell research and restriction of federal funding to work on the 20 stem-cell lines derived before August 2001, several states responded by launching campaigns to raise money for stem cell research.

New Jersey

New Jersey was the first state to approve \$9.5 million in January 2004 to fund research on stem cells, including those derived from human embryos. New Jersey is the home to 17 of the world's biggest pharmaceutical companies, so there is every reason to think New Jersey can be a major player in stem cell research. This effort was pioneered by Wise Young, a Stanford and Iowa-educated physician-scientist who started neurosurgery residency but quit after having to tell the parents of a 17-year-old wrestler that their son would never walk again. He then dedicated his time to research on spinal cord injury and was recruited to Rutgers University.

When human embryonic stem cells were described in 1998 (Thomson, 1998), Young saw its potential use to treat spinal cord injury and attracted the support of Christopher Reeve, the former actor who grew up in Princeton, New Jersey. Reeve established the Christopher and Dana Reeve Foundation and became a stem cell advocate after he was paralyzed in a riding accident in 1995. In 2004, Young convinced New Jersey governor James McGreevey (Democrat) to sign a law permitting research using human embryonic stem cells in New Jersey and proposed a \$50 million bond initiative to establish the Stem Cell Institute of New Jersey. The state allocated \$5 million in grants in December 2005 among 17 projects, with only three involving human embryonic stem cells and others studying animals or using adult stem cells. In 2005, Jon Corzine, who was running for governor shortly after Christopher Reeve's death in October 2004, made stem cell research part of his campaign. In December 2006, Corzine signed a bill into law to establish several stem-cell research facilities in New Jersey, and the New Jersey Senate approved a \$350 million bond referendum to fund stem cell research. Overall, there

were estimated capital expenditures of \$270 million for construction and equipping of stem cell research and other biomedical facilities and \$450 million in funds for on-going stem cell research. Interestingly, it was estimated that the stem cell research initiative may have "total economic benefits in New Jersey of almost \$2.2 billion" and result in "the creation of almost 30,000 job-years and will generate over \$115 million in state revenues" (www.policy.rutgers.edu/reports/other/stemcelloct07.pdf). However, in June 2008, the voters rejected a state-wide bond (the New Jersey Stem Cell Research Bond Act) to borrow \$450 million over 10 years to fund stem cell research and build stem cell institutes, thus significantly limiting the development of stem cell research in New Jersey.

California

In November 2004, partly under the leadership of Irv Weissman from Stanford University, the California voters passed **Proposition 71: The California Stem Cell Research and Cures Act** and established the California Institute for Regenerative Medicine (CIRM). The statewide ballot measure authorized \$3 billion in funding on embryonic stem cell research over 10 years at California universities and research institutes. This amount dwarfed what was approved in New Jersey, and encouraged many states to campaign for stem cell research. The proposition called for the establishment of an entity to make grants and provide loans for stem cell research, research facilities, and other vital research opportunities.

Because CIRM is established with tax-payer money, there is inherently more transparency, and the institutions that are supported by the fund as of October 2012, are found at www.cirm.ca.gov/InstitutionList:

