

IMPROVING CLINICAL DRUG DEVELOPMENT REGULATORY PROCEDURES FOR ANTICONVULSANTS

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ПОБОЉШАЊЕ РЕГУЛАТИВЕ ЗА КЛИНИЧКО ИСПИТИВАЊЕ АНТИЕПИЛЕПТИКА

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ABSTRACT

Background: Clinical development of anti-epileptic drugs is demanding due to complex character of the disorder and to diversity of its forms and etiologies.

Objective: The aim of this review was to suggest improvements in regulatory procedures for clinical development of antiepileptic drugs.

Methods: The following databases of scientific articles were searched: MEDLINE, SCOPUS and SCINDEKS. In total 558 publications were retrieved. The types of articles selected were reviews, reports on clinical trials and letters to the Editor.

Results: There are several changes of regulatory documents necessary for improving process of clinical development of antiepileptic drugs: preference of parallel groups design for add-on trials should be explicit; the non-inferiority design for monotherapy clinical trials should be acceptable; restrictive formulations when trials of antiepileptic drugs in children are in question should be avoided; requirements in regard to the efficacy measures should be harmonized among the regulatory bodies; proactive attitude towards discovery of adverse events; and precise requirements for clinical trials specifi-

cally designed to prove anti-epileptogenic effects should be made clear.

Conclusion: Current regulatory documents are incomplete in many aspects; an international effort to improve and harmonize guidelines for clinical development of antiepileptic drugs is necessary for improvement of this process.

Key Words: anticonvulsants, clinical development, regulatory documents

САЖЕТАК

Увод: Клинички развој антиепилептика је захтеван процес због комплексног карактера епилепсије, њених различитих облика и етиологије.

Циљ: Циљ овог прегледног чланка је да укаже на могућа побољшања регулативе клиничког развоја антиепилептика.

Метод: Следеће базе података су претражене: MEDLINE, SCOPUS и SCINDEKS. Укупно је пронађено 558 публикација из категорије прегледни чланак, клиничка студија и писмо аутору.

Резултати: Постоји неколико промена регулативе које су неопходне за побољшање процеса клиничког развоја антиепилептика: у студијама где се нови антиепилептик додаје

на постојећу терапију треба обавезно применити дизајн са паралелним групама; у студијама са монотерапијом треба доказати да нови лек није мање ефикасан од компаратора; рестрикције везане за клиничке студије код деце треба ублажити; агенције за лекове С.А.Д. и Европске уније треба да ускладе захтеве у погледу мера ефикасности антиепилептика; став према откривању нежељених дејстава нових лекова треба да буде проактиван; захтеви за студије у којима се доказује антиепилептогени ефекат треба да буду јаснији.

Закључак: Постојећа регулатива је у много чему некомплетна; неопходан је међународни напор да се побољшају и хармонизују водичи за клинички развој антиепилептика како би се тај процес побољшао.

Кључне речи: антиепилептици, клинички развој лека, регулатива

INTRODUCTION

Developing an antiepileptic is more difficult than developing drugs from other therapeutic groups due to chronic character of the disease, its temporal variability in seizure frequency and severity, diversity of seizure types and grave consequences of treatment interruption or non-treatment. The existing regulation of drug development process is based on guidelines for clinical investigation (evaluation) of antiepileptic products issued by the European Medicines Agency (EMA)¹ and by Food and Drug Administration (FDA) of U.S. Department of Health and Human Services². The guidelines are not too prescriptive, which in some cases could be an advantage, but many problematic issues remain untouched, rising difficult dilemmas in the field of antiepileptic drug development, and even more after drug is being used in clinical practice.

Clinical trials with antiepileptic drugs designed according to the regulatory guidelines usually do not give sufficient prediction of their effectiveness and safety in clinical practice settings³. Clinicians who have to prescribe new antiepileptic drug are frequently frustrated, because from the summary of product characteristics they cannot have clear understanding: is the drug effective as initial therapy, could it be used as mono-therapy, what is the optimal dosing regimen, what inter-individual differences could be expected in responsiveness to the drug, what are long-term effectiveness, tolerability and safety of the drug⁴. The situation is even more challenging when antiepileptic drugs are to be prescribed to children, especially in regard to the

generalized seizures and epilepsy syndromes encountered only in childhood⁵.

The aim of this review is to focus on the gaps in current knowledge about optimal use of new antiepileptic drugs in clinical practice, and to suggest changes in regulatory procedures for clinical development of these drugs which could result with improved treatment of patients with epilepsy.

