EVALUATING RISKS FOR VIGABATRIN TREATMENT

Gregory L. Krauss, MD

Johns Hopkins Department of Neurology, Baltimore, Maryland

Approximately 30 to 40 percent of adults with epilepsy treated chronically with vigabatrin develop concentric visual field constrictions. These deficits are generally mild and asymptomatic, but are usually irreversible, so risks and benefits for vigabatrin treatment must be carefully reviewed. Infantile spasms, a particularly severe form of epilepsy, may respond to vigabatrin; however, some infants treated with the drug develop MRI evidence of possible intramyelinic edema in subcortical structures. This article reviews the benefits of vigabatrin treatment, the risks it poses to the retina and the developing brain, as well as possible subgroups of adults and infants with severe epilepsy for whom treatment may, nevertheless, be warranted.

Vigabatrin was developed as a treatment for partial onset seizures and has been found to be very effective; 43 to 51 percent of patients with medically refractory partial seizures responded to vigabatrin treatment, with a greater than 50% seizure reduction (1–3). Vigabatrin, or γ -vinyl-GABA, irreversibly binds to GABA-transaminase in presynaptic neurons (4) and has a several day long anticonvulsant effect, despite a 5 to 8 hour plasma half-life (5). Vigabatrin also is effective for treating infantile spasms, an especially severe form of epilepsy in infants (particularly in infants with tuberous sclerosis), though whether or not treatment benefits are increased compared with ACTH and prednisone is unclear (6). Vigabatrin is also an important potential agent for treating cocaine (7), and other addictions (8), with a unique nondopaminergic influence on drug reinforcement (9).

Major safety risks, however, strictly limit vigabatrin use, necessitating a careful review of the risks and benefits prior to treating patients. In the United States, development of vigabatrin was initially halted after preclinical research showed that

it produces intramyelinic edema with brain vacuolation in animals (10,11). Subsequent animal studies demonstrated that brain MRI and somatosensory-evoked potential testing could detect intramyelinic edema (12). After it was shown that adult patients treated for epilepsy with vigabatrin did not develop similar changes (13,14), clinical development for vigabatrin was permitted to resume in the 1990s, and the drug was eventually released for use in more than 50 countries. Vigabatrin's use declined (and approval in the United States and Japan halted); however, after several series of patients in Europe and the United States were reported to have developed concentric peripheral visual field deficits following chronic treatment (15,16). A large number of controlled and uncontrolled studies subsequently characterized a relatively unique vigabatrin-induced retinopathy: approximately 30 to 40 percent of patients develop concentric visual field deficits following approximately 6 to 24 months of treatment (17–21). Detection of peripheral field loss associated with vigabatrin treatment was initially missed because the field losses are usually mild to moderate in severity, with many patients remaining asymptomatic and adapting with ocular targeting. Some patients also report small decreases in visual acuity, color vision, and complex visual perception. The incidence rate of vigabatrin-induced visual abnormalities varies, largely because of different methods used to measure and classify visual fields. Although the shortest duration of treatment associated with vigabatrin field deficits is not well defined, the majority of patients with visual field abnormalities received treatment for greater than 6 to 12 months. Patients receiving treatment for more than 2 years have had stable visual fields, with no increases in deficits during several years of continued vigabatrin therapy (22). Typically, vigabatrin field deficits are characterized by concentric peripheral visual loss averaging 20 to 40 axial degrees for each eye (normal horizontal fields are approximately 140 degrees for both eyes), with occasional nasal sparing (see Figures 1 and 2). Though usually asymptomatic, as mentioned, vigabatrin field deficits are largely irreversible. Some central retinal functions, as measured by electroretinography, may improve slightly after discontinuing treatment (19–21).

