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Sustained Efficacy and Long-term Safety of Oxcarbazepine: One-year Open-label Extension of a Study in Refractory Partial Epilepsy

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Summary: *Purpose:* To evaluate the long-term efficacy, tolerability, and safety of oxcarbazepine (OXC) in medically refractory partial epilepsy.

Methods: This study is the open-label extension phase that followed a multicenter, randomized, double-blind, dose-response clinical study of OXC monotherapy in patients with medically refractory partial epilepsy. We analyzed the efficacy, tolerability, and safety of OXC during the first 48 weeks of open-label therapy. To evaluate efficacy, we compared the change in seizure frequency throughout the 48 weeks of treatment with OXC with the baseline seizure frequency that preceded the double-blind phase of the core study by an intent-to-treat and completer analysis. Safety and tolerability were evaluated by using an intent-to-treat analysis.

Results: Of the 87 patients enrolled in the double-blind study, 76 patients participated in the open-label extension phase. Fifty-five (72%) patients completed 48 weeks of open-label treatment on a median OXC dose of 2,400 mg/day. Based on an intent-to-treat analysis, the median reduction in seizure frequency was 47% ($p = 0.0054$); the 50 and 75% responder rates were 46.1 and 25.0%, respectively, with 6.6% of patients remaining seizure free. The completer analysis yielded comparable efficacy results. OXC was well tolerated, with 13% of patients exiting because of adverse events. The six most common adverse events, irrespective of their causal relation to OXC, were dizziness, headache, fatigue, diplopia, nausea, and rash. For the most part, these adverse events tended to be transient.

Conclusions: The efficacy of OXC is sustained with good safety and tolerability profiles during long-term treatment of patients with medically refractory partial epilepsy. **Key Words:** Oxcarbazepine—Clinical study—Efficacy—Adverse events—Epilepsy.

Oxcarbazepine (OXC; Trileptal) is a second-generation antiepileptic drug (AED) with proven efficacy as monotherapy and combination therapy in the treatment of partial seizures (including seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) in adults and children with epilepsy.

OXC possesses some distinct mechanisms of action (1) and is characterized by a more favorable pharmacokinetic, safety, and tolerability profile (2) than its structural analogue, carbamazepine (CBZ). Its efficacy was evaluated in a number of superiority trials that unequivocally demonstrated its efficacy as monotherapy (3–6) and as combination therapy (7,8) in patient populations ranging from the recently diagnosed to the highly refractory with localization-related epilepsy. Those studies demonstrated the efficacy of OXC as monotherapy at dosages of 1,200 to 2,400 mg/day (3–6). A linear dose-response relationship, when used as combination therapy, was shown at dosages ranging from 600 to 2,400 mg/day (8). One of those pivotal studies was an 18-week conversion to monotherapy dose-response study that evaluated its efficacy as monotherapy in outpatients with medically refractory partial epilepsy (3). The time to exit, the primary efficacy variable, was significantly longer in patients randomized to OXC, 2,400 mg/day, compared with those taking 300 mg/day.

The aim of the open-label extension phase of this multicenter study was to evaluate whether the efficacy results demonstrated in this randomized study were sustained during long-term open-label treatment. Additionally, the long-term safety and tolerability of OXC were assessed, together with the reasons for its discontinuation after long-term use.

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METHODS

Study design

This study is the open-label extension phase of a multicenter, randomized, double-blind, dose-controlled clinical study that evaluated the efficacy and safety of OXC as monotherapy for the treatment of partial-onset seizures (3). During the double-blind phase of the study, patients with medically refractory partial epilepsy experiencing at least two partial-onset seizures per 28 days during a 56-day baseline period while maintained on constant doses of one or two AEDs were randomized to treatment with OXC administered as monotherapy at daily doses of 300 or 2,400 mg (3). Patients who completed the 18-week double-blind phase of the study or who met protocol-defined individualized exit criteria could participate in a long-term open-label extension phase. Before entering the open-label extension phase, patients randomized to OXC 300 mg/day during the core study had their dose titrated to 2,400 mg/day during an 8-day blinded conversion period, whereas those randomized to OXC 2,400 mg/day, continued to receive the same dose. Eligible patients were men and women, age 12 years and older, weighing ≥41 kg (90 pounds) and who continued to satisfy the inclusion criteria of the core study (3).