Institution	# Awards	Total Amount
Stanford University	80	\$260,859,319
University of California, Los Angeles	57	\$182,566,320
University of California, San Francisco	48	\$131,731,435
University of California, San Diego	58	\$128,995,744
University of California, Davis	35	\$127,785,894
University of California, Irvine	30	\$99,146,156
University of Southern California	24	\$84,650,713
University of California, Berkeley	19	\$53,635,290
Beckman Research Institute Of The City Of Hope	20	\$51,136,965
The Scripps Research Institute	18	\$49,577,333
Sanford Consortium for Regenerative Medicine	4	\$43,120,000
StemCells, Inc.	3	\$40,098,050
The J. David Gladstone Institutes	19	\$39,129,263
Buck Institute for Research on Aging	8	\$37,923,863
Sanford-Burnham Medical Research Institute	20	\$37,049,856
The Salk Institute for Biological Studies	16	\$35,981,679
Cedars-Sinai Medical Center	11	\$30,668,770
ViaCyte, Inc.	4	\$26,281,356
University of California, Santa Cruz	9	\$22,673,248
Children's Hospital of Los Angeles	8	\$21,532,437
Capricor, Inc	1	\$19,782,136
University of California, Santa Barbara	8	\$15,880,455
The Parkinson's Institute	4	\$13,231,042
Viacyte Inc	1	\$10,075,070
Bluebird Bio	1	\$9,363,335
University of California, Merced	5	\$8,494,301
iPierian, Inc.	2	\$7,123,887
University of California, Riverside	4	\$6,918,642
Children's Hospital of Orange County	2	\$5,510,764
San Diego State University	2	\$5,323,007
BioTime, Inc.	1	\$4,721,706
The Jackson Laboratory West	1	\$3,841,240
San Jose State University	1	\$3,614,907
California State University, Channel Islands	1	\$3,614,553
California State University, San Marcos	1	\$3,613,311
Pasadena City College	1	\$3,609,138
San Francisco State University	1	\$3,594,705
Humboldt State University	1	\$3,497,510
California State University, Northridge	1	\$3,382,877
Scripps Health	1	\$3,118,431
California State University, Long Beach	1	\$3,042,698
California Polytechnic State University, San Luis Obispo	1	\$3,020,182
California State Polytechnic University, Pomona	1	\$3,008,975

California State University, Sacramento	1	\$2,773,463
California State University, Fullerton	1	\$2,710,703
Fluidigm Corporation	2	\$2,693,424
California State University, San Bernardino	1	\$2,607,705
Gamma Medica-Ideas, Inc.	2	\$2,478,347
Ludwig Institute for Cancer Research	3	\$2,473,053
City College Of San Francisco	1	\$2,454,307
Berkeley City College	1	\$2,450,257
Palo Alto Institute for Research and Education, Inc.	2	\$2,408,275
California Institute of Technology	2	\$2,368,580
(grants < \$2 million dollars omitted from this list)		
Grand Total	568	\$1,684,919,302

Texas

Through the activity of Celltex, a company that opened in December 2011 and houses the largest stem cell bank in the US, stem cell transplantation appears to be taking place in Texas for a variety of conditions including multiple sclerosis and Parkinson's disease. The stem cells from Celltex are harvested based on technology licensed from RNL Bio in Seoul, South Korea. Stem cells are harvested from about five grams of fat from the patient's abdomen and grown in vitro for three weeks. The stem cells are injected over at least 3 injections at \$7,000 per 200 million mesenchymal cells each and \$500 per injection. Although the company states it only banks and processes stem cells, there was a well publicized stem cell treatment of Texas governor Rick Perry for back pain (also see "Stem Cell Therapy: a Political Hot Potato"). Reportedly, at least one other patient received stem cell injections since she blogged about them in detail. There is currently no FDA approved trial for Celltex.

New York, Other States, and Private Foundations

Encouraged by the success in California, the state of New York allocated \$600 million for stem cell research and established the New York Stem Cell Foundation (www.nyscf.org). Other states that have proposed money for stem cell research include Connecticut (\$100 million), Illinois (\$10 million), Maryland (\$38 million), Massachusetts (\$1 billion), and Wisconsin (\$750 million).

Interestingly, six states have *criminalized* stem cell research based on opposition to embryonic stem cell research and that personhood begins at the moment of conception. The Michigan-based StemCellResearchCures.com, a right-to-life organization, lists 310 organizations that support human embryonic stem cell research including American Association of Neurology, Ophthalmology, Neurosurgery, and Otolaryngology, and many universities, including Baylor, Boston University, Columbia, Cornell, Harvard, Hopkins, Stanford, University of California, University of Pennsylvania, and many others.

Stem cell research is also supported by many private enterprises including Eli and Edythe Broad Foundation, which awarded 25 million dollars to UCSF in 2008. The Bedford Stem Cell Research Foundation based in Massachusetts openly solicits donations to reach a goal of \$560,000 on its website to sponsor stem cell study. It draws analogy of the importance of stem cell research to the development of the polio vaccine using non-federal resources by the Salk Institute in San Diego, CA. The National Stem Cell Foundation is a non-profit organization that has supported adult stem cell research and clinical trials in Northwestern, Duke, and University of Louisville, Kentucky. Its website seeks \$25,000,000 over three years to fund more than 200 patients in FDA approved stem cell clinical trials in the US.

