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Analysis of three lamotrigine extended-release clinical trials: Comparison of pragmatic ITT and LOCF methodologies

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Summary Early withdrawal of patients from a clinical trial can compromise the robustness of the data by introducing bias into the analysis. This is most commonly addressed by using the ''intent to treat'' (ITT) population and ''last observation carried forward'' (LOCF) methodology, where a patient's last assessment is carried forward. This can lead to overstatement of treatment efficacy especially if events indicative of treatment failure are infrequent. An alternative methodology, labeled ''pragmatic ITT'' (P-ITT), requires patients to have a positive outcome and to complete the trial in order to be considered a treatment success by that outcome measure. Data from 3 randomized multicenter lamotrigine extended-release (LTG XR) trials were analyzed and response (proportions seizure-free and with 50% response) were compared using LOCF and P-ITT methodologies.

In 2 of the 3 trials, a lower response for both seizure freedom and 50% response was seen during the Maintenance phase using the P-ITT methodology. In the trial that did not show a difference, only a small number of patients withdrew early, thus negating the benefit brought by the P-ITT method. Differences between methodologies were not noted when evaluation was applied to the entire treatment period, most likely a reflection of the fact that a therapeutic dose of lamotrigine is not rapidly achieved.

We propose that the P-ITT may be a simpler, more informative method for evaluating the effectiveness of a drug, especially in comparison to another active drug(s).

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Introduction

Randomized double-blind controlled trials are considered to be the highest level of evidence for determining whether therapies are effective or ineffective. The methodology of these trials needs to be rigorous, and the results need to be interpretable. Even when the methodology of performing the trial is of the highest standard, interpretability of the results can depend on the method of analysis.

It is universally accepted that the optimal methodology for assessing outcome in a clinical trial is to use ''intention to treat'' (ITT), which considers data from all patients, even if they drop out. Failure to use ITT can introduce bias, since patients who drop out may be doing worse than patients who choose to stay in the trial. Performing an ITT analysis raises the question of how to analyze patients who dropped out. To date, this has been handled in AED trials by a methodology called ''last observation carried forward'' (LOCF). In this type of analysis, patients who drop out are analyzed based on any efficacy data that is obtained prior to the time of discontinuation. Thus, a patient who has a substantial reduction in seizures, but who discontinues therapy due to an intolerable side effect contributes to a favorable efficacy outcome in the trial. It has already been demonstrated that LOCF can produce misleading results in reference to assessment of seizure freedom. For example, in an analysis by Gazzola et al., it was determined that a number of patients who discontinued therapy were counted as seizure free if no seizures had occurred by the time of dropout, even if they dropped out only days or weeks after randomization (Gazzola et al., 2007). This could inflate seizure freedom numbers substantially, particularly in cases where the drug produces significant toxicity during titration, and causes substantial discontinuations early, since a very short period of seizure freedom is un-interpretable. In one such case, the seizure free rate as assessed by LOCF was 12%, compared to 1.3% who completed the trial seizure free. An alternative methodology was suggested by the authors for assessment of efficacy outcome and was labeled ''pragmatic ITT'' (P-ITT). This analysis only considers patients seizure free if they remain seizure free and do not drop out of the trial prematurely. We now present data from 3 randomized multicenter lamotrigine extended release (LTG XR) trials not included in the Gazzola analysis, and compare seizure freedom rates when calculated with LOCF vs P-ITT methodology. We also compare 50% responder rates, using P-ITT and LOCF. Using this method, patients who discontinued the trial are considered to be non-responders irrespective of their seizure outcome prior to discontinuation, since they cannot benefit from a drug they are no longer taking. This is similar to an analysis called ''baseline observation carried forward'' (Shao et al., 2009).

Methods

Data from three international, multicenter, double-blind, randomized epilepsy trials evaluating once-daily LTG XR in patients $\geq$13 years of age were used to compare the LOCF and P-ITT methodologies of endpoint analysis. LTG XR was the test medication in all 3 trials. Two of the trials (LAM100034 and LAM100036) were adjunctive therapy trials with placebo control. LAM100034 was conducted in patients with partial onset seizures (Naritoku et al., 2007) and LAM100036 evaluated LTG XR for treatment of primary generalized tonic-clonic seizures (PGTC) (Biton et al., 2010). LAM30055 was a conversion to monotherapy trial for partial onset seizures and used an historical control (French et al., 2012). All three trials had an 8-week baseline phase from which baseline seizure frequency was determined and in all trials a daily record of seizure type and frequency was maintained. Following the Baseline phase, all trials had an Escalation phase to a target dose followed by a 12-week Maintenance phase. In LAM100034 and LAM100036, the Escalation phase was 7 weeks. In LAM30055, escalation was part of the Conversion phase in which patients were converted from their background antiepileptic drug (AED) monotherapy to monotherapy with LTG XR. Therefore, 4 weeks of background AED withdrawal followed the 7 weeks of LTG XR escalation before start of the 12 weeks of Maintenance phase. For all trials, results are presented for both the entire treatment period and separately for the Maintenance phase.

Dosing escalation and final dose were consistent with approved labeling and were based on concurrent AED (Table 1).

All analyses were based on the ITT population (all randomized patients who received trial drug and had at least 1 post-baseline evaluation). Under LOCF, prematurely discontinued patients remained in the analysis with their final evaluation as a success (seizure-free) or failure (not seizure-free) determined by their seizure record up to the time of discontinuation. Under P-ITT, patients who did not complete the trial, for any reason, were failures regardless of whether or not they had experienced any seizures during their participation. Therefore, a patient who left the trial after 3 weeks for any reason without having experienced a seizure since Day 1 was considered a success under LOCF, but was a failure under P-ITT. These evaluations were applied to the entire treatment period and to the Maintenance phase only for each trial. The same analyses are presented for

Table 1 Target dosing.

	LAM100034	LAM100036	LAM30055
Concurrent EIAED (e.g., carbamazepine)	500 mg/day (400—600 mg/d)	500 mg/day (400—600 mg/d)	NA
Concurrent valproate	200 mg/day (150—250 mg/day)	200 mg/day (150—250 mg/day)	250 mg/d; 300 mg/day[a]
Concurrent neutral AED	300 mg/day (200—400 mg/d)	300 mg/day (200—400 mg/d)	250 mg/d; 300 mg/day[a]

[a] Monotherapy doses. Concurrent AED was withdrawn during conversion phase.