The open-label extension phase consisted of patient clinic visits scheduled at 4-week intervals for the first three visits, followed by clinic visits at 12-week intervals (Fig. 1). At each visit, interim physical and neurologic examinations were performed, and blood was drawn for routine laboratory analysis. In addition, patients were asked about concomitant medications, and their seizure diaries were reviewed for seizure types and frequency. Patients also were queried about adverse events, and their severity and relation to the study drug were noted. An electrocardiogram and urine drug screen was performed at least once a year.

OXC was administered on a b.i.d. schedule. The dose of OXC was individualized for each patient with the aim of achieving the best seizure control with acceptable tolerability. The maximum dose of OXC was, however, not to exceed 3,000 mg/day. Concomitant treatment with other AEDs was allowed, as clinically indicated and based on each investigator's clinical judgment. In addition, although there were no specific exit criteria for lack of efficacy, patients could be withdrawn from the study at any time according to the clinical judgment of the investigator. Moreover, their participation could be terminated by the investigator in the event of significant adverse events, relevant laboratory test abnormalities, or noncompliance. The Institutional Review Board of all participating centers approved the study, and all patients were required to sign an informed consent before participating in this study.

Data analysis

For this study, we reviewed the efficacy, tolerability, and safety data from the first 48 weeks of the open-label extension phase (visits 1 through 6; Fig. 1). The seizure frequency per 28 days was calculated by dividing the total number of seizures from the patients' diaries by the number of days in the extension phase and multiplied by 28. The efficacy results were analyzed by comparing the seizure frequency throughout open-label treatment phase to the baseline seizure frequency that preceded the double-blind phase of the core study. The efficacy analyses consisted of the median reduction in seizure frequency, the percentage of patients with at least a 50 or 75% reduction in seizure frequency, and the percentage of seizure-free patients. For the efficacy data, we performed an intent-to-treat analysis that included all patients who received at least one dose of the study drug during the open-label extension phase and who provided at least one seizure diary. In this analysis, efficacy data from patients who withdrew without completing 48 weeks of treatment was based on the last observation carried forward. In addition, we performed a completer analysis that included all patients who completed the first 48 weeks of open-label treatment. In that group, the change in seizure frequency during the first 24 weeks and the subsequent 24 weeks of open-label treatment also was compared. The safety and tolerability data

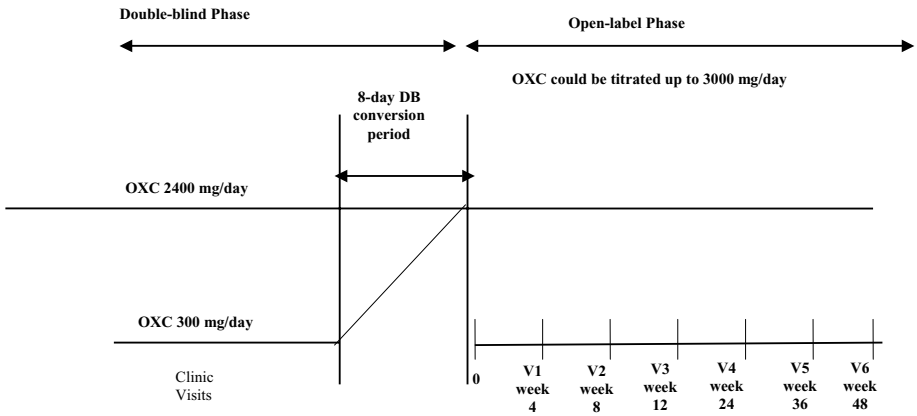

FIG. 1. Design of the open-label extension phase of the clinical study.

TABLE 1. *Demographic characteristics of patients enrolled in the open-label oxcarbazepine treatment extension phase*

Gender N (%)	
Male	32 (42)
Female	44 (58)
Race N (%)	
White	71 (93)
Black	5 (7)
Age (yr)	
Mean	35
Range	11–66
Baseline seizure frequency/28 days	
Median	7.8
Mean	11.6
Range	2–74
OXC daily dose	
Mean	2,406 mg
Median	2,400 mg

OXC, oxcarbazepine.

were evaluated by using an intent-to-treat analysis. An adverse event that occurred at any time during the 48 weeks of open-label treatment was included in this analysis. In addition, abnormalities in laboratory tests and physical and neurologic examinations were summarized.

