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ORIGINAL ARTICLE

Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study: a pragmatic multicentre, prospective, randomized, controlled study

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Abstract Antiepileptic drug withdrawal may be an option for patients who have been seizure free for some years. The best withdrawal rate is questionable; in particular, it is unknown whether "rapid" withdrawal is associated with a higher risk of relapse as compared to "slow" withdrawal. We aim to establish if a slow or a rapid withdrawal schedule of antiepileptic monotherapy influences relapse rate in adult patients with focal or generalized epilepsy who have been seizure free for at least 2 years. This multicentre, prospective, randomized controlled study will enroll adult patients with focal or generalized epilepsy, who are seizure free on monotherapy. Patients will be randomized to a slow (160 days) or a rapid (60 days) schedule. Follow-up will last 1 year after randomization. The primary endpoint is the time to seizure relapse; secondary endpoints are compliance to the assigned schedule, occurrence of status epilepticus, of seizure-related injuries and mortality. A sample size of 350 patients has been planned. Univariate and multivariate analysis by Kaplan–Meier curves and Cox regression (primary endpoint) and by logistic regression (secondary endpoint) will be performed. The present study should contribute to better define the best withdrawal period for AED treatment in adult patients with epilepsy.

Keywords Slow withdrawal · Rapid withdrawal · Anti epileptic drug · Randomized controlled trial

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Introduction

A substantial proportion of subjects with epilepsy achieves sustained remission after introduction of antiepileptic treatment [1, 2]. Antiepileptic drug (AED) withdrawal may be an option for patients who have been seizure free for some years: a careful evaluation of risks and benefits should be undertaken before the decision to stop or continue AED treatment. Actually, benefits of discontinuation include disappearance of drug-related side effects, particularly on neuropsychological performance, and reduction of costs [3–5]. On the contrary, a relapse of seizures may have short-term consequences (seizure-related injuries and even death [6, 7]) as well as more widespread and long-term effects on social life and employment. Relapse rate after AED withdrawal is highest in the first 6–12 months after withdrawal, and the cumulative probability of maintaining long-term remission is 45–85 % [3–5], with a higher proportion among patients who were previously on monotherapy [5]. Risk factors associated with relapse have been investigated in many studies [3–5, 8–12], but results are somewhat inconclusive. The Guidelines by Italian League Against Epilepsy [13] identify some conditions that may increase the relapse rate, like adult age, presence or

worsening of EEG abnormalities, specific aetiologies and epileptic syndromes, female sex, partial-onset seizures. With regard to tapering rate, few data are available to determine whether a "rapid" withdrawal is associated with a higher risk of relapse compared with a "slow" withdrawal. A survey among UK and Eire clinicians [14] revealed a substantial lack of consensus in tapering rates. Some prospective studies have been conducted on children, with variable timelines [8, 9, 11]. A single study [11] documented an independent association between rapid discontinuation of AED treatment and a higher risk of relapse. A Cochrane review of randomized controlled studies on rapid versus slow withdrawal of AEDs [15] defined rapid tapering when the AED was discontinued within 3 months, and slow tapering when discontinuation took more than 3 months. This review identified a single study comparing a rapid withdrawal schedule (6 weeks) to slow withdrawal (9 months) in children who had been seizure free during 2–4 years [16]. That study failed to identify significant differences in terms of relapse between the groups. Thus, the Italian Guidelines [13] recommend a "slow" treatment discontinuation, without specifying a time schedule. Moreover, little is known about patients' preferences and adherence to different withdrawal schedules, and on the severity of relapses after AED discontinuation. The main objective of the present study will be to establish whether a slow (within 160 days) or a rapid (within 60 days) withdrawal schedule of antiepileptic monotherapy influence relapse rate in adult patients with epilepsy, who have been seizure free for at least 2 years. Secondary objectives will be to establish the compliance rates with these two schedules and the differences in terms of severity of relapses, based on the occurrence of status epilepticus, seizure-related injuries and death.

Patients and methods

The rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients (RASLOW) study is a multicentre, prospective, randomized controlled trial. Inclusion criteria are: diagnosis of focal or generalized epilepsy (according to ILAE 1989 criteria [15]); age at epilepsy onset of 16 years or older; seizure freedom for at least 2 years; treatment with one of the AEDs currently available for monotherapy in Italy: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid zonisamide; and adherence to the protocol and visit schedules. Exclusion criteria are: inability to understand the aims or modalities of the study; current pregnancy or plans to become pregnant during withdrawal period; history of seizure relapse after discontinuation of treatment; history of psychogenic non-epileptic seizures (PNES); history of status epilepticus.

The primary endpoint is the time to recurrence of an epileptic seizure. Secondary endpoints are the compliance with the assigned withdrawal schedule and the severity of relapses, in terms of seizure-related injuries (contusions, wounds, fractures, strain/sprain, head injury, burns, whiplash), status epilepticus (SE) during or after withdrawal period, and mortality.

Study design

Patients will be informed on the aims and modalities of the study. Included subjects will be randomized to AED discontinuation following one of the two following schedules:

1. Rapid withdrawal: reduction by about 20 % of initial dosage every 15 days until complete discontinuation (total withdrawal time: 60 days);
2. Slow withdrawal: reduction by about 20 % of initial dosage every 40 days, until complete discontinuation (total withdrawal time: 160 days).

A 1:1 central randomization will be stratified for type of epilepsy (focal versus generalized).

