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Randomized controlled antiepileptic drug trials miss almost all patients with ongoing seizures

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ABSTRACT

In spite of the marketing of numerous new antiepileptic drugs (AEDs), their real-life effectiveness has often been disappointing. We therefore retrospectively investigated how many adult patients with drug-resistant epilepsy would have been potential candidates for the last five phase II and III trials that have been performed at our center. Out of a group of 216 consecutively collected patients, only 18 (8.3%) would have been acceptable for recruitment. Treatment with enzyme-inducing AEDs or concomitant medications (47.2%), too few seizures during a baseline period (41.7%), and EEGs showing a pattern not consistent with a diagnosis of focal epilepsy (e.g. generalized spike-wave) (31.5%) were the leading exclusion criteria. If only one criterion prevented recruitment, too few seizures during the baseline period and treatment with enzyme-inducing medications were the most frequent limitations for potential recruitment. Due to the limiting inclusion and exclusion factors of clinical AED trials, only a small fraction of patients with drug-resistant epilepsy is suitable. When new AEDs have passed such trials and are introduced, we have no information about the potential efficacy and tolerability in >90% of our patients with AED-resistant epilepsies. This may be one reason for the disappointing efficacy of many new AEDs after launch.

1. Introduction

Prior to the era of the new antiepileptic drugs (AEDs) that started globally around 25 years ago, the percentage of patients with drug-resistant epilepsy was around 20–30% [1]. Although many new AEDs have been introduced since then, around 15% to 35% of all epilepsy patients do not achieve sustained seizure freedom [2]. Apparently the development of new AEDs and their licensing after randomized placebo-controlled trials has widened the selection of AED treatment but not considerably increased the proportion of seizure-free patients. This indicates that drug development may be impaired by systematic practices that prevent the introduction of more effective new compounds.

In our out-patient department we see more than a thousand patients per year, many of them suffering from drug-resistant epilepsy. With the marketing of every new AED over the last decades, we have faced the problem that the study data and the resulting labeling have not necessarily allowed us to estimate their real-life effectiveness and their practical value in our patients with drug-resistant epilepsy. Appropriate dosing and effectiveness are among the typical unsolved practical issues after marketing in patients who represent groups that are often excluded from randomized controlled add-on trials, like patients on enzyme-inducing AEDs or patients with severe co-morbidities.

Furthermore, many of our patients have intellectual disabilities and electro-clinical signs of secondary generalized epileptogenesis and may respond differently from the previous study population.

These clinical observations led us to suggest that because many of our drug-resistant patients are not covered by phase II and III trials, the results of these trials might be representative only for a small fraction of difficult-to-treat epilepsies.

Therefore we investigated retrospectively how many of our adult out-patients with AED resistance according to the ILAE criteria [3] would have been potential candidates for the randomized controlled add-on AED trials we participated in.

2. Material and methods

From July of 2014 until February of 2015, we studied adult consecutive out-patients with drug-resistant epilepsies according to the ILAE classification [3]. They were seen and treated exclusively by one of us (BJS) in his out-patient clinic who also compiled the clinical characteristics, co-morbidities, classification of seizures and epilepsies according to the latest proposal of the ILAE [4], and seizure burden, as well as clinical, imaging, and EEG findings, and the anticonvulsant and additional medications.

One of us (BCH) correlated this profile with the inclusion and exclusion criteria of the last five phase II and III randomized controlled add-on trials in patients with difficult-to-treat epilepsies with partial-onset seizures that have been performed at our center. All

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studies had been submitted to and approved by a principle and our local ethical committee which is located in the University of Freiburg, Germany. Three of the studies used for this investigation are still not finished or published, two of them are [5,6]. The trials (Pharmaceutical company, study title, phase, Eudract numbers) we used for this paper were the following:

1. GlaxoSmithKline 113905: Retigabine (IR), AED add-on study to specified monotherapy antiepileptic treatments (Phase IIIa) in adults with partial epilepsy, Eudract-No. 2009-0177444-14, Eudract-No. 2010-0227772-3
2. Pfizer A0081194: Pregabalin CR, AED add-on study in focal epilepsy (phase III), Eudract-No. 2010-019035-35
3. SK Life SCIENCE Inc YKP3089C017: Dose-response trial of YKP3089 as adjunctive therapy in subjects with partial onset seizures (phase II) Eudract-No. 2013-001858-10
4. Marinus 1042-0603: Ganaxolone as adjunctive therapy in subjects over 18 years with simple onset seizures, with or without generalized seizures (phase III), Eudract-No. 2014-004363-21
5. UCB EP0069:UCB0942, Randomized, Double Blind, Placebo Controlled Study for patients with drug resistant focal epilepsy, Phase IIA, Eudract-No. 2014-003330-12.

We investigated how many patients would have been suitable for all studies, the limiting criteria and in how many instances there was only one excluding criterion, and which one. Due to the structured requirements of such studies most criteria were identical. If criteria varied such as the minimum seizure frequency during baseline we chose the lowest figure (two seizures in eight weeks). The co-medication with enzyme-inducing drugs or agents was an exclusion criteria in two of the five trials. We kept this criterion in our analysis because it has a considerable impact but also assessed the potential number of appropriate patients without this criterion. Since the consideration of the last five studies performed at our center might have prevented too many patients from being potential candidates in all single studies and the phase II trials might have had too much impact on the general result presented here, we performed a separate analysis of the phase III trial with the least strict inclusion and exclusion criteria that was performed with an already licensed compound as a slow-release formulation (Pfizer A0081194: Pregabalin CR, AED add-on study in focal epilepsy (phase III), Eudract-No. 2010-019035-35) [6].