METHODS

In order to identify articles on methodology and regulatory guidelines of clinical trials with anticonvulsants the following databases of scientific articles were searched: MEDLINE⁶, SCOPUS⁷ and SCINDEKS⁸. The following combinations of keywords were used: "clinical investigation + anticonvulsants + guidelines", "clinical investigation + drug development + epilepsy" and "medicinal products + development + epilepsy + regulation", including all records from 1969 to 2015. The types of articles selected among the retrieved papers were reviews, reports on clinical trials and letters to the Editor.

The combination of keywords "clinical trial + anticonvulsants + guidelines" retrieved 287 publications from MEDLINE, 558 from SCOPUS and 0 from SCINDEKS; the combination "clinical investigation + drug development + epilepsy" retrieved 53 publications from MEDLINE, 213 from SCOPUS and 2 from SCINDEKS. Finally, the combination of keywords "medicinal products + development + epilepsy + regulation" retrieved 15 publications from MEDLINE, 3 from SCOPUS and 0 from SCINDEKS.

ADD-ON TRIALS

The add-on clinical trials where an investigational antiepileptic drug is added to antiepileptic therapy which a patient received for a long time, but it did not completely controlled the seizures, are usually the first to be undertaken during clinical development of an anticonvulsant. The pool of potential patients is large, since the existing antiepileptic drugs cannot achieve complete control of seizures in many patients. The patients with partial seizures with or without secondary generalization are usually chosen first, and later trials include the patients with primary generalized seizures. The add-on trials use placebo as comparator, since it could not make additional harm, while it is not known whether any additional therapy (including the investiga-

tional drug) will improve the patient's condition. Whenever possible, the add-on trials include demonstration of dose-response relationship, which is an additional proof of efficacy⁹.

The only regulatory issue with the add-on trials is question of cross-over design. Although used a lot in the past, the cross-over design is now considered inappropriate as primary proof of anticonvulsant efficiency¹⁰. If a patient is to be switched from one treatment regimen to another, during the washout period seizure frequency and severity should return to baseline values. This is sometimes difficult to achieve because there are individual, periodic changes in the disease activity regardless of the therapy, and certain antiepileptic drugs are more prone to carry-over effect from first to the second study period. Besides, if a patient was well on the first therapy regimen, it could be unethical to switch her/him to less efficient second regimen, not to mention that despite of blinding the patient will understand when she/he was taking placebo or the investigational drug¹¹. Therefore, majority of regulatory bodies prefer that parallel group design should be used for add-on trials.

The preference of regulatory agencies towards parallel groups design for add-on trials should be made more explicit in the guidelines for clinical development of antiepileptic drugs. This would direct sponsors on time to avoid cross-over design and methodological issues it carries, but to start from the very beginning with the design which will bring higher level of evidence.

THE PROBLEM OF MONOTHERAPY TRIALS

Since the add-on clinical trials with antiepileptic drugs recruit the patients with chronic refractory epilepsy, their results cannot be extrapolated to new, treatment-naïve patients (the patients who did not take anticonvulsants prior the current clinical trial), who are in many ways different from the former group¹². Establishing efficacy of an anticonvulsant as monotherapy is difficult to achieve during clinical drug development due to low availability of treatment-naïve patients with epilepsy who are ready to be enrolled in a clinical trial. Usual way to overcome this problem is to use conversion or presurgical withdrawal-type design of clinical trials with short duration. In conversion design the outpatients stabilized on certain anticonvulsant medication at first receive adjunctive therapy with either investigational anticonvulsant (usu-

ally both high and low doses) or comparator, and then the baseline anticonvulsants are gradually withdrawn, until the patients remain on monotherapy¹³. The comparator is usually another antiepileptic drug or low-dose regimen of the investigational drug (so called "pseudoplacebo"), use of true placebo is ethically unacceptable, since the patients in the placebo arm could have worsening of their condition with grave consequences: injuries, decreased working capacity, psychological problems, etc. Primary efficacy outcome in such studies is treatment retention time, i.e. time which elapsed until the patient's condition worsened up to a predefined degree. While the FDA accepts this type of trials for the purpose of granting marketing approval to the investigational drug for withdrawal-to-monotherapy in refractory patients, the EMA still requires monotherapy trials with treatment-naïve patients^{3,4,5}. In order to make withdrawal-to-monotherapy type of clinical trials more feasible, the FDA now accepts the results of previous studies as "historical controls" for establishing efficacy and safety of new drugs in patients who were stable, but not seizure-free on a single anticonvulsant. The first drug that was granted marketing authorization for monotherapy after the studies with historical controls was extended-release formulation of lamotrigine¹⁴.

