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Challenges of Drug Development in Drug Resistant Focal Epilepsy

Epilepsy is one of the most common and disabling chronic neurologic disorder that affects more than 50 million people worldwide.[1] Despite current of over two dozen antiepileptic drugs (AEDs), about one third of people with epilepsy fail to achieve complete freedom from seizures with existing medications employed alone or in various combinations. This phenomenon is known as a Drug Resistant Epilepsy (DRE) and represents a major challenge in epilepsy treatment.

Several clinical types of DRE have been recognised to date including resistance from the onset of seizure treatment (ab initio), delayed resistance (after an initial seizure-free period), and a fluctuating pattern where seizure-free periods alternate with resistant periods. Long-term outcome studies in newly treated patients with epilepsy suggest that after failure of two well-tolerated AED schedules appropriately chosen for the seizure type(s), the chance of success with further drug manipulation becomes progressively less likely,[2] which supports the operational definition of DRE as a failure of two appropriately selected and tolerated AED regimens.[3] Although clinical trials of novel investigational agents repeatedly demonstrate that 30% to 40% of treatment-resistant participants are likely to improve with each drug tried,[4] it is essential for patients to achieve either a seizure-free status or non-drug resistant epilepsy status with long-term treatment (usually more than a year).

The strategy for assessing the effectiveness of AEDs has not substantially changed in the last 30 years. Typically, AEDs are tested initially as an adjunctive therapy in patients with treatment-resistant focal (partial) epilepsy. This patient population is studied initially because it comprises the largest population of adult patients with DRE, making trial enrolment more achievable. Adjunctive or "add-on" trial designs are utilised in early studies as Food and Drug Administration (FDA) guidance demanding that these studies demonstrate superiority.[5] While it is much easier to demonstrate superiority when a placebo control is used than an active comparator, it would not be ethical to expose patients to prolonged monotherapy with an experimental agent.

Due to the accessibility of many efficacious AEDs, it has become increasingly difficult for investigators to enrol patients in novel AED trials.[6] This is particularly true in high income countries, where specialised centres usually have access to the entire therapeutic armamentarium, and physicians and patients are understandably reluctant to participate in trials which require prolonged exposure to compounds with unproven efficacy. It is often easier for these potential trial participants to simply try the complete list of already available AEDs[7] than to enrol in a study. These concerns have been further exacerbated by the finding that patients with refractory epilepsy randomised to placebo treatment in trials have a seven-fold increase in the risk of dying of sudden unexpected death in epilepsy (SUDEP) compared with patients randomised to active treatment.[8] Faced with difficulties in enrolling sizeable number of patients in highly specialised centres, the pharmaceutical industry reacted by steadily enlarging the recruitment base through involvement of less experienced investigators and inclusion of study sites located in geographical regions where availability of AEDs (or patient's ability to afford expensive medications) is severely restricted.[9]

Of course, including less experienced investigators may adversely impact the quality of the trial conduct and negatively influence trial outcomes. Evidence from other therapeutic areas suggests that the recent shift toward large multi-site trials can also lead to an increase in response to placebo and to a decrease in effect size of active medications.[10] It appears that a similar situation may be occurring in epilepsy trials as well.[11] Indeed, systematic reviews have shown that placebo response in epilepsy trials has increased gradually over the years, together with a trend toward a decreased effect size for efficacious AEDs. Post-hoc analyses of data from recent AED trials also suggest that the ability to discriminate active medication from placebo may be related to geographical location of study sites and this ability may decrease drastically for sites located in regions that do not have a long-standing history of participation in AED trials.[12] Considering this heightened placebo response in AED research, study protocols in DRE should attempt to systematically evaluate predictors of placebo response which include age of seizure onset, pre-study number of seizures, and history of AEDs used in treatment.[13]

The circumstances outlined above have important implications for drug development in epilepsy. On one hand, enrolling difficulties related to practical and ethical concerns with prolonged placebo exposure severely restrict the possibility of conducting trials at sites possessing the optimal expertise/experience. On the other hand, extending recruitment to less experienced study sites can reduce the effect size and weaken the ability to differentiate active treatments from placebo.[7] To date, the industry's reaction to a decreased effect size has been to increase statistical power simply by enrolling larger number of patients through the involvement of additional sites, leading to a vicious circle that has only compounded the problem with the possible unintended effect of increasing the overall failure rate of epilepsy trials.[5]

DRE Study Design

Traditional study designs to evaluate AEDs in DRE usually require that patients be on a stable background treatment with one to three AEDs, have a seizure frequency of at least three to four focal seizures per month (but not weekly frequency), and no 21 to 28-day period of being seizure free. A retrospective screening phase can be used to determine the patient's refractory status, followed by a prospective baseline evaluation during which baseline AEDs are held constant and the patient's seizure diaries are kept. This phase should be of sufficient length to detect any fluctuations in seizure frequency (usually 8 to 12 weeks). Shorter baseline periods (i.e., 8 weeks) are preferred, as longer ones can hamper patient recruitment. The minimum exposure period in traditional randomised double-blind trial designs accepted by regulatory agencies is 12 weeks. The proper training of patients and their caregivers who will record seizures in the diary is crucial for study success. Investigators should explore the exact phenotype(s) of the seizures and make sure that patients or caregivers are recording seizures and not adverse events.