3. Results

We identified 216 patients (115 females, 101 males) with AED-resistant epilepsy according to the ILAE definition[3]. Mean age was 42,4 ± 14,2 (range 19–76) years. Only 18 (8.3%) would have been appropriate candidates. Table 1 shows the importance of the major criteria for eligibility, and the ranking of the limiting criteria.

One might speculate that in most patients only one criterion might have been responsible for a lack of eligibility. However, this was the case in 50 patients (23.1%) only. The main limiting factors in this group are shown in Table 2.

Pure focal epilepsies without any additional signs for generalized epileptogenesis except secondary generalized seizures and not suffering from epileptic encephalopathies such as Lennox Gastaut syndrome were present in 148 patients (68.5%).

Of these 148 patients 16 (10.8%) would have been possible candidates for recruitment.

When we applied the inclusion and exclusion criteria of the phase III trial within the selection of five studies that offered the least limited inclusion and exclusion criteria, 33 of our 216 patients would be potential candidates (15.2%). Still, even in this trial 85% of our drug-resistant epilepsy patients would not have been addressed. Inclusion and exclusion criteria of this trial were reported elsewhere [6].

Table 1
Decisive inclusion-/exclusion criteria.

Criterion	Ratio (n)	%
Exclusion: Subject is currently treated with carbamazepine, phenytoin, primidone, or phenobarbital or any other drug known to induce CYP3A4 liver enzymes[a]	102/216	47.2
Inclusion: During the 8 weeks baseline, subject must report having had at least 2 spontaneous and observable focal seizures ("focal seizures" does not include auras or pure somatosensory seizures) without clustering[b]	90/216	41.7
Exclusion: Subject has had EEGs showing a pattern not consistent with a diagnosis of focal epilepsy (e.g. generalized spike-wave)	68/216	31.5
Inclusion: Subject and/or caregiver (not allowed in Germany by the Ethic Committee) is considered reliable and capable of adhering to the protocol (e.g., able to understand and complete diaries), visit schedule, and the medication intake scheme as instructed according to the judgment of the Investigator	64/216	29.6
Exclusion: Subject has a current or past psychiatric condition that, in the opinion of the Investigator, could compromise his/her safety or ability to participate in this study	55/216	25.5
Exclusion: Subject has a history of liver disease, including but not limited to (stable on repeat testing) elevation of liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >1.5 times the upper limit of laboratory reference ranges or alkaline phosphatase [ALP] >2 times the upper limit of laboratory reference range). Other clinically significant lab values and any other medical condition or serious systemic disease that may jeopardize the patient's safety (e.g. clin.sig.abnormalities of ECG, history of malignant neoplasm, history of drug allergies, pregnancy)	43/216	19.9
Exclusion: Uncountable seizures due to clustering are not allowed	28/216	13.0
Inclusion: Limited intake of only 1–3 concomitant AEDs	25/216	11.6
Inclusion: Limited intake of benzodiazepines	21/216	9.7
Exclusion: Subject has had pseudoseizures, conversion disorder, or other nonepileptic ictal events	15/216	6.9
Exclusion: Epilepsy syndromes that are not allowed (e.g. Lennox Gastaut syndrome)	13/216	6.0
Exclusion: Subject has a history of status epilepticus or has been hospitalized for status epilepticus within the 6-month period prior to screening visit	12/216	5.6
Exclusion: Acute or progressive neurological diseases	10/216	4.6
Exclusion: Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt or aborted attempt) or has had suicidal ideation in the past 6 months as indicated by a positive response	6/216	2.8

[a] Exclusion criterion in two of the five studies investigated: GlaxoSmithKline 113905: Retigabine (IR), AED add-on study to specified monotherapy antiepileptic treatments (Phase IIIa) in adults with partial epilepsy, Eudract-No. 2009-0177444-14, Eudract-No. 2010-0227772-3 and UCB EP0069:UCB0942, Randomized, Double Blind, Placebo Controlled Study for patients with drug resistant focal epilepsy, Phase IIA, Eudract-No. 2014-003330-12. Without this criterion 12 more patients would have been appropriate candidates.

[b] Only in one study (GlaxoSmithKline 113905: Retigabine (IR), AED add-on study to specified monotherapy antiepileptic treatments (Phase IIIa) in adults with partial epilepsy, Eudract-No. 2009-0177444-14, Eudract-No. 2010-0227772-3). The minimum seizure frequency per 8 weeks was at least 6 in the four other trials. This would have excluded 10 more patients or a percentage of 46.2%.

4. Discussion

Our data show that we have no information about potential efficacy and tolerability in >90% of our patients with AED-resistant epilepsies when new AEDs have passed such trials and are ready to be launched. It could be argued that many patients who turned out not to be appropriate candidates in our study did not have pure focal epilepsies or even worse epileptic encephalopathies with at least additional electroclinical signs of generalized epileptogenesis. However, when we considered the 148 patients (68.5%) with pure focal epilepsy only, 10.8% of those would have been appropriate for study recruitment and thus only slightly more than the 8.3% over all. Even if we consider one single phase III trial dealing with an already licensed compound as a slow-release formulation [6] this did not have a relevant impact on the