Presurgical withdrawal studies use the opportunity created when inpatients with epilepsy who are prepared for surgical treatment discontinue their prior antiepileptic drugs during diagnostic process of localizing seizures. Then the patients receive either investigational drug or placebo, and are maintained on such therapy until their condition is worsened according to previously defined criteria (e.g. certain frequency of seizures, increase in severity of seizures)¹⁵.

Both conversion-type and presurgical withdrawal designs are actually "proof-of-concept" studies which cannot give information about long-term efficacy of an investigational drug, due to their short duration in the first place¹⁶. Therefore, in order to be granted approval for monotherapy in patients which are not treatment-resistant, investigational antiepileptic drugs have to be tested in monotherapy trials with treatment-naïve patients. Such trials are using parallel-group design with active control (use of placebo in such settings is ethically problematic, since the patients would not have any benefit of participation in a trial like this). These patients are not drug resistant (unlike the patients in add-on trials) and a delay in receiving the appropriate treatment may only worsen their clinical con-

dition. Although resource-demanding, monotherapy trials in treatment-naïve patients are long-term and give unique opportunity to establish efficacy of the investigational drug and to compare it head-to-head with already established antiepileptic drugs. However, while the EMA imposed realistic requirements demanding that an investigational drug only should not be less effective of the comparator (the best existing therapy), i.e. the non-inferiority design is acceptable, the FDA requires from the investigational drugs to demonstrate superiority over the comparator¹⁷. This regulatory request require large sample size, especially when the comparator is truly effective (as it is usually the case nowadays). Before the onset non-inferiority trials the extent of meaningful difference in efficacies of the investigational drug and comparator should be set. The difference, which should be shown as non-existent in these trials, is usually 10% of the value of the main study end-point^{18,19}.

Although monotherapy trials on treatment-naïve patients with epilepsy cannot be avoided, clinical development of new antiepileptic drugs would become more productive if all major drug agencies (including the FDA) accept the non-inferiority design in their guidelines as standard requirement for such clinical trials. The trials would enroll less treatment-naïve patients, and their cost and duration would decrease (because the overall enrollment period for the whole trial would be of less duration), shortening time necessary for obtaining regulatory approval. True effectiveness of new antiepileptic drugs would then be established by carefully designed observational studies, as it was already the case with older anticonvulsants²⁰.

TESTING ANTIEPILEPTIC DRUGS IN CHILDREN

Current guidelines for clinical development of antiepileptic drugs either preclude participation of children with age-nonspecific epilepsies (i.e. with seizures types other than absence, infantile spasms and akinetic seizures) in clinical trials until late phase II or phase III (FDA), or suggest short-term trials in children younger than 4 years and suffering from non-specific epilepsies (focal epilepsies, especially cryptogenic and symptomatic, and idiopathic generalised epilepsies, with absences, myoclonic and/or generalised convulsive seizures) with EEG surrogate end points (EMA)^{1,2}. Children should be included in early clinical trials only after safety studies were already conducted in adults. EMA also

suggests that children with age-specific epilepsies (e.g. West syndrome, Dravet syndrome, myoclonic-astatic epilepsy, Lennox Gastaut Syndrome and Continuous Spike-Wave in Slow Sleep syndromes) should be enrolled in add-on clinical trials as soon as the dose for children has been established. According to EMA requirements, at least 100 pediatric patients should be followed for a year or longer in order to establish safety of new anticonvulsant in children. However, these requirements are not based on evidence of adverse consequences of enrolling children with age-nonspecific epilepsies in early clinical trials, and on the other hand, without pharmacokinetic data, optimal dosing information and tolerability data gathered from a pediatric clinical trial it is very difficult to administer antiepileptic drug optimally to this vulnerable population^{5,21,22}. Regulatory documents should be less restrictive when trials of antiepileptic drugs in children are in question, the sponsors will then have more options for clinical development of their drugs and the trial results will be more useful for pediatric clinical practice.

