Epileptic Disord 2003; 5 (Suppl 1): S27–S31

Efficacy of levetiracetam in partial seizures

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ABSTRACT – Controlled clinical trials and routine clinical practice demonstrate that levetiracetam is effective as add-on therapy and appears to allow for withdrawal to monotherapy in patients who respond well in the add-on setting. In pivotal clinical trials of adjunctive therapy with levetiracetam 1000 to 3000 mg/day (pooled data), 40% to 54% of patients experienced a 50% or greater reduction in seizure frequency, compared with 18% to 28% of patients treated with placebo. The median percent reduction from baseline in seizure frequency ranged from 36% to 68% for levetiracetam, versus 10% to 23% for placebo. Seizure freedom was achieved by 11% to 35% of those in the levetiracetam treatment group, compared with 3% to 18% of those in the placebo group. (All comparisons statistically significant versus placebo for simple partial, complex partial, and secondarily generalized seizures except for percentage of seizure-free patients with simple partial seizures.) Clinical observations are consistent with these findings.

KEY WORDS: Levetiracetam, partial seizures, antiepileptic drugs, epilepsy

Introduction

Treatment for partial seizures is generally initiated with a first-line antiepileptic drug (AED) such as carbamazepine or oxcarbazepine [1]. If seizure control is inadequate despite treatment with the maximum tolerated dose, another AED is added [1]. The challenge in treating refractory epilepsy is finding a treatment regimen that reduces seizure frequency without increasing the risk for adverse events or further impacting the patient's quality of life ; hence, the continuing search for newer and better AEDs with novel mechanisms of action.

One such agent, levetiracetam, is particularly well suited as add-on therapy in patients with partial seizures not completely controlled by monotherapy with a first-line agent. Its favorable pharmacokinetic profile is characterized by rapid, almost complete absorption after oral administration, and the extent of bioavailability is not affected by food [2]. Levetiracetam is not protein bound (< 10%), and steady-state plasma levels are generally achieved after 2 days of twice-daily dosing. Although the elimination half-life is approximately 6 to 8 hours, evidence that the drug's duration of action can last much longer led to twice-daily dosing in clinical trials. Levetiracetam is eliminated primarily (66%) as unchanged drug in the urine, and the liver cytochrome P450 enzyme system is not involved in its metabolism. As a result, levetiracetam has a low potential for drug interactions and low intra- and inter-subject variability in its pharmacokinetic profile [2].

Preclinical studies showed that levetiracetam is well-tolerated and has a broad spectrum of activity, including potent activity against partial seizures [3-5]. Following promising phase II

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studies [6, 7], levetiracetam achieved a significant reduction in partial seizures in a pilot clinical study [8]. This paper focuses on results obtained in three pivotal double-blind, placebo-controlled trials that included 904 patients with partial seizures, 592 of whom were exposed to levetiracetam [9-11].

Pivotal clinical trials

Shorvon *et al.* [9] conducted a European multicenter, double-blind, randomized, placebo-controlled trial of levetiracetam (500 or 1000 mg twice daily) versus placebo as add-on therapy in 324 patients with refractory simple and/or complex partial seizures with or without secondary generalization. A baseline period of 8 to 12 weeks was followed by a 4-week titration interval and a 12-week evaluation period**.** A response to treatment was defined as a ≥ 50% reduction in seizure frequency. Levetiracetam significantly decreased partial seizure frequency compared with placebo. Seizures were reduced by ≥ 50% in 22.8% of patients who received 1000 mg/day (n = 106) and 31.6% of those treated with 2000 mg/day (n = 106), versus 10.4% of patients in the placebo group (n = 112) ($P < 0.05$ for each dose versus placebo). Levetiracetam 1000 and 2000 mg/day were effective against all seizure types, reducing simple partial seizures by 38.1% and 46.3% (versus 9.1% for placebo), complex partial seizures by 12.4% and 24.4% (versus 9.1% for placebo), and secondarily generalized seizures by 37.4% and 28.2% (versus an increase of 16.8% for placebo), respectively [9]. Levetiracetam was well tolerated, with no significant difference in the overall incidence of adverse events among treatment groups (70.8% for 1000 mg and 75.5% for 2000 mg) or between the levetiracetam and placebo groups (73.2% for the placebo group). Events reported more frequently in levetiracetam- than placebo-treated patients included headache, asthenia, and somnolence. (For a detailed discussion of the safety profile of levetiracetam, see the article by Drs. Arroyo and Crawford.)

