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Clinical features associated with placebo response in refractory focal epilepsy

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ABSTRACT

For clinical trial design and for clinical practice, it is of importance to assess factors associated with placebo response in patients with refractory epilepsy. We determined factors associated with placebo response in 359 adult patients with refractory focal epilepsy participating in three randomized placebo-controlled trials of the new antiepileptic drug lacosamide. At the end of the randomized 12-week maintenance period, 81 (23%) of the 359 patients randomized to placebo achieved at least a 50% seizure reduction (responders) compared to baseline. In contrast, 278 (77%) patients did not achieve a 50% seizure reduction (non-responders) compared to baseline. In multivariate analysis, five factors, which were present prior to the exposure to placebo, were found to be associated with placebo response. Higher age at study entry improved the chances of placebo response for each year [$p = 0.023$, odds ratio (OR) 1.034 (95% confidence interval (95% CI): 1.005–1.063)]. In contrast, a lower chance of placebo response was seen with age at diagnosis of epilepsy of 6–20 years compared to ≤5 years [$p = 0.041$, OR 0.475 (95% CI: 0.232–0.971)]. A history of 7 or more prior lifetime AEDs lowered the chance of achieving placebo response compared to 1–3 prior lifetime AEDs [$p < 0.001$, OR 0.224 (95% CI: 0.101–0.493)] as did a baseline seizure frequency >10 seizures per 28 days compared to ≤5 seizures per 28 days [$p = 0.026$, OR 0.431 (95% CI: 0.205–0.904)]. Prior epilepsy surgery lowered the likelihood of placebo response [$p = 0.02$, OR 0.22 (95% CI: 0.062–0.785)]. We suggest that age at exposure to placebo, age at diagnosis of epilepsy, the number of prior lifetime AEDs, baseline seizure frequency and a history of epilepsy surgery appear to be associated with placebo response in adults with refractory focal epilepsy.

1. Introduction

It is well known that a wide range of patients with refractory focal epilepsy will experience improvement in seizure control versus baseline during exposure to placebo in controlled clinical trials. In a systematic review of 54 trials in adults and children with refractory epilepsy, 606 of 4124 (15%, range 0–39%) patients receiving adjunctive placebo reported ≥50% seizure reduction, while 51 of 2420 (2.1%, range 0–17%) controls receiving adjunctive placebo in 30 trials became seizure-free [1]. However, there is uncertainty which features, if any, that are present prior to exposure to placebo contribute to the wide range of placebo response and are associated with placebo response in adults with refractory focal epilepsy. Although it has been suggested that placebo response is higher in adult patients with only one baseline AED, later age at onset and shorter duration of epilepsy than in those with more than one baseline AED, earlier age at onset, and longer duration of epilepsy, only a univariate analysis was performed [2]. Another analysis, published as an abstract, showed that a prior history of resective epilepsy surgery or vagus nerve stimulation (VNS) was associated with a lower placebo response compared with that of non-surgical patients [3]. Other than that, we found no published data on individual predictors of placebo response among adults with refractory epilepsy. A meta-analysis of placebo-controlled antiepileptic drug (AED) trials showed that response to placebo was significantly greater in the maintenance period than in the entire treatment period [4]. Whether responder rates for placebo have increased over the last few decades remains controversial [4,5]. In summary, there is a paucity of data indicating whether individual clinical features, if any, are associated with the magnitude of placebo response in refractory epilepsy. This is surprising given that, according to FDA guidance, placebo is a standard control for randomized controlled trials of adjunctive AED treatment [6]. In AED trials, placebo is often perceived to be an inert control independent of study population [7], yet no studies have verified this theory. In a recent trial of perampanel, a new AED, unexplained higher placebo response in South vs. North America was observed [8]. Furthermore, an unpredictably high placebo response was seen as a factor critically reducing the effect size of adjunctive carisbamate, an experimental

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AED [9]. A higher-than-expected placebo response was also considered responsible for the failure in showing a difference between placebo and controlled release pregabalin in a trial for the treatment of refractory focal epilepsy [10]. Uncertainty about what drives the placebo response in AED trials has added to the concern that exposure to placebo may be associated with increased mortality [11]. Knowing which factors drive placebo response in refractory epilepsy could not only improve AED trial design but may also be important for clinical practice. Placebo is not considered to be a suitable treatment for patients with epilepsy, as there are no data indicating that it is better than no treatment. However, predicting placebo response may help to better understand this response that may be inherent in any active drug treatment that we give to patients, and thus, applying this knowledge optimizes our clinical practice. Taken together, it may be of great clinical interest to elucidate the factors that drive placebo response in patients with refractory epilepsy. The purpose of the present study was to examine which baseline clinical features, if any, predict the magnitude of placebo response in individual patients with refractory focal epilepsy.

2. Methods

Placebo data from three Phase II/III randomized, placebo-controlled trials [Study SP667 (12); Study SP755 (13); Study SP754 (14)] were kindly provided by UCB. The placebo data formed part of the clinical development evaluating lacosamide (Vimpat®) as adjunctive therapy in patients with partial-onset seizures. The trials were conducted between February 2002 and August 2006 and had similar designs consisting of an 8-week baseline period followed by a 4–6 week titration period and a 12-week maintenance period.

