DEBATE: A 50% REDUCTION IN SEIZURE FREQUENCY IS A USEFUL MEASURE TO ASSESS TREATMENT RESPONSE IN EPILEPSY

YES

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Evaluation of AED performance based on clearly defined and consistently applied outcome measures is essential for the optimal management of patients. The design of AED clinical trials should be relevant to real-world settings, providing reliable, valid, and comprehensive information on efficacy, tolerability, and quality of life. Several types of outcome parameters have been elaborated: percent seizure reduction, responder rate based on > or =50% seizure reduction, seizure-free rate, time to first seizure, time to Nth seizure, adverse events, QOL, retention, and compliance. Each provides important information about a drug's performance.

Seizure freedom is the ultimate goal of epilepsy treatment. It reduces morbidity and mortality, prevents sudden death from epilepsy, and improves quality of life. In the series of 780 newly diagnosed patients, 50% became seizure free on the first AED; 31% never had another seizure after starting AED. Also, calculating seizure freedom rates relative to a comparator is an ideal way to document efficacy of a new AED. (Kwan, Brodie, 2000; Mohanraj, Brodie, 2006). In fact, Committee for medicinal products for human use Guidelines (2009) requires, that in newly or recently diagnosed patients, the primary efficacy variable should be based on the proportion of patients remaining seizure free for at least six months (excluding the dose escalation period).

However, **adjunctive therapy trials designed** to gain regulatory approval of new AEDs are usually conducted in patients resistant to mono- or polytherapy. Because this population is particularly refractory to drug therapy, **complete seizure control is not really a realistic expectation in these patients**. Also, high seizure-freedom rates cannot be expected, and seizure freedom often is not reported.

In add-on therapy, the period over which seizure frequency is measured should be pre-defined. The primary endpoint should dichotomise the data into responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency (**a 50% reduction is commonly used**). The other variable should be some parameterisation using the actual change in seizure frequency (Committee for medicinal products for human use Guidelines, 2009).

Traditionally, changes in seizure frequency are determined by counting seizures during the baseline and treatment period and then comparing the results. A problem with **analyzing seizure frequency** data, however, relates to the **non-normal distribution of the data** and the high degree of variation both between subjects and within subjects (French, 2001; Ryvlin, 2008).

The most commonly reported outcome is the proportion of 50% responders.

In the recently published systematic review and meta-analysis (Beyenburg et al., 2009) in a total of 54 studies, overall 2,450 of 6,982 (35%, range 14–60%), adults and children with refractory epilepsy showed a 50% seizure reduction with adjunctive AED treatment compared to 606 of 4,124 (15%, 0–39%) controls receiving adjunctive placebo, giving a weighted **pooled risk differences RD of 21% (95% CI 19–24, z = 17.13, p < 0.001) for 50% seizure reduction of adjunctive AED treatment versus placebo that is in favor of AEDs.**

In each clinical trial, it is relevant to compare the **relative risk (RR)** of being a responder on drug treatment in relation to the responder rate on placebo. Also, it is quite important to evaluate the placebo response in meta-analysis.

The pooled placebo response in adults was estimates as 12.5% (95% CI: 10.03–14.94%) (Guekht et al., 2010). Rheims et al. (2008) demonstrated that responder rates were higher among children than adults (19% vs 9.9%, P < 0.001).

Seizure freedom was reported not in all the add-on trials. Overall in 30 studies, 339 of 4,134 (8.2%, range 0–35%) adults and children with refractory epilepsy were seizure free compared to 51 of 2,420 (2.1%, 0–17%) controls receiving adjunctive placebo, giving a weighted pooled RD of 6% (95% CI 4–8, z = 6.47, p < 0.001) in favor of AEDs (Beyenburg et al., 2009)

In addition to those becoming seizure-free, 35% of patients benefit from seizure reduction of at least 50% compared to 15% of those receiving adjunctive placebo. This provides a weighted pooled RD of 21% (95% CI 19–26) for 50% seizure reduction in favor of AEDs.

Once again, seizure freedom is the ultimate goal of AED treatment. Still, is add-on trials on refractory epilepsy, apart **from the low probability of seizure freedom, there are other methodological issues to be considered**.

Given that refractory epilepsy is a chronic disorder, uncertainty and concerns exist about how predictive such a **short-term seizure-free result** can be for the long-term seizure outcome of the patient (Gazzola et al., 2007).

Seizure freedom rates may be significantly impacted by all methods that allow investigators **to define as seizure-free those patients who did not complete** the entire treatment period. When one compares the seizure-freedom rates allowing dropouts to be counted as seizure-free, versus counting only completers as seizure free, in several cases there is a dramatic difference in the results. For example, OXC displays a high percentage of seizure freedom of 12% in the LOCF analysis. Yet when one considers the completer data, the percentage declines to 1.3% (p < 0.0001). (Barcs et al., 2000). It is important to understand that the seizure-free rates presented from the ITT LOCF population included patients who were seizure-free for only 1 week. Including such patients as seizure-free inflates the apparent rate of seizure freedom.

Another factor influencing the seizure-free data is **titration**. Long titration period could diminish the proportion of seizure-free patients due to the the long subtherapeutic window (Gazzola et al., 2007).

Conclusion.

According to the huge experience in AEDs trials and clinical practice worldwide, there appears to be a consensus that a 50% decrease in seizure frequency from baseline represents a clinically relevant outcome criteria (except for patients with newly diagnosed epilepsy). Regulatory agencies and healthcare providers

acknowledge 50% seizure reduction as a sign of efficacy in many AEDs trials. Indeed, seizure reduction as a direct effect of AED treatment is a welcome benefit for those who have not become seizure free.

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