To look at the dose-response relationship to levetiracetam in this trial, Boon and colleagues conducted a crossover study to analyze data from two 12-week evaluation periods, treatment period A (reported by Shorvon et al) and treatment period B [12]. They confirmed that both doses significantly reduced seizure frequency compared with placebo, with reductions over placebo of 17% for the 1000 mg/day dose and 18.6% for the 2000 mg/day dose. A within-patient comparison for 93 individuals who received both levetiracetam doses revealed a significantly greater responder rate for the 2000 mg/day dose (P = 0.018). During the entire evaluation period, 5.5% of patients who received 1000 mg/day and 5.7% of those treated with 2000 mg/day were seizure-free.

Levetiracetam doses of 1000 and 3000 mg/day were evaluated by Cereghino *et al* in the United States in a double-blind, randomized, placebo-controlled, parallel-group, multicenter trial [10]. After a 12-week baseline period, patients with partial seizures were randomly assigned to adjunctive therapy with placebo (n = 95), levetiracetam 500 mg twice daily (n = 98), or levetiracetam 1500 mg twice daily (n = 101). Upward titration over 4 weeks was followed by 14 weeks of fixed-dose treatment. Levetiracetam 1000 and 3000 mg/day reduced partial seizure frequency from baseline by 32.5% and 37.1%, respectively, versus 6.8% for placebo ($P < 0.001$). As in the European study, the responder rates were also significantly greater in the levetiracetam treatment groups (33.0% and 39.8% for 1000 and 3000 mg/day, respectively, versus 10.8% for placebo ($P < 0.001$ for each dose versus placebo). Overall, 5.5% of those who received levetiracetam became seizure-free, versus 0% for placebo. Treatment-emergent events tended to be mild to moderate in severity, with asthenia, dizziness, headache, and somnolence among those most commonly reported.

The third pivotal trial was a double-blind, randomized, placebo-controlled, parallel-group, multicenter trial conducted by Ben-Menachem *et al.* [11]. Levetiracetam 1500 mg twice daily was administered for 12 weeks to 181 patients; 105 received placebo. As in the other two trials, adding levetiracetam to ongoing therapy significantly reduced seizure frequency compared with placebo. The median percent reduction in partial seizure frequency from baseline to the add-on phase was 39.9% in the levetiracetam group, versus 7.2% in the placebo group ($P < 0.001$). The responder rate was 42.1% for levetiracetam, versus 16.7% for placebo ($P < 0.001$). Patients who responded well were then eligible to enter a monotherapy phase of the trial (see the article by Dr. Ben-Menachem in this supplement). As in the other two pivotal trials, levetiracetam was well tolerated, with the overall incidence of adverse events comparable among treatment groups. Adverse events more common in the levetiracetam compared with the placebo group included asthenia, headache, and somnolence.

At the end of the pivotal studies patients could enter either an open-label follow-up study or a progressive medication withdrawal period.

Combined efficacy analyses

Similarities in the characteristics of patients enrolled and efficacy end points in the pivotal clinical trials permitted a pooling of results to assess the efficacy of levetiracetam in larger numbers of patients with specific seizure types. This combined analysis focused on simple partial, complex partial, and partial secondarily generalized seizures and on data obtained after dose titration was complete and patients were on stable treatment. Percentage reduction from baseline, responder rate, and seizure freedom were analyzed for 592 patients in the levetiracetam group and 312 in the placebo group [13].

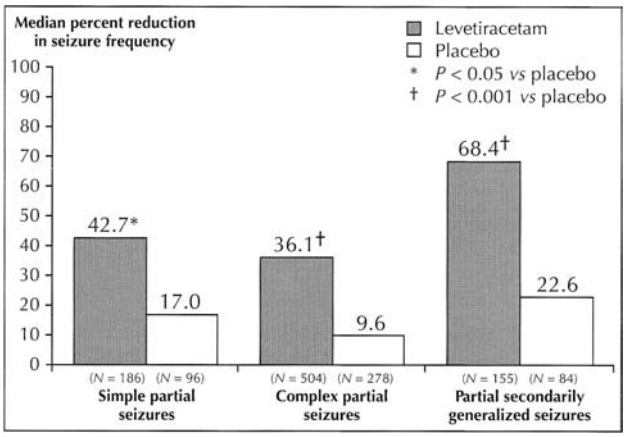

Fig. 1. *Pooled efficacy of levetiracetam in partial seizures: median percent reduction in seizure frequency.*