Physiology of Vigabatrin-Induced Retinal Injury

The mechanisms for vigabatrin-induced retinal injury is only partially understood: vigabatrin concentrates in the mammalian eye (23,24), interfere with photopic cone system function (16), and produce a distinctive pathology in animal studies, including marked gliosis and disorganization in the peripheral retina as well as smaller photoreceptor losses in central cone segments (25). This pattern of injury is confirmed in

Address correspondence to Gregory L. Krauss, MD, Assoc. Prof. Neurology, Johns Hopkins Dept. Neurology, Meyer 2-147, 600 N. Wolfe St., Baltimore, MD 21287. E-mail: gkrauss@jhmi.edu

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FIGURE 1. Typical vigabatrin-induced visual field deficits. Abbreviations: OS = left eye; OD = right eye.

multifocal and flash electroretinography studies and by a single human pathology study (24). Flash electroretinography shows dysfunction in the inner retinal cone system (including the central retina), with abnormalities in flicker and oscillatory responses, suggesting dysfunction in GABA-innervated horizontal and amacrine cells (16,26). Muller glial cells are also key sites for vigabatrin-induced injury in the inner retina: vigabatrin causes abnormal accumulation of GABA in Muller glial cells, which probably is due to the inhibition of GABA-transaminase in mitochondria (27,28). Muller glial cells have progenitor capacity. Developmental alterations in both GABA-receptor expression and Muller glial cells may underlie an apparent decreased vulnerability of infants to vigabatrin-provoked retinal injury compared with adults (29–31); please see com-

mentary by Ben Menachem in this issue. Recently, it was shown that taurine deficiency in albino rodents treated with vigabatrin increased retinal sensitivity to light-induced injury (32). Taurine deficiency can produce desensitization of GABA_A receptors and neuronal disinhibition (33). This finding, however, needs to be evaluated in pigmented animals, including humans who are less prone to light-induced retinal injury. Recently, it was shown that retinal nerve fiber layer thinning may be an accurate measure of vigabatrin-induced retinal injury (34).

Appropriate Candidates and Managing Risks for Vigabatrin Therapy

As noted, vigabatrin typically produces visual dysfunction only after 6 months or more of therapy, and some patients might potentially receive short-term vigabatrin treatment with limited visual risks (e.g., patients with infantile spasms). Patients with partial onset epilepsy, however, require chronic therapy, and thus will need careful assessment and counseling about the risks for chronic vigabatrin treatment. Consequently, vigabatrin is a third-line therapy for the treatment of epilepsy in patients with severe and disabling partial onset seizures, who are not candidates for curative surgery. The following two brief case studies are examples of the types of patients with severe epilepsy who may be candidates for treatment with vigabatrin.

Patient 1: An 18-year-old male high school senior with childhood cerebral malaria has several secondary generalized seizures per week with frequent severe injuries (concussions and head contusions), despite treatment with all standard antiepileptic drugs (AEDs). He has multifocal (independent right temporal and left frontal) seizures on intracranial recordings. His school performance declined during combined AED therapy, and his principal is asking him to have home schooling because of frequent convulsions and falls at school.

Patient 2: A 55-year-old female patient had several severe complex partial seizures several times per week for more than

FIGURE 2. Right and left eye mean visual fields for 30 patients treated with vigabatrin compared to epilepsy controls and tiagabine-treated patients. Vigabatrin-treated patients typically develop an average of 20 to 40 degrees of field loss compared to controls, as measured with Goldmann kinetic fields. OS, left eye; OD, right eye; TGB, tiagabine; VGB, vigabatrin.

10 years, with multiple head injuries, despite therapy with all standard AEDs and vagal nerve stimulation. The patient must wear a helmet and is unable to walk unassisted outside her home because of a high risk of injury during seizures. She is largely housebound and is unable to walk her dog or attend social activities outside home. The patient cannot have epilepsy surgery, as she has bilateral temporal lobe involvement. She had prolonged status epilepticus during seizure monitoring and required inpatient rehabilitation. She recently had a large subdural hemorrhage during a seizure-related fall, which required evacuation.