International Efforts

When US implemented restrictions on stem cell research and treatment, this indirectly led to an explosion of stem cell therapies being developed abroad and the beginning of medical tourism for stem cell therapy. According to the Deloitte Center for Health Solutions, approximately 750,000 Americans per year travel abroad for medical care, although the number for those seeking stem cell therapy abroad is unclear. Estimate of cost of stem cell treatment abroad was \$21,500, excluding travel and living expenses.

China

Of all countries, there has been the most activity involving stem cell transplantation in China since 1999. One estimate of the number of stem cell companies based in China is at around 100. Those clinics all claim success in treating patients, but none has published data from controlled clinical trials. Beike Biotechnology has used umbilical cord stem cells to treat over 10,000 patients with many disorders including multiple sclerosis, congenital optic atrophy, cerebellar ataxia, amyotrophic lateral sclerosis, spinal cord injury, muscular dystrophy, autism, and others in over 30 hospitals in China. Beike's website lists links to 8 trials registered with the clinical trials.gov, although Beike has not published the efficacy of its treatments. The Tong Yuan

Stem Cell also claims to have treated more than 10,000 patients. In May 2009, the Chinese Ministry of Health classified stem-cell treatment as a high-risk procedure that requires approval before use. Reportedly, no approval has been granted and, despite increased effort to crack down on illegal human use, many companies openly operate and have websites that are easily accessible for many clinical indications. The stem cells injected include umbilical cord or adipose-tissue-derived mesenchymal cells and cost about \$5000-7000 per injection.

Japan

In August 2012, the Japanese health ministry committee approved the creation and banking of cell lines from thousands of samples of fetal umbilical-cord blood. This effort was led by Kyoto University's Shinya Yamanaka, who showed that mature mouse and human fibroblasts can form induced pluripotent stem cells. This approach can bypass the ethical issues surrounding stem cells derived from embryos and address the increased risk of autoimmune responses in non-autologous transplantation. A key difference between the Japanese approach and that of those outside Japan regarding **induced pluripotent stem cells (iPSC)** is that the Japanese approach aims to use these cells for therapeutic purposes, while most induced pluripotent stem cell banks outside Japan specialize in cells from people with disease in order to facilitate research rather than treatment. The relatively lower genetic diversity in Japan makes the possibility and banking of healthy individuals and the use of induced pluripotent stem cells for therapy more feasible and less expensive. In contrast, the California Institute for Regenerative Medicine (CIRM) aims to bank 3000 cell lines for research. Criticism of the use of induced pluripotent stem cells for therapeutic use includes accumulation of mutations and risk of tumor formation since it involves de-differentiating differentiated cells. *The first human trial using iPSCs to treat retinopathy at the RIKEN Center for Developmental Biology in Kobe is planned for 2013*, and there is also intense research using induced pluripotent stem cells to treat Parkinson's disease in Kyoto University.

Other Countries

Some countries like Korea and Costa Rica ban the use of stem cell treatment but allow banking of stem cells. The Chum Life Center in Seoul, South Korea is the largest stem cell bank in Korea. Since stem cell treatment is illegal in South Korea, more than 10,000 patients have been sent to Japan and China to receive injections. Stem cells are being banked and analyzed with the presumption that stem cell transplantation will be legal soon. Countries like Brazil, India, Russia, and Panama also offer stem cell treatment.