The outcome of interest for most therapeutic trials of AEDs is usually based on seizure frequency. This is typically specified as

median seizure reduction from baseline, or the number of subjects with a greater than 50% seizure reduction or both; preferences vary depending on the regulatory agency. While this outcome is obviously clinically relevant, it is notoriously difficult to measure reliably.[14] In epilepsy trials, subjects are asked to complete seizure diaries often using paper calendars in which they note the date of their seizure and as well as the type of seizure they had. However, it is well known that patients with epilepsy are often not reliable reporters of their seizures. In a study of patients on an epilepsy monitoring unit which permitted observation and objective confirmation of seizure activity, only 26% of subjects reported being aware of all their seizures and 30% of subjects recalled none of their seizures.[15] Even when subjects are aware of the seizure, they may fail to record this contemporaneously and diaries are often not completed in real time. The diary may not be available at the time of the seizure or in many cases the postictal state may be prolonged preventing accurate and timely recording.

Although a single study in subjects with epilepsy has noted good reliability of a paper diary compared with random subject interviews,[16] studies in other fields have demonstrated very poor compliance with daily diary completion.[17] Backfilling or the retroactive completion of the diary just prior to the study visit is a common practice and can lead to inaccurate recollection of seizure frequency and type. It is also not clear that subjects can reliably distinguish among their seizure types. In clinical practice, it is common that subjects mistake focal motor seizures with impaired awareness (previously known as a complex partial seizure) for non-motor seizures with preserved awareness (previously known as a simple partial seizure) because they are amnestic for part of the seizure. This phenomenon has significant implications for the accuracy of reported outcomes in clinical trials. Therefore, a reduction in seizure severity (e.g., from motor to non-motor) can be missed because subjects are unable to distinguish seizure types accurately and reliably. Tonic-clinic seizures are less likely to be misidentified or forgotten because they are less frequent and often associated with characteristic signs, such as muscle soreness or tongue biting, that are more obvious to the patient even if they are amnestic for the event.

Time to Event Designs

As noted above, traditional randomised placebo-controlled add-on designs that have been the mainstay for the clinical development of AEDs for decades are now facing major implementation difficulties which include both the ethical and practical concerns with exposing patients to placebo or ineffective treatments for prolonged periods of time (typically 12 to 24 weeks).[7] One attractive approach which can circumvent these concerns involves the use of a time-to-event design whereby patients are required to exit the trial after a pre-determined but not excessive number of seizures has occurred.[18] In this paradigm, patients who receive a drug which reduces the frequency of their seizures will remain on treatment for longer periods of time compared with patients randomised to placebo, and the time elapsed before meeting exit criteria can be used as an efficacy endpoint.[9] These time-to-event designs have been used before in epilepsy studies, mostly in clinical trials designed to assess conversion to monotherapy.[19] Its application to adjunctive trials would be especially attractive to patients because only trial participants who show a beneficial response are required to remain on double-blind treatment for a prolonged period of time. The validity of this design has been demonstrated in three randomised double-blind placebo-controlled add-on trials of becampanel in adults with focal seizures.[20] Using an endpoint of the time to return to pre-randomisation seizure count, a significant difference between perampanel and placebo was obtained for all focal seizures and secondarily generalized tonic–clonic seizures. The time-to-event design is beleaguered by reduced retention of patients allocated to placebo which will not permit appropriate comparison of late-onset adverse events between study arms. In this case, a definition of a minimum duration of placebo exposure is warranted, as well as carefully planned extension studies after the double-blind phase is complete.

Conclusions

The efficiency of randomised controlled trials of AEDs can be improved not only by minimising trial duration, particularly for patients exposed to placebo, but also by reducing the number of patients needed to demonstrate efficacy.[9] The latter goal can be best achieved by ensuring a large effect size, either by developing medications with higher expected efficacy and/or by increasing the accuracy and reliability of outcome measures (decreasing the variance). This is done by confirming accurate/contemporaneous ratings and assessments of seizure frequency and type, ensuring proper patient selection, and by refining the ability to identify beforehand those patients who are most likely to show a good response. The ongoing shift towards precision medicine or the development of treatments rationally designed to target well-characterised patient groups represents an important step in maximising effect size.[21] There have been increased efforts to ensure that only the patients who have the disease of interest are enrolled in trials, and that these patients' seizures are correctly counted. One method to ensure appropriate patient selection is by use of external individual patient review prior to randomisation.[9] Optimising trial design features and using novel designs that will take advantage of the mechanisms of novel drugs with improved efficacy and tolerability profiles is essential to the approval of AEDs in DRE.

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