The recruitment period will last for 16 months and enrolled patients will be followed for 1 year after randomization. Enrolled patients will undergo periodic visits with a predetermined schedule: every 15 days from 1st to 60th day (visits 1–5), every 30 days from 61st to 180th day (visits 6–9), and every 3 months until the end of the study (visits 10, 11). An unscheduled phone contact will also take place soon after a relapse: the patients will also be instructed to call a member of the study staff within 24 h after an ictal event. If the study staff is confident about the epileptic nature of the event, the patient will be instructed to restart AED treatment and to come for the final visit within 72 h. Otherwise, the patient will be invited to come for a clinic visit within the next 72 h.

Baseline evaluation

The following assessments will be accomplished:

(a) Verification of all inclusion and exclusion criteria.
(b) Recording of demographic data and clinical parameters: date of birth, sex, height, weight, arterial blood pressure and heart rate.
(c) Physical, neurological, psychiatric and mental status examination.
(d) General clinical history: concomitant diseases and medications.
(e) Assessment of birth control methods for women in childbearing age.

(f) History of epilepsy: family history of epilepsy, history of febrile seizures, date of onset, type of seizures, seizure frequency at onset, epileptic syndrome, current AED treatment, period of seizure freedom before enrolment.
(g) Administration of a quality of life scale for epileptic patients (QOLIE-31) [17].
(h) Performance of a standard, 30-min EEG.
(i) Blood sample withdrawal to analyze plasma level of AEDs.
(j) Randomization and assignment of a withdrawal schedule.
(k) Delivery of a seizure diary.
(l) Appointment for the next visit in 15 ± 2 days.

Follow-up

Visits # 2, 4, 6, 8, 9 and 10 will be performed by telephone or clinic visit. Subjects will be asked to report changes in concomitant diseases and medications, compliance to withdrawal schedule, adverse events and seizures. If the subject is compliant with the withdrawal schedule and no seizures are reported, he/she will be advised to come to the Centre for the next visit; otherwise, he/she will exit the study and the final visit will be performed within 72 h.

Visits # 3, 5, 7 unscheduled visits and final visit (visit # 11 or end of study in case of a relapse) will be performed as clinic visits. The following evaluations will be performed:

(a) Evaluation of possible relapses, compliance with withdrawal schedule and adverse events;
(b) Recording of clinical parameters: weight, arterial blood pressure, heart rate:
(c) Neurological examination;
(d) General clinical history: concomitant diseases and medications;
(e) Administration of a quality of life (QoL) scale (QOLIE-31) at visits #3, 7 and 11 (final visit);
(f) Performance of a standard, 30-min EEG.
(g) Blood sample withdrawal to analyze plasma level of AED will be performed at visit 5 ("fast" withdrawal schedule) or at visit 11 ("slow" withdrawal schedule);
(h) Acquisition of the compiled seizure diary and delivery of a new one.

The patient will exit the study and antiepileptic treatment will be restarted in case of seizure relapse, appearance of new EEG abnormalities or increase of pre-existing EEG abnormalities.

Sample size estimates and statistical analysis

For the primary endpoint, a non-inferiority analysis on the group "rapid" versus "slow" withdrawal will be performed. The expected relapse rate in the two groups is 35 % (non-inferiority limit). The sample size is calculated at 159 patients/group with a 80 % power and an α error of 0.05. Allowing for a 10 % of patients lost to follow-up, a total of 350 participants will be required.

All subjects randomized and starting the withdrawal schedule will be included in the analyses (intention-to-treat analysis). Differences between groups (rapid versus slow withdrawal) will be assessed by Chi-square and *t* test for independent samples, as appropriate. For the primary analysis, Kaplan–Meier survival curves will be built, to be compared with log-rank test. Multivariable analysis will be performed with Cox regression. For secondary analyses, univariate and multivariate logistic regression will be performed to assess factors predicting compliance to withdrawal schedule, occurrence of SE, seizures-related injuries and mortality.

Informed consent

All included patients will be informed in detail about study design, visit schedule and the specific risk factors for relapse. All subjects will sign an informed consent and a privacy module; a copy of this documentation will be released to the patients, together with a synopsis of the study protocol for the family doctor.

Ethical and legal considerations

Protocol approval will be obtained from the responsible ethic committees at all participating study centers. The study conforms to the Declaration of Helsinki and the current GCP guidelines.

Summary and conclusions

The decision on whether and how to discontinue AED treatment in seizure-free patients is often controversial and based on common sense and personal opinions, rather than scientific evidence. In particular, while a number of factors associated with relapse were identified [3, 4, 7–11], the proper timing for discontinuation is unknown. Results obtained from a single study on a pediatric population [18] suggest that the risk of relapse is independent from the withdrawal rate. This is the first prospective, randomized controlled study that compares two different schedules for

AED withdrawal in adult epileptic patients. The present study should contribute to better define the best withdrawal period for AED treatment in adult patients with epilepsy. The demonstration that seizure relapse, compliance with withdrawal schedule and occurrence of status epilepticus, seizure-related injuries and death do not differ in patients who undergo rapid versus slow AED withdrawal would provide a scientific basis in support of a rapid discontinuation of AED. This would be of great importance for patients that should not have to wait for many months/years before stopping AED treatment, with reduction of side effects and improvement in their quality of life.

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Compliance with ethical standards

Conflict of interest This research project is financed by Italian Health Ministry (Targeted Research for Young Investigators, 2013). Project code is GR-2013-02358677. Dr. Beghi serves on the editorial advisory boards of Amyotrophic Lateral Sclerosis, Clinical Neurology and Neurosurgery, and Neuroepidemiology; he has received funding for travel and speaker honoraria from UCB-Pharma, Sanofi-Aventis, GSK, EISAI; funding from GSK for educational presentations, and from AIFA, Sanofi-Aventis, Janssen-Cilag, EISAI, Lombardy Region, Istituto Superiore di Sanità and American ALS Association for the coordinating activity of RCT and observational study protocol.

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