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Why are epilepsy trials failing? Interview with Russell Katz

Russell Katz is the director of the Division of Neurology Products in the US FDA’s Center for Drug Evaluation and Research. Katz’s division is responsible for regulating research with investigational treatments for neurologic diseases, including epilepsy, as well as making decisions about which treatments should be approved. He has written and lectured extensively about all aspects of the development of treatments for neurologic diseases. Katz speaks to Laura Harvey at the journal, on the difficulties facing antiepilepsy drug trials today.

Q You recently attended the antiepileptic drug trials XI meeting in Florida, what would you say were the most important points of debate?

There was considerable discussion on why epilepsy trials seem to be failing more often than in the past, although I am not convinced that this is so; whether the placebo rate in these trials is considerably greater than in the past – I am also not convinced that the case has been made for this; novel trial designs (including novel designs for monotherapy), an increase in sudden unexplained death in epilepsy (SUDEP) in placebo patients in trials and the continuing controversy about the reliability of generics.

Q What issues were raised on new suicidality concerns and their impact on antiepileptic drug trials?

No new issues were raised specifically about the results of our meta-analyses of suicidality with antiepilepsy drugs. There was, however, discussion about the best way to assess suicidality during drug development, and some issues were raised about the specific scales we have proposed that sponsors use. No definitive objections to our proposed scales were raised; we have continued to state that other scales may be used if they can adequately map to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) scale, so that the data from the various development programs can be compared and, ultimately, used in other meta-analyses.

Q What about issues raised on the impact generic antiepileptic drugs have on both clinical epilepsy trials and the epilepsy marketplace?

There was discussion about generic drugs, and the epilepsy community’s concerns about how well they perform. Everyone seemed to agree that there are no definitive data that adequately addresses this point, one way or the other. All agreed that a study or studies be done to address this question. The US FDA is continuing to work with the community and NIH to design a trial or trials that can address various aspects of this issue.

Q One of the most pressing issues at the moment in the epilepsy community is the lack of agreement between US and European regulators on a monotherapy trial design. Do you think an increased dialogue between

regulatory bodies would help in reaching a consensus on trial design?

It would be good to have a consensus, I think, in order to decrease the cost and time of drug development in certain areas (such as monotherapy), and with regard to standardizing diagnoses and data collection. I think in other areas of study design, there probably is a fair amount of consensus. But I agree that the regulatory bodies should talk and try to reach consensus in those areas where there is none, if that is possible.

Q What impact would you say this lack of consensus is having on epilepsy research and the path to development?

It is hard for me to say what the impact is, although, of course, if we had uniform requirements, sponsors would not need to perform different studies for us and the Europeans. This, of course, increases the time and cost of drug development. Whether this inhibits sponsors from pursuing monotherapy claims I cannot say.

Q Is the FDA concerned about globalization of trials? Does this mean that you (the FDA) will require that a substantial portion of patients be recruited in the USA for future studies?

We are, to some extent, concerned about globalization of trials, especially as trials move into geographical areas where we have little to no experience, and especially in conditions in which local practices may differ, in diagnoses and standard of care. We have recently approved a treatment as monotherapy based on a comparison to a historical control group, which was composed of data from eight previous trials, all of which were done in the USA. In a study where a new treatment is compared with a historical control, it is imperative that the patients in the new study be as similar to the patients in the historical control group as possible. In the study that was recently performed (and that served as the basis for the approval), only 25% of the patients were from the USA, which raised many questions about the interpretability of the study. So in certain studies, it may be critical that there be many US patients. As a general rule, we do ask sponsors to enroll a substantial number of US patients, but we typically do not insist on this.

Q The meeting included several discussions on the placebo effect in epilepsy trials; what would you say was the main reason why several recent epilepsy trials have failed to demonstrate a separation between active drug and placebo?

I don't know the reason why some epilepsy studies fail, and I'm not at all sure that the rate of failure is any higher than it used to be. There are many reasons studies fail, and we usually don't know why. Certainly, there are cases where sponsors do not do adequate dose finding, and take the wrong dose into Phase III studies. But, as I said, I am not at all sure that it is established that studies fail more frequently than they used to.

Q So you don't think placebo rates are rising in epilepsy trials?

No, I am not convinced that placebo rates are rising. Although I do think, in terms of mitigating potential confounders when designing and conducting a trial, picking the right patients would help in any event. One could imagine enriching studies in several ways, including randomizing patients who have previously shown a response to the treatment.

Q Do you think there is a safety issue using a placebo as a comparator in add-on studies?

We have not yet seen in detail the data that were presented about SUDEP. We want to get that data and look at them closely, because it was intriguing, and, if true, could certainly have a profound effect on trial design. It is a very important observation that we need to examine closely.

Q In the case that it does prove to be a factor, what would you say were the alternatives?

I am not sure what the alternatives would be; one can imagine trial designs that radically shorten the placebo period, for example. I certainly am not ready to conclude that active control, non-inferiority designs are the only alternative. Of course, a head to head comparison between two or more antiepileptic drugs with the goal of showing superiority to the control AED would be a design that we would enthusiastically endorse.

Q What is the current FDA opinion on active control equivalence trials as a design for epilepsy trials?

We have not accepted these designs. There are two possible interpretations of a study in which two drugs have been shown to be 'equivalent'; either both drugs worked, or neither drug worked. In order for these designs to be interpretable, one has to conclude that the active control must have been better than placebo in the study. The only way we can be sure that this is true is to know, based on a robust experience of placebo-controlled studies of that active comparator, that the active comparator always

was superior to placebo in those studies, and always by at least some minimal amount. This way, we would be confident that the active control was also better than placebo in the study in which it was compared with the new drug and, by extension, we could conclude that the new drug was also effective. Unfortunately, we do not believe that there is such a robust clinical trial database for any drug that would be proposed as a comparator.

Q Why is the FDA perspective on this different than that of the European Medicines Agency?

My reasons for not accepting these trials are given above. Apparently, the European Medicines Agency believes that such a database exists for some active drug (perhaps carbamazepine); we do not.

Q Is the FDA willing to consider novel add-on trial designs (such as time to nth seizure) that reduce exposure to placebo?

We are certainly willing to consider such designs. Work needs to be done to explore the specifics of such a design (for example, what should n be; how does such a design address the question of persistent effect of a treatment). There was discussion of this topic at a meeting held after the AED XI meeting, and I believe a working group was set up to explore these and related questions.

Q How do you see the landscape of epilepsy trials progressing from here?

I think more work will be done in the area of monotherapy trials. Although, as I've said, we recently approved a treatment as monotherapy based on a comparison to

a historical control, this approach has many problems, and the community is going to be examining the question of whether or not studies of monotherapy should be necessary at all if the drug is already approved as adjunctive therapy.

Q This question of approving a treatment for a certain patient group/therapy type applies to other areas concerning the epilepsy community?

Yes, other issues of interest to me are the question of whether or not controlled trials of extended/controlled-release products should be required (as they are now) if an immediate-release product is available, and whether controlled trials should be required (as they now are) in pediatrics if the drug is already approved in adults.

Q What about other concerns raised at the Miami meeting and for future investigation?

Indeed, other continuing issues also include the generics issue, and I hope we can get a study done that will definitively address the community's concerns in this regard. As I also stated, we do need to look at the SUDEP rates on placebo.

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