RESULTS

Demographics and patient disposition

Of the 87 patients randomized in the double-blind study, 79 (91%) completed 18-weeks of treatment or met a protocol-defined exit criterion (3). Seven patients withdrew from the double-blind phase of the trial, six because of adverse events and one because of asymptomatic hyponatremia. Of the 79 eligible patients, 77 (97%) patients elected to participate in the long-term, open-label extension phase of the study. Because one patient failed to provide any efficacy, tolerability, or safety data, this study is based on the results obtained from 76 patients.

Participants were 44 female and 32 male patients with a mean age of 35 years, ranging from 11 years to 66 years. The mean and median daily OXC doses during open-label treatment were 2,406 and 2,400 mg, respectively (Table 1). OXC was titrated up to 3,000 mg/day in 33 (43%) patients.

A total of 42 (55%) patients were treated with monotherapy throughout the 48 weeks, whereas 34 (45%) patients received polytherapy treatment for $\geq$1 day during open-label treatment. Topiramate (TPM) was the most common concomitantly administered AED (22%), followed by CBZ (18%), lamotrigine (LTG; 18%), phenytoin (PHT; 14%), gabapentin (GBP; 14%), and valproate (VPA; 10%).

Fifty-five (72%) patients completed $\geq$48 weeks of follow-up in the open-label extension phase. Of the 21 who exited, 10 (13.0%) did so because of adverse events, eight (10.5%) because of unsatisfactory seizure control, and three (3.9%) were lost to follow-up or withdrew consent.

Efficacy

The efficacy results derived from an intent-to-treat and completer analysis are summarized in Tables 2 and 3, respectively. In the intent-to-treat analysis, the median reduction in the 4-week seizure frequency compared with baseline was 47% ($p = 0.0054$). In addition, 46.1 and 25.0% of patients experienced at least a 50 and 75% improvement in seizure frequency, respectively, whereas 6.6% remained seizure free. The 50 and 75% responder rates were higher for the group of patients maintained on OXC as monotherapy compared with patients treated with concomitant AEDs (Table 2). If one considers all patients treated with polytherapy at some point during the trial as nonresponders, the 50% responder rate with OXC as monotherapy would be 24 (32%) of 76. We performed an efficacy analysis for the patients treated with OXC as monotherapy, with the last observation carried forward at the time of exit or when treatment with polytherapy was initiated. In this analysis, the median reduction in seizure frequency was 51.7%. In addition, the 50% responder, 75% responder, and seizure-free rates were 53.5, 28.2, and 8.5%, respectively.

The results obtained from the completer analysis were comparable to the intent-to-treat data, with a 54% median reduction in seizure frequency and a better efficacy for patients maintained on monotherapy. In this group, also, the 50 and 75% responder rates were significantly higher for the group of patients maintained on OXC as monotherapy

TABLE 2. *Efficacy data based on an intent-to-treat analysis with stratification of results according to patients maintained on monotherapy and combination therapy*

Seizure reduction	OXC monotherapy (n = 42)	OXC combination therapy (n = 34)	All patients (N = 76)
Median reduction from baseline	59.7%	28.0%	47.2%
>50% (n)	57.1% (24)	32.4% (11)[a]	46.1% (35)
>75% (n)	38.1% (16)	8.8% (3)[a]	25.0% (19)
Seizure free (n)	9.5% (4)	2.9% (1)	6.6% (5)

OXC, oxcarbazepine.
[a]Significant difference ($p < 0.05$) between OXC monotherapy and OXC combination therapy groups.