TAKE-HOME MESSAGE AND WHAT TO TELL PATIENTS

The rapid advances in stem cell-based therapy in the last decade have led to growing excitement for treatment of patients with vision loss. There are still substantial challenges to overcome before regenerative therapy can

be effectively and safely restore functional vision. Given the myriad of possibilities around the world, patients are increasingly more likely to consider traveling in order to receive special treatments that are not available locally. The key issue is actually not incompetent physicians or inadequate facilities providing these treatments. The main problem is the potential lack of efficacy, side effects, and lack of accountability. The reputable trials are all registered at **ClinicalTrials.gov**. Despite the paucity of good clinical trials data and the relatively modest benefit, there is already substantial profit that can be made from stem cell treatment. This financial gain is balanced with the fact that no country or institution wants to be known as the place for unproven, dangerous therapy. As a result, there are substantial efforts in every country to regulate this complex process and weed out the equivalent of snake oil.

In addition, the **International Society for Stem Cell Research (ISSCR)** is an independent, nonprofit organization established in 2002 to "promote and foster the exchange and dissemination of information and ideas relating to stem cells, to encourage the general field of research involving stem cells and to promote professional and public education in all areas of stem cell research and application." (www.isscr.org) With more than 3,500 members worldwide, the ISSCR has become the voice of the stem cell research community. They published guidelines for human embryonic stem cell therapy (www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf) and a patient's handbook in 2008 (www.isscr.org/The_Patient_Handbook).

Governmental regulation can only do so much, and the patients ultimately need to advocate for their own health and to ask questions regarding any treatment. The role of the physician is to inform the patient regarding the state of stem cell therapy and caution the patients to recognize the consequences of undergoing an unproven treatment, no matter how successfully it has been advertised. The desperate patients seeking a cure for devastating conditions like vision loss need to be aware that there is significant harm in addition to financial and psychological costs to these treatments. The lack of benefit is not the worse case scenario.

WHAT TO TELL PATIENTS

1. There are abundant data and intense efforts in basic and clinical research to make stem cell therapy a reality for the treatment of neuro-ophthalmic conditions.
2. There are currently stem cell clinical trials for neuromyelitis optica and multiple sclerosis, using autologous bone marrow-derived or hematopoietic stem cell transplantation, and we do not know if stem cell therapy is superior to traditional treatments. There are many ongoing stem cell trials for the treatment of vision loss from retinopathies using human embryonic stem cells and autologous stem cells, and the result of these studies will help form the foundation for future trials for neuro-ophthalmic conditions.

3. While many countries advertise stem cell therapy for many neuro-ophthalmic conditions including optic atrophy, Leber's hereditary optic neuropathy, multiple sclerosis, cerebellar ataxia, and others, these stem cell therapies may be poorly regulated, expensive, and potentially harmful even when they are autologous. There are no published clinical trials results that warrant recommendation to undergo stem cell treatment for these conditions at this time.

IMPORTANT LINKS

California Institute for Regenerative Medicine (CIRM)
(www.cirm.ca.gov)

Clinical Trials Registry by the US National Institute of Health
(www.clinicaltrials.gov)

2009 NIH guidelines for stem cell research
(<http://stemcells.nih.gov/policy/2009guidelines>)

International Stem Cell Society Guidelines for the Conduct of Human Embryonic Stem Cell Research, 2006
(www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf)

International Stem Cell Society Patient's Handbook, 2008
(www.isscr.org/The_Patient_Handbook).

New York Stem Cell Foundation (www.nyscf.org)

Top Ten Things to Know about Stem Cell Treatments
(www.closerlookatstemcells.org/Top_10_Stem_Cell_Treatment_Facts.htm)