However, some current regulatory requirements that apply for drugs intended for use in children in general may be helpful in the meantime. Extrapolation of results from clinical trials in adults to children is allowed in U.S.A. if a drug is thought to act in the same way to similar condition in both adults and children, and such drug may be licensed with small additional pediatric studies. Besides, for certain drugs (listed by the FDA) market exclusivity could be prolonged for 6 months if a pediatric clinical trial is done²³.

TRIAL END POINTS

The regulatory acts require the following measures of efficacy to be used in clinical trials with antiepileptic drugs: fraction of patients without seizures for at least six months, percentage of patients with reduction of seizure frequency for less than 25%, 25-50%, 50-75% and more than 75%, seizure severity, treatment retention time, scales for working and social capacity and EEG patterns for specific epilepsy types^{1,2}. Some additional measures of efficacy should also be mentioned in the regulatory documents, since they could make administration of new antiepileptic drugs in clinical practice much easier. For example, number of seizure-free days, time not only to the first, but also to the *n*th seizure, and change in seizure frequency expressed as continuous parameter should also

be used as outcome measures in clinical trials^{19,22}. Especially quality of life should be taken into account as an outcome measure²³. However, the end points should be specified for each of different populations of patients separately, since they cannot be used interchangeably. Additional measures of efficacy will increase sensitivity of clinical trials for revealing more subtle, yet important, differences in efficacy of the investigational drug compared with alternative therapy. It will also give better overall picture of the new drug's clinical utility. Since the FDA and EMA guidelines differ in requirements concerning efficacy measures, their harmonization in this sense would beneficially affect sponsors, who frequently develop their drugs for both "new" and "old world" markets.

SAFETY ISSUES

More proactive attitude towards discovery of adverse events should be explicit in regulatory documents, in order to avoid overlooking of frequent functional adverse actions of antiepileptic drugs²⁴. The regulatory documents only mention that special attention should be paid to central nervous system adverse effects of antiepileptic drugs, but specific requirements are not set up^{1,2}. Many validated scales for measurement of potential central adverse effects of antiepileptic drugs (with excellent psychometric properties) are now available for precise measurement of anxiety, depression, cognition, and quality of life in general^{25,26}. Such instruments should be stated in the regulatory acts, at least as examples, in order to stimulate their use in practice. In the past, some central adverse effects were discovered only after the marketing authorization was obtained²⁷, and it could have been done much earlier with proactive use of measurement scales during the process of clinical development of all new anticonvulsants, both for adults and children. However, it should be taken into account that the uses of validated scales for measurement of potential central adverse effects could sometimes lead to an increase in the number of reported adverse events.

EPILEPTOGENESIS

Preclinical testing of antiepileptic drugs includes specific assays which may discover not only anticonvulsant, but also anti-epileptogenic effect of an investigational drug²⁸. Although there are drugs which are not anticonvulsants, but have anti-epileptogenic properties, some of the anticonvulsants may have anti-epileptogenic

action, too (e.g. anti-absence drug ethosuximide), which is important to know if such a drug is going to be used for prophylactic purposes (e.g. after neurosurgery)²⁹. Ideal clinical trial investigating anti-epileptogenic properties of an anti-convulsant should include patient population with very high epilepsy risk (e.g. patients with traumatic brain injury), it should be clear which factor and when causes epilepsy and there should be short latency from the moment when causative factor starts its action until the onset of seizures³⁰. However, regulatory documents do not require clinical trials specifically designed to prove anti-epileptogenic effects. Specific guidance for this type of clinical trials would be very useful for sponsors, and probably would widen approved indications for new antiepileptic drugs. The design of antiepileptogenic trials should have two phases: the first, parallel groups phase, which would estimate antiseizure effect, and second phase after washout of the drug, which would show prevention against emergence of new seizures without the drug present in the blood for at least 2 years^{29,31,32,33}.

CONCLUSIONS

Current regulatory documents are incomplete in many aspects, and in a few instances make unnecessary obstacles to clinical development of anticonvulsants. An international effort to improve and harmonize guidelines for clinical development of antiepileptic drugs is necessary, and probably will result with improvement of this process in respect of both efficacy and quality. The harmonization should be guided and possibly managed (hopefully with financial support from national drug agencies) by one or more of the leading international professional organizations devoted to studying epilepsy and transferring acquired knowledge to clinical practice, like International League against Epilepsy, which recently celebrated its Centenary anniversary. Besides, this process should be tuned with efforts on international harmonization of requirements for drug registration at national Drug Agencies undertaken by The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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