TABLE 3. *Efficacy data based on a completer analysis with stratification of results according to patients maintained on monotherapy and combination therapy*

Seizure reduction	OXC monotherapy (n = 29)	OXC combination therapy (n = 26)	All patients (N = 55)
Median reduction from baseline	61.5%	28.0%	54.1%
>50% (n)	69.0% (20)	30.8% (8)[a]	50.9% (28)
>75% (n)	41.4% (12)	7.7% (2)[a]	25.5% (14)
Seizure free (n)	6.9% (2)	0 (0)	3.6% (2)

OXC, oxcarbazepine.
[a]Significant difference ($p < 0.05$) between OXC monotherapy and OXC combination therapy groups.

compared with patients treated with concomitant AEDs (Fisher's test; $p < 0.05$; Table 3).

The efficacy of OXC was sustained throughout the 48 weeks of the study. As can be seen from Fig. 2, the improvement in seizure frequency during the last 24 weeks of the open-label extension phase was very similar to that attained during the first 24 weeks. Similar results were obtained for patients who remained taking OXC as monotherapy throughout the trial. In this group, the 50% responder, 75% responder, and seizure-free rates were 62.1, 27.6, and 10.3%, respectively, during weeks 1 through 24, compared with 62.1, 37.9, and 6.9%, respectively, during weeks 25 through 48 of the trial.

Safety and tolerability

Long-term treatment with OXC was well tolerated, with 13% of patients discontinuing the study because of adverse events. It should be noted that the tolerability data have an inherent bias because patients who participated in the open-label extension phase of the trial already tolerated OXC during the double-blind phase of the core trial. Adverse events, irrespective of their causal relation to OXC and experienced by ≥10% of patients, are summarized in Table 4. The majority of the adverse events were rated as mild or moderate in severity, with the most common consisting of dizziness, headache, fatigue, diplopia, nausea, and rash (Table 4). These adverse events were similar to those reported in the controlled clinical studies, tended to occur during the early phase of treatment, especially for patients who were titrated up, and were transient. Most adverse events, especially fatigue, headache, diplopia, and somnolence, were more frequent for patients receiving polytherapy (Table 4).

All adverse events experienced were rated as mild to moderate in severity except in a few patients. A total of five patients experienced severe adverse events assessed to have a relation to OXC. Five additional patients experienced serious adverse events with a possible causal relation to OXC. Three patients had an exacerbation of their seizure frequency, whereas hyponatremia and psychosis occurred in one patient each.

No patient was discontinued because of laboratory abnormalities in liver function tests or white blood cell counts. In four patients, transient hyponatremia (<125 m*M*) developed at only one visit during the open-label extension phase, which resulted in the withdrawal of one patient from the study. The other three patients continued on OXC, and their sodium levels normalized. One pregnancy was reported in a woman who delivered a term, healthy male infant while continuing on OXC therapy throughout her pregnancy.

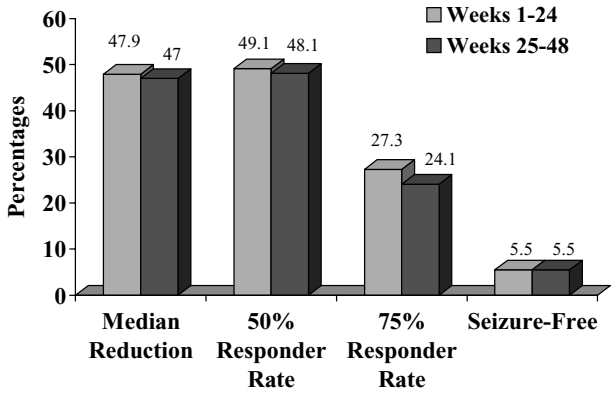

FIG. 2. Comparison of efficacy results during weeks 1–24 versus weeks 25–48 in the 55 patients who completed 48 weeks of open-label treatment with oxcarbazepine.