CME ANSWERS

1. E
2. C
3. B
4. D

REFERENCES

1. Baylis O, Figueiredo F, Henein C, Lako M, Ahmad S. 13 years of cultured limbal epithelial cell therapy: a review of the outcomes. *J Cell Biochem*. 2011 Apr;112(4):993-1002.
2. Boucherie C, Sowden JC, Ali RR. Induced pluripotent stem cell technology for generating photoreceptors. *Regen Med*. 2011 Jul;6(4):469-79.
3. Canola K, Angénieux B, Tekaya M, Quiambao A, Naash MI, Munier FL, Schorderet DF, Arsenijevic Y. Retinal stem cells transplanted into models of late stages of retinitis pigmentosa preferentially adopt a glial or a retinal ganglion cell fate. *Invest Ophthalmol Vis Sci*. 2007 Jan;48(1):446-54.
4. Dahlmann-Noor A, Vijay S, Jayaram H, Limb A, Khaw PT. Current approaches and future prospects for stem cell rescue and regeneration of the retina and optic nerve. *Can J Ophthalmol*. 2010 Aug;45(4):333-41.
5. de Lima S, Koriyama Y, Kurimoto T, Oliveira JT, Yin Y, Li Y, Gilbert HY, Fagioli M, Martinez AM, Benowitz L. Full-length axon regeneration in the adult mouse optic nerve and partial recovery of simple visual behaviors. *Proc Natl Acad Sci U S A*. 2012 Jun 5;109(23):9149-54.
6. Fischer D, Leibinger M. Promoting optic nerve regeneration. *Prog Retin Eye Res*. 2012 Nov;31(6):688-701.
7. Lebrun-Julien F, Di Polo A. Molecular and cell-based approaches for neuroprotection in glaucoma. *Optom Vis Sci*. 2008 Jun;85(6):417-24.
8. Moore DL, Blackmore MG, Hu Y, Kaestner KH, Bixby JL, Lemmon VP, Goldberg JL.
9. KLF family members regulate intrinsic axon regeneration ability. *Science*. 2009 Oct 9;326(5950):298-301.
10. MacLaren RE, Pearson RA, MacNeil A, Douglas RH, Salt TE, Akimoto M, Swaroop A, Sowden JC, Ali RR. Retinal repair by transplantation of photoreceptor precursors. *Nature*. 2006 Nov 9;444(7116):203-7.
11. Nakano T, Ando S, Takata N, Kawada M, Muguruma K, Sekiguchi K, Saito K, Yonemura S, Eiraku M, Sasai Y. Self-formation of optic cups and storable stratified neural retina from human ESCs. *Cell Stem Cell*. 2012 Jun 14;10(6):771-85.
12. O'Callaghan AR, Daniels JT. Concise review: limbal epithelial stem cell therapy: controversies and challenges. *Stem Cells*. 2011 Dec;29(12):1923-32.
13. Ong JM, da Cruz L. A review and update on the current status of stem cell therapy and the retina. *Br Med Bull*. 2012 Jun;102:133-46.
14. Park KK, Liu K, Hu Y, Smith PD, Wang C, Cai B, Xu B, Connolly L, Kramvis I, Sahin M, He Z. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. *Science*. 2008 Nov 7;322(5903):963-6.
15. Phillips MJ, Wallace KA, Dickerson SJ, Miller MJ, Verhoeven AD, Martin JM, Wright LS, Shen W, Capowski EE, Percin EF, Perez ET, Zhong X, Canto-Soler MV, Gamm DM. Blood-derived human iPS cells generate optic vesicle-like structures with the capacity to form retinal laminae and develop synapses. *Invest Ophthalmol Vis Sci*. 2012 Apr 18;53(4):2007-19.
16. Schmeer CW, Wohl SG, Isenmann S. Cell-replacement therapy and neural repair in the retina. *Cell Tissue Res*. 2012 Jul;349(1):363-74.
17. Schwartz SD, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, Mickunas E, Gay R, Klimanskaya I, Lanza R. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012 Feb 25;379(9817):713-20.
18. Singh MS, MacLaren RE. Stem cells as a therapeutic tool for the blind: biology and future prospects. *Proc Biol Sci*. 2011 Oct 22;278(1721):3009-16.
19. Stern JH, Temple S. Stem cells for retinal replacement therapy. *Neurotherapeutics*. 2011 Oct;8(4):736-43.
20. Sun F, Park KK, Belin S, Wang D, Lu T, Chen G, Zhang K, Yeung C, Feng G, Yankner BA, He Z. Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. *Nature*. 2011 Nov 6;480(7377):372-5.
21. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998 Nov 6;282(5391):1145-7.
22. Tibbetts MD, Samuel MA, Chang TS, Ho AC. Stem cell therapy for retinal disease. *Curr Opin Ophthalmol*. 2012 May;23(3):226-34.