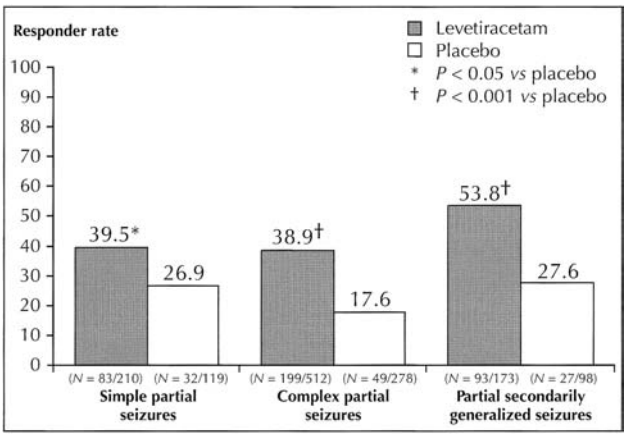

Fig. 2. *Pooled efficacy of levetiracetam in partial seizures: responder rate (50% or greater reduction in seizures).*

Percentage reduction from baseline

In patients from the three trials with simple partial seizures, the median percent reductions from baseline in seizure frequency for levetiracetam and placebo were 42.7% and 17.0%, respectively ($P = 0.039$) *(figure 1)* [13]. In patients with complex partial seizures, the median percent reductions from baseline in seizure frequency were 36.1% and 9.6% for levetiracetam and placebo, respectively ($P < 0.001$) *(Figure 1)*. In patients with partial secondarily generalized seizures, levetiracetam was again significantly more effective than placebo in reducing seizure frequency. The median percent reductions from baseline were 68.4% and 22.6%, respectively ($P < 0.001$) *(Figure 1)*.

Responder rate

Significantly more levetiracetam-treated patients were responders (50% or greater reduction in seizure frequency) compared with placebo-treated patients, regardless of seizure type *(Figure 2)* [13]. From 40% to 54% of patients treated with levetiracetam achieved a ≥ 50% reduction in seizure frequency, compared with 18% to 28% of patients in the placebo group.

Seizure freedom

During the evaluation period, 19% of levetiracetam-treated patients with simple partial seizures achieved seizure freedom, compared with 14.3% of patients in the placebo group ($P = 0.293$) *(Figure 3)* [13]. Among patients with complex partial seizures, 11.3% of those who received levetiracetam achieved seizure freedom, versus 2.9% of those given placebo ($P < 0.001$). Adding levetiracetam to the treatment regimen of patients with secondarily generalized seizures yielded seizure freedom in 34.7%, versus 18.4% in those who received placebo ($P = 0.005$).

Dose-response effect

An attempt was made to evaluate the effect of each dose on the three seizure types. However, the results presented below should be viewed with caution because of a highly significant study by dose interaction, creating confounding between the effect of the study and that of the dose. Among patients with simple partial seizures, all three doses of levetiracetam (1000, 2000, or 3000 mg/day) appeared to effectively reduce seizure frequency; no one dose appeared to be significantly better than another. The median percent reductions in seizure frequency were 44.1%, 46.3%, and 36.4%, respectively, compared with 17% for placebo [13].

Higher doses (especially the 3000 mg/day dose) may be more effective than lower doses in controlling complex partial and partial secondarily generalized seizures. Levetiracetam 3000 mg/day reduced the weekly frequency of complex partial seizures by 45.3%, compared with 23.3% and 24.4% for the 1000 and 2000 mg/day doses (and