DISCUSSION

This is the first published study that demonstrates the sustained efficacy and long-term safety and tolerability

TABLE 4. *Adverse events stratified for the groups on monotherapy and polytherapy and experienced by ≥10% of patients during open-label treatment with oxcarbazepine*

Adverse events	Monotherapy (n = 42) n (%)	Polytherapy (n = 34) n (%)
Dizziness	13 (31)	12 (35)
Headache	6 (14)	12 (35)
Fatigue	8 (19)	10 (29)
Diplopia	7 (17)	9 (26)
Nausea	7 (17)	3 (9)
Rash	5 (12)	5 (15)
Abnormal vision	4 (10)	5 (15)
Upper respiratory infection	5 (12)	4 (12)
Somnolence	3 (7)	5 (15)
Vomiting	5 (12)	3 (9)
Tremor	4 (10)	4 (12)

of OXC to treat patients with medically refractory partial epilepsy. Based on an intent-to-treat analysis, there was a 47% median reduction in seizure frequency, a 46% responder rate, and seizure freedom in 7% of the patients. Previous open-label studies reported the responder and seizure-free rates during the last 4 weeks (9), the last 8 weeks (10), or the last 6 months of participation in the studies (11). In this study, we analyzed the efficacy results throughout the 48 weeks of treatment by using an intent-to-treat analysis. We believe that this approach gives a more accurate and conservative estimate of what can be expected in clinical practice. The efficacy results obtained in this study compare very favorably with those reported in the preceding double-blind phase of the study, in which the 50% responder and seizure-free rates for patients randomized to OXC at 2,400 mg/day were 42 and 12%, respectively (3).

The efficacy data among patients who completed the 48 weeks of treatment were concordant with the results of the intent-to-treat analysis. In an intent-to-treat analysis, all patients randomized are included in the analysis, including those who drop out prematurely. This analysis with the last-observation-carried-forward approach is usually favored because it is considered to be more conservative and pragmatic (12). However, it might occasionally result in spuriously inflating the efficacy results by including data from patients who might have exited the study early because of adverse events while responding well to treatment up to that time (13). In our study, the concordance of the intent-to-treat and completer analysis strengthens the validity of the results, and when coupled with the subsequent comparative analysis of the first and last 24 weeks of treatment strongly suggest that the efficacy of OXC is sustained during the first year of treatment with no evidence for the development of tolerance.

The aim of therapy in patients with medically refractory epilepsy is to achieve the best seizure control with acceptable tolerability. This usually entails titration of a drug to the maximum tolerated dose, and for some patients, might require treatment with more than one drug. In this study, 42 (55%) of 76 patients were maintained on OXC monotherapy throughout their participation in the open-label extension phase. In this group, the efficacy results were significantly better compared with those in patients treated with polytherapy. This suggests that a subset of patients with medically refractory partial epilepsy will achieve adequate seizure control with OXC as monotherapy, whereas others will require treatment with polytherapy. Our sample size was too small to evaluate whether the underlying epilepsy syndrome or baseline characteristics would allow distinguishing *a priori* between those likely to respond to OXC as monotherapy and those who will not.

OXC was well tolerated in the extension phase of this study, with 13% of patients withdrawing because of adverse events. The adverse events experienced by patients throughout the duration of this study were similar to those reported in the pivotal studies (3). The fact that adverse events were more common in the group receiving polytherapy is not surprising, because it is well documented that the frequency and severity of adverse events is usually related to the total AED load administered (14). Only one patient exited this study because of hyponatremia. Hyponatremia can result from treatment with OXC, with patients taking concomitant natriuretic drugs being most at risk. A recent study showed that patients who develop hyponatremia with OXC do not have an elevation of their serum antidiuretic hormone (ADH) level, suggesting that the hyponatremia is probably due to an increased sensitivity of the renal tubules to the circulating level of ADH or to an ADH-like effect of OXC (15).

There is no doubt that the pivotal double-blind, randomized, phase II or III clinical studies are the gold standard to evaluate the efficacy and tolerability of new AEDs. The main strength of such superiority studies is their statistical soundness that allows an unequivocal determination of efficacy (16). However, they also have a number of limitations, including the relatively short duration of the double-blind phase and the randomization to fixed-dosage groups. The open-label extension phase, although hindered by the lack of scientific rigor imparted by double-blind studies, expands on the data obtained from the latter and provides clinically relevant data that more closely mirror clinical practice by allowing dose adjustments according to the clinical response, in addition to providing needed long-term safety, tolerability, and efficacy data.

In conclusion, this study indicates that the efficacy of OXC is sustained during long-term treatment in a subset of patients with medically refractory partial epilepsy. It is also safe and well tolerated by the majority of patients.

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