2.1. Patients

All three trials had similar patient eligibility criteria and included male and female adults ages 16–71 years [13,14] and 18–65 years [12] with partial-onset seizures with or without secondarily generalized seizures [15]. Patient diagnosis was supported by electroencephalography (EEG) and either magnetic resonance imaging (MRI) or computed tomography (CT) scan. The disposition of patients randomized to placebo is given in Fig 1.

Patients in all three studies were required to be experiencing at least four partial-onset seizures per 28 days, with no seizure-free period longer than 21 days during the 8 weeks prior to baseline and during the 8-week baseline period. Patients were to have been on a stable dosage regimen of one to three AEDs [13,14] or one to two AEDs [12] with or without VNS (stable settings), in the 4 weeks before enrolment, during baseline, and throughout the trial. Patients with prior surgical intervention for epilepsy were categorized by type of procedure: VNS only, resection only, and VNS and resection. Patients were excluded if they had a history of chronic alcohol or drug abuse and any medical condition that might jeopardize the patient's health or compromise the patient's ability to participate in the trials.

2.2. Definitions

Trial SP667 was conducted in 68 centers across Germany, Hungary, Lithuania, Poland, Sweden, Switzerland, the United Kingdom, and the United States. A total of 418 patients were randomized; 97 received placebo, and one of whom did not have post-baseline efficacy assessments [12]. Trial SP755 was conducted in 75 centers across Australia, Croatia, Czech Republic, Finland, France, Germany, Hungary, Lithuania, Poland, Russia, Spain, Sweden, and the United Kingdom. A total of 485 patients were randomized; 163 received placebo, four of whom did not have post-baseline efficacy assessments [13]. Trial SP754 was conducted in 72 centers in the United States only. This study

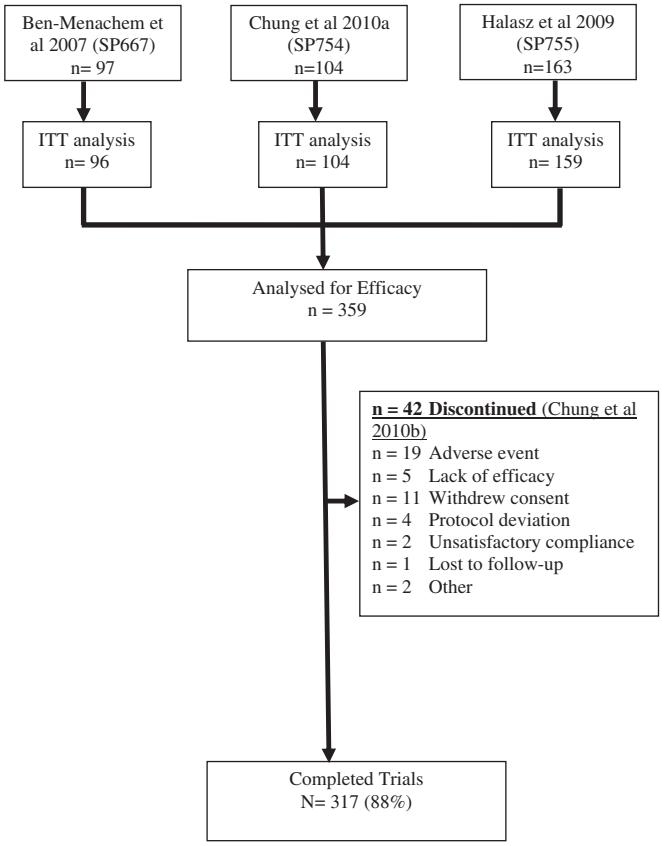

Fig. 1. Disposition of patients randomized to placebo.

randomized 405 patients, 104 of whom received placebo and all these patients received at least one dose of trial medication and had at least one post-baseline efficacy assessment [14]. Nineteen patients randomized to placebo dropped out due to adverse events (AEs), 5/97 in SP667, 5/104 in SP755 and 9/163 in SP755.

The *a priori* responders to placebo were defined as those patients who had a reduction of at least 50% in their seizure frequency from baseline to maintenance. The intent-to-treat (ITT) approach was taken which included all patients who received at least one dose of placebo and had at least one post-baseline efficacy assessment. For patients who discontinued before the maintenance period, efficacy data were carried forward from the titration period for inclusion in the maintenance period analysis. For patients who discontinued during the maintenance period, seizure frequency was calculated using all available data in the maintenance period [12–14]. Epileptic seizures were classified by the investigator in the case report form according to the 1981 ILAE classification of seizures [15]. The etiology of the epilepsy was identified in the case report forms by the investigator as either symptomatic, idiopathic or other. By design of the case report forms, symptomatic etiology included all known causes (genetic propensity, congenital abnormality, ante- and perinatal injury, trauma, infections, vascular causes, toxic causes, and degenerative causes). More than one cause could be chosen by the investigator for each patient. Idiopathic etiology was reserved for patients when no known cause was identified in the case report forms. The case report forms of patients identified to have other causes in whom the etiology was unclear underwent review by two medical reviewers of the pharmaceutical company, and the etiology was classified as either idiopathic (which included cryptogenic etiology) or symptomatic. Modern AEDs were the second and third generation AEDs as defined by Löscher and Schmidt [16].