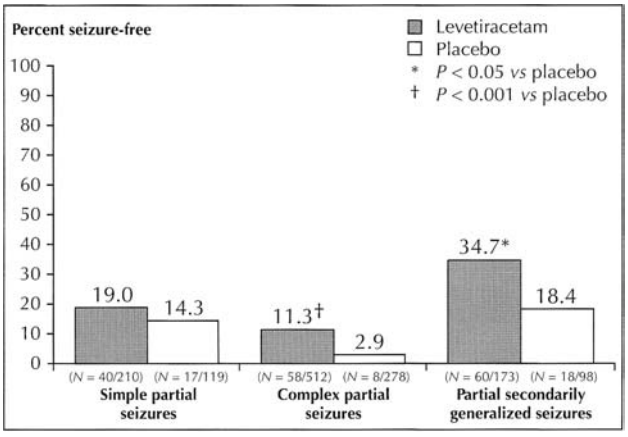

Fig. 3. *Pooled efficacy of levetiracetam in partial seizures: percent seizure-free.*

9.6% for placebo). Among patients with partial secondarily generalized seizures, the median reduction in seizure frequency was 91.2% for the 3000 mg/day dose. Levetiracetam 1000 mg/day and 2000 mg/day had a percentage reduction from baseline of 66.1% and 28.1%, respectively, versus 22.6% for placebo.

Clinical observations

Results from pivotal clinical trials have thus proven levetiracetam to have antiepileptic activity by seizure reduction and seizure freedom in a significant number of patients. Extrapolating the results of pivotal clinical trials with AEDs to effectiveness in clinical practice should be done with caution. Therefore, it is important to also assess experience with an AED after the drug is marketed, with regard to both efficacy and safety.

Experience with levetiracetam at the Department of Epileptology, University of Bonn, has been extensive. The results are consistent with the clinical trial results [14]. The computer-aided analysis of patient reports from this institution permitted the assessment of efficacy for 505 patients (48% females; age range 3 to 81 years). The mean duration of treatment was 23 ± 13 weeks; 192 were treated for 30 weeks or longer. Treatment was stopped in 16%; the reason was side effects (mainly agitation) in 6% and insufficient efficacy in 7%, while in 3%, the reason was unclear. More than 60% of the patients received levetiracetam in doses ranging from 2000 to 3000 mg/day. Most (96%) were taking from one to five AEDs (average, two) in addition to levetiracetam. The drugs used most often were lamotrigine, carbamazepine, and valproic acid. The most common seizure types were complex partial seizures (70.2%; five/month), followed by secondarily generalized seizures (41%; two/month). A statistically significant seizure reduction (median, 50%; $P > 0.0001$) was seen in all seizure types. Considering responder rates, 43% experienced a 50% reduction and 32% a 75% reduction of seizure frequency, and 20% became seizure-free during the observation period. Side effects were mild; levetiracetam was well tolerated in this cohort of patients. Only 24% reported side effects, with fatigue (6%) and vertigo (5%) dominant.

Long-term efficacy

Long-term experience with levetiracetam is reviewed by Dr. Abou-Khalil elsewhere in this supplement. A retention rate of 32% was reported for 1422 patients from randomized clinical trials followed for up to 5 years [15].

Steinhoff *et al.* recently reported a 1-year retention rate of 63% in 90 patients [16]. After 1 year, 21% of patients still responded to therapy, with seizure reduction > 50%, and 12% were seizure-free. Somnolence and behavioral disorders were the most common adverse events; these effects were transient. In a group of patients followed by Mohanraj *et al.*, 29.8% (23/77) were seizure-free for 6 months on an unchanged dose of levetiracetam, and an additional 20.7% (16/77) had a > 50% reduction in seizure frequency [17]. Sedation was the most commonly reported side effect. Sake *et al.* suggested duration of treatment (> 8 month) is a significant factor in obtaining optimal efficacy with levetiracetam [18].

Meta-analyses

Using data from standard types of clinical trials, Cramer *et al.* compared the efficacy and tolerability of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide in patients with poorly controlled partial seizures [19]. Overall success (AED response rate [50% or greater decrease in partial seizures] minus placebo response rate) was highest for levetiracetam, oxcarbazepine, and topiramate (27% to 29%, versus 12% to 20% for the other AEDs). Complaint scores were lowest for gabapentin, levetiracetam, tiagabine, and zonisamide. Most of the AEDs with high success rates also had high complaint scores, except for levetiracetam, which had both a high success rate (28%) and very low complaint score (- 27; the next best score was - 45 for gabapentin and - 71 for both tiagabine and zonisamide).

