JUVENILE MYOCLONIC EPILEPSY: MORE TRIALS ARE NEEDED TO GUIDE THERAPY

Levetiracetam for the Treatment of Idiopathic Generalized Epilepsy with Myoclonic Seizures. Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J, For the N166 Levetiracetam Study Group. *Neurology* 2008;70:607–616. BACKGROUND: Currently, there are no published randomized controlled trials evaluating the efficacy and safety of adjunctive antiepileptic therapy in idiopathic generalized epilepsy with myoclonic seizures. METHODS: This randomized, double-blind, placebo-controlled multicenter trial assessed the efficacy and tolerability of adjunctive treatment with levetiracetam 3,000 mg/day in adolescents (12 years) and adults (65 years) with idiopathic generalized epilepsy, who experienced myoclonic seizures on 8 days during a prospective 8-week baseline period, despite antiepileptic monotherapy. The 8-week baseline period was followed by 4-week up-titration, 12-week evaluation, and 6-week down-titration/conversion periods. RESULTS: Of 122 patients randomized, 120 (levetiracetam, $n = 60$; placebo, $n = 60$) were evaluable. Diagnoses were either juvenile myoclonic epilepsy (93.4%) or juvenile absence epilepsy (6.6%). A reduction of 50% in the number of days/week with myoclonic seizures was seen in 58.3% of patients in the levetiracetam group and in 23.3% of patients in the placebo group ($p < 0.001$) during the treatment period. Levetiracetam-treated patients were more likely to respond to treatment than patients receiving placebo (OR = 4.77; 95% CI, 2.12 to 10.77; $p < 0.001$). Levetiracetam-treated patients had higher freedom from myoclonic seizures (25.0% vs 5.0%; $p = 0.004$) and all seizure types (21.7% vs 1.7%; $p < 0.001$) during the evaluation period. The only adverse events more frequent with levetiracetam were somnolence and neck pain. CONCLUSION: These results suggest that levetiracetam is an effective and well-tolerated adjunctive treatment for patients with previously uncontrolled idiopathic generalized epilepsy with myoclonic seizures.

COMMENTARY

Juvenile myoclonic epilepsy is the most common idiopathic generalized epileptic syndrome, accounting for about 10% of all patients with epilepsy. The diagnosis requires the presence of generalized myoclonic seizures, thus 100% of patients have these seizures. About 90% of patients also have generalized tonic–clonic seizures and approximately 30% have generalized absence seizures. Approximately 15 years ago, valproate emerged as the antiepileptic drug of choice for juvenile myoclonic epilepsy, with reported seizure-free rates of about 80% (1,2). Nevertheless, some patients are resistant to valproate and others do not tolerate it well. Lamotrigine, topiramate, and zonisamide have been suggested as possible alternatives for these patients (3). However, one large, prospective, randomized study (the Standard and New Antiepileptic Drugs, or SANAD, trial) that compared valproate, lamotrigine, and topiramate for idiopathic generalized epilepsy showed that valproate was more effective than lamotrigine and better tolerated than topiramate (4). These data highlight the need for alternative or adjunctive therapeutic options for patients with juvenile myoclonic epilepsy who do not become seizure-free with valproate, cannot tolerate it, or are concerned about its risks.

The international, multicenter study by Noachtar and colleagues evaluated adjunctive levetiracetam for patients with idiopathic generalized epilepsy and myoclonic seizures. Most epileptologists would consider idiopathic generalized epilepsy with myoclonic seizures to be juvenile myoclonic epilepsy, by definition, even though 8 patients in the study were given the diagnosis of juvenile absence epilepsy by the local investigator. The most commonly used baseline antiepileptic drugs in the active arm of the trial were valproate (60.7% of patients) and lamotrigine (24.6% of patients). Levetiracetam add-on treatment rendered 21.7% of this refractory patient group completely seizure-free and therefore, should be considered an adjunctive treatment option for similar patients with juvenile myoclonic epilepsy and persistent myoclonic seizures. Another recent study supported adjunctive levetiracetam use for patients with idiopathic generalized epilepsy and refractory generalized tonic–clonic seizures (5). Approximately one-third of the patients in that study carried the diagnosis of juvenile myoclonic epilepsy. These two studies combined support the use of adjunctive levetiracetam for juvenile myoclonic epilepsy, with either refractory generalized myoclonic or tonic–clonic

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seizures. However, there are no solid data regarding the efficacy of adjunctive levetiracetam for juvenile myoclonic epilepsy patients who have refractory absence seizures. In fact, one retrospective study showed that absence seizures, compared with myoclonic or tonic–clonic generalized seizures types, are the least likely to benefit from levetiracetam for patients with refractory idiopathic generalized epilepsy (6).

The syndrome of juvenile myoclonic epilepsy is heterogeneous, both genetically and clinically. One large study of 257 patients suggested four subgroups (7). The largest subgroup, accounting for 72% of patients, was represented by classic juvenile myoclonic epilepsy with adolescent onset myoclonic or generalized tonic–clonic seizures, and infrequent absence seizures following in one-third of patients. The second largest subgroup was childhood absence epilepsy evolving to juvenile myoclonic epilepsy; it included 18% of the total patients. These patients were easily distinguished from classic juvenile myoclonic epilepsy because their first seizure type was absence seizures, which began in the first decade of life, with myoclonic and tonic–clonic seizures following in adolescence. This group was refractory to treatment, with only 7% of patients becoming seizure-free. The remaining two small groups, juvenile myoclonic epilepsy with adolescent absence (7%) and juvenile myoclonic epilepsy with astatic seizures (3%), had seizure-free rates (56–62%) that were fairly similar to those seen in the classic juvenile myoclonic epilepsy subgroup.

A study exploring factors in drug resistance found that juvenile myoclonic epilepsy patients with a combination of all three seizure types (myoclonic, absence, and tonic–clonic) were much more likely to be resistant to therapy (8). Considering that all patients in the study by Noachtar and colleagues were refractory to treatment, it is likely that the investigators had an over-representation of patients with childhood absence epilepsy that evolved to juvenile myoclonic epilepsy and of patients with all three seizure types. Noachtar et al. did not identify juvenile myoclonic epilepsy subgroups. An analysis of the efficacy of levetiracetam by juvenile myoclonic epilepsy subgroup (for example, by initial seizure type and its age at onset) could be very instructive in discriminating which subgroup is most likely to respond to levetiracetam.

There are no class I studies to guide the initial therapy of juvenile myoclonic epilepsy, and no drug is specifically approved by the Federal Drug Administration for this indication. Class IV studies suggest that in addition to valproate, the new antiepileptic drugs lamotrigine, topiramate, levetiracetam, and zonisamide can be considered; however, more rigorous trials are needed. The SANAD trial for idiopathic generalized epilepsy classified only 26% of the patients with juvenile myoclonic epilepsy (4). Thus, there is also a need for a comparative trial of initial therapies for patients with juvenile myoclonic epilepsy. Such a trial could stratify patients by juvenile myoclonic epilepsy subgroups and analyze the response of all seizure types within this syndrome.

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