Vigabatrin is being considered for release in the United States with a risk mitigation program that would include monitoring visual function during treatment. Vigabatrin treatment would be limited to patients who continue to have severe, uncontrolled partial onset seizures or infantile spasms, despite standard treatments. Patients will require baseline perimetry testing and repeated testing every 3 to 6 months. In most studies, Goldmann kinetic perimetry has been more sensitive for detecting and monitoring visual field deficits than computerized static perimetry (19). Computerized static perimetry, however, is more widely available and can be used to screen and monitor patients at most centers—mean deviation scores in addition to visual classification of fields can be used to identify treatment-related peripheral vision loss. Automated kinetic perimetry may eventually help to improve rapid screening of vigabatrin field loss. Patients with epilepsy frequently have associated ophthalmologic disorders and often have difficulty performing perimetry as a result of sedation or cognitive impairment; thus, abnormal perimetry findings usually require replication.

It is very difficult to evaluate visual function in infants who are candidates for vigabatrin therapy for infantile spasms. Gross vision appears to develop normally after in utero (29) and infant exposure (30) to vigabatrin; however, perceptual function may be slightly altered by treatment (35). A small proportion of infants treated with vigabatrin develop MRI signal abnormalities in the thalamus and subcortical regions. These abnormalities are usually transient but are similar in distribution to animals with intramyelinic edema (36,37); please see commentary by Ben Menachem in this issue. Possible effects of these changes on motor development remain to be evaluated. Because of the difficulties in monitoring visual development in infants and the potential harm to myelin, the risks-benefits for vigabatrin treatment of infantile spasms is currently unclear (5).

Several steps can be used to evaluate possible treatment candidates and their risks for vision loss with treatment:

- 1) Document that the treatment candidate has failed treatment with effective standard AEDs for partial onset seizures, has severe, disabling seizures, and is not an epilepsy surgical candidate. Patients with persisting in-

fantile spasms on ACTH/prednisone therapy are also candidates for vigabatrin treatment; however, there is no consensus on use of vigabatrin as first-line therapy for infantile spasms.

- 2) Carefully review with patients the risks associated with vigabatrin therapy and the safety monitoring requirements. Potential patients can be counseled that with long-term vigabatrin therapy, they are at a 40% risk for peripheral visual field loss, which usually is not severe or symptomatic, but it is likely to be irreversible. It is helpful to illustrate typical vigabatrin-related visual field losses with patients—the normal boundaries of peripheral vision with two eyes can be illustrated by having the patient and examiner extend their arms out and then moving them horizontally together until the limits of peripheral vision are demonstrated (generally at 140 degrees of separation). Average ranges of vigabatrin-related field loss can be demonstrated by moving the arms forward horizontally until they are 100 to 60 degrees apart. Patients can be reassured that visual loss equivalent to blindness is highly unlikely: the U.S. disability standard specifies that less than 20 degrees of total visual field is equivalent to blindness. However, they should be counseled that this degree of field loss may interfere with or prohibit driving privileges, in some cases.
- 3) Patients will require baseline ophthalmology examination and perimetry, using either automated static or Goldmann kinetic perimetry. Abnormal perimetry findings must be verified with a second test to exclude false positive findings from poor test performance.
- 4) Patients' response to standard vigabatrin doses (typically 3 g/day for adults) can be evaluated after 2 to 3 months of therapy. Patients who do not improve with vigabatrin therapy should be switched to alternative treatments. Patients with marked seizure improvement (>50% reduction) who elect to remain on vigabatrin treatment will require repeat perimetry at 3- to 6-month intervals and regular reassessment of their treatment response to justify continued therapy.
- 5) Many patients will develop mild, asymptomatic visual field constrictions after a year or more of therapy. Patients with marked reductions in seizures could decide to continue vigabatrin therapy despite mild field constrictions; continued perimetry monitoring would be required. It is unclear, however, whether continued treatment will be permitted by regulatory agencies. Many patients with marked seizure reductions with vigabatrin treatment are able to slowly convert to alternative AEDs, sometimes even returning to previous unsuccessful therapies, with continued seizure reductions. Patients only

rarely develop visual deficits after several years of therapy; most who develop field constrictions do so within 2 years of initiating treatment (38).

Patients with disabling partial onset seizures or infantile spasms may be candidates for vigabatrin treatment. The large number of available alternative medical and stimulation therapies limit numbers of treatment candidates. Patients receiving therapy must agree to careful monitoring of visual function and evaluation of treatment responses in order to continue treatment.

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