Marson *et al.* undertook a systematic review and meta-analysis of levetiracetam and three other AEDs—oxcarbazepine, remacemide, and zonisamide—for patients with drug-resistant localization-related epilepsy [20]. Synthesizing data from 11 randomized placebo-controlled add-on trials (including four of levetiracetam: three on efficacy and four on safety), they were able to make some broad comparisons. They found that levetiracetam and oxcarbazepine were most likely to achieve a 50% or greater reduction in seizure frequency, and that levetiracetam had the lowest relative risk for drug withdrawal. Thus, levetiracetam had the most favorable "responder-withdrawal ratio" than the other agents evaluated.

Conclusion

Clinical experience with levetiracetam corroborates the results observed during the drug's development. Levetiracetam is recommended as add-on therapy for patients with refractory partial seizures, and preliminary evidence suggests that it appears to allow for withdrawal to monotherapy in patients who respond well in the add-on setting. Levetiracetam is effective in all partial seizure subtypes.

Only head-to-head trials will allow direct comparisons with other AEDs. However, levetiracetam appears to be one of the most effective and one of the better-tolerated AEDs.

Acknowledgements

The authors thank G. Widman, MD, for the computerized analysis of the levetiracetam data from Bonn.

References

1. Browne TR, Holmes GL. Epilepsy. *N Engl J Med* 2001; 344: 1145-51.

2. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther* 2000; 85: 77-85.

3. Klitgaard H, Matagne A, Gobert J, *et al.* Evidence for a unique profile of levetiracetam in rodent models of seizures and epilepsy. *Eur J Pharmacol* 1998; 353: 191-206.

4. Löscher W, Hönack D. Profile of ucb L059, a novel anticonvulsant drug, in models of partial and generalized epilepsy in mice and rats. *Eur J Pharmacol* 1993; 232: 147-58.

5. Gower AJ, Noyer M, Verloes R, *et al*. ucb L059, a novel anti-convulsant drug: pharmacological profile in animals. *Eur J Pharmacol* 1992; 222: 193-203.

6. Grant R, Shorvon SD. Efficacy and tolerability of 1000-4000 mg per day of levetiracetam as add-on therapy in patients with refractory epilepsy. *Epilepsy Res* 2000; 42: 89-95.

7. Sharief MK, Singh P, Sander JWAS, *et al*. Efficacy and tolerability study of ucb L059 in patients with refractory epilepsy. *J Epilepsy* 1996; 9: 106-12.

8. Stodieck S, Steinhoff BJ, Kolmsee S, *et al*. Effect of levetiracetam in patients with epilepsy and interictal epileptiform discharges. *Seizure* 2001; 10: 583-7.

9. Shorvon SD, Löwenthal A, Janz D, *et al*. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 2000; 41: 1179-86.

10. Cereghino JJ, Biton V, Abou-Khalil B, *et al*. Levetiracetam for partial seizures. Results of a double-blind, randomized clinical trial. *Neurology* 2000; 55: 236-42.

11. Ben-Menachem E, Falter U, for the European Levetiracetam Study Group. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 2000; 41: 1276-83.

12. Boon P, Chauvel P, Pohlmann-Eden B, *et al.* Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res* 2002; 48: 77-89.

13. Data on file. UCB S.A., Brussels, Belgium.

14. Elger C. Experience with levetiracetam in partial seizures. Presented at: 24th International Epilepsy Congress; May 16, 2001; Buenos Aires.

15. Krakow K, Walker M, Otoul C, *et al*. Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology* 2001; 56: 1772-4.

16. Steinhoff B, Bacher M, Frenck W, *et al*. Levetiracetam add-on treatment: one-year-retention in an epilepsy centre. *Epilepsia* 2002; 43 (Suppl 8): 116.

17. Mohanraj R, Stephen L, Parker P, *et al*. Adjunctive levetiracetam for refractory epilepsy in clinical practice. *Epilepsia* 2002; 43(Suppl 8): 116.

18. Saké JK, De Decker M, Janssen G. Efficacy of levetiracetam: open label assessment. *Epilepsia* 2002; 43(Suppl 8): 117.

19. Cramer JA, Ben-Menachem E, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res* 2001; 47: 17-25.

20. Marson AG, Hutton JL, Leach JP, *et al*. Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review. *Epilepsy Res* 2001; 46: 259-70.