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An Italian multicentre study of perampanel in progressive myoclonus epilepsies

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ABSTRACT

Perampanel (PER) is a novel anti-seizure medication useful in different types of epilepsy. We intended to assess the effectiveness of PER on cortical myoclonus and seizure frequency in patients with progressive myoclonus epilepsy (PME), using quantitative validated scales.

Forty-nine patients aged 36.6 ± 15.6 years with PME of various aetiology (18 EPM1, 12 EPM2, five with sialidosis, one with Kufs disease, one with EPM7, and 12 undetermined) were enrolled between January 2017 and June 2018. PER at the dose of 2–12 mg (5.3 ± 2.5) was added to existing therapy. Myoclonus severity was assessed using a minimal myoclonus scale (MMS) in all the patients before and after 4–6 months of steady PER dose, and by means of the Unified Myoclonus Rating Scale (UMRS) in 20 patients. Logistic regression analysis was used to identify the factors potentially predicting treatment efficacy.

Four patients dropped out in the first two months due to psychiatric side effects. In the remaining patients, PER reduced myoclonus severity as assessed using MMS (Wilcoxon test: $p < 0.001$) and UMRS ($p < 0.001$), with the 'Action myoclonus' section of the UMRS showing the greatest improvement. The patients with EPM1 or EPM1-like phenotype were more likely to improve with PER ($p = 0.011$). Convulsive seizures which have recurred at least monthly in 17 patients were reduced by >50%. Side effects occurred in 22/49 (44.8%) patients, the most common being irritability followed by drowsiness.

Abbreviations: MMS, minimal myoclonus scale; UMRS, unified myoclonus rating scale; PER, perampanel

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PER is effective in treating myoclonus and seizures in PME patients. The frequency of psychiatric side effects suggests the need for careful patient monitoring.

1. Introduction

Progressive myoclonus epilepsies (PMEs) include genetically heterogeneous diseases such as Unverricht-Lundborg disease (EPM1, MIM #254800), Lafora disease (EPM2, #254780), sialidoses (#256550) and other rare disorders (Franceschetti et al., 2014). Frequent symptoms are myoclonic and tonic-clonic seizures, possible cognitive decay and variable ataxia, but the most characteristic symptom is stimulus-sensitive multifocal cortical myoclonus mainly occurring during active movements. This partially responds to some anti-seizure medications (ASMs), but often becomes the most disabling symptom.

Perampanel (PER) is a novel ASM that is mainly used to treat partial and generalised seizures, but is also effective on myoclonic seizures (Gil-López et al., 2018) and has been successfully used to treat PMEs in small patient series, including patients with EPM1 (Crespel et al., 2017) and EPM2 (Goldsmith and Minassian, 2016). Previous studies of PMEs have involved small patient cohorts and have not used validated myoclonus quantification scales. The aims of this study were to quantify the effect of PER on the frequency of tonic-clonic seizures and on the cortical myoclonus using appropriate scales, and verify the tolerability of PER as there has been a special warning concerning frequent psychological and behavioural effects in PER-treated EPM1 patients (Crespel et al., 2017). The patients were prospectively enrolled and evaluated using a standardized protocol including application of validated scales before and during PER treatment.

2. Methods

The study involved 14 epilepsy centres, and patients with all types of PME and variably severe action myoclonus. The diagnosis of PME was based on clinical history and the identification of cortical myoclonus (Franceschetti et al., 2014). The exclusion criteria were the presence of medical or severe psychiatric conditions that were medically judged to be possible confounders.

PER was added to the ongoing treatment in 2 mg steps every two weeks up to a total of 4–12 mg/day, which was reduced in the event of side effects with an individual approach. The treatment at stable dose was continued for at least four months; otherwise, the patient was considered a drop-out. The severity of myoclonus was assessed using a minimal myoclonus scale (MMS) (Magaudda et al., 2006) in all the patients and the Unified Myoclonus Rating Scale (UMRS) (Frucht et al., 2002) in a patient subset, before starting PER and when the patients were on a steady daily dose from 4 to 6 months (Fig. 1). During this period, concomitant ASMs were maintained unchanged. The UMRS scores for “patient questionnaire”, “myoclonus with action”, “myoclonus at rest”, “stimulus sensitivity”, “negative myoclonus” and “functional tests” were added together to obtain a “total score”. The clinical data, side effect reports, and scale scores were sent to Milan’s C. Besta Neurological Institute for analysis. During the treatment, the patients were observed or interviewed monthly to assess the tolerability, type of side effect and seizure frequency.

The primary efficacy index was the decrease in the MMS and the total UMRS scores; the secondary efficacy outcome was the decrease in the mean monthly frequency of generalised tonic-clonic seizures from baseline to the last observation on PER. The paired Wilcoxon signed rank test was used to assess post-treatment changes, and binary logistic regression analysis was used to identify factors potentially predicting treatment efficacy: age, disease duration, number of concomitant ASMs. The analysis was made by separating the patients with and without a reduction in the MMS score of at least one point. The study was approved by institutional Ethical Committee, and the patients gave their informed consent before enrolment.

3. Results

Forty-nine patients aged 36.6 ± 15.6 years (27 female) were enrolled between January 2017 and June 2018 among those already diagnosed and followed in the referring centres. Thirty-seven patients had a molecular diagnosis, namely 18 had EPM1 associated with *CSTB* gene mutations; 12 had EPM2 associated with *EPM2A* or *EPM2B* (*NHLRC1*) mutations; five had sialidosis (*NEU1* mutations); one had Kufs disease (*CLN6* mutation); and one had EPM7 (*KCNC1* mutation) (Oliver et al., 2017). The other 12 remained genetically undetermined despite an extensive diagnostic work-up (Table 1).

PER was added at a mean dose of 5.3 ± 2.5 mg/day to the ongoing treatment with 2–6 ASMs (median: 3): valproate (n = 40), clonazepam (n = 35), levetiracetam (n = 30), zonisamide (n = 19), topiramate (n = 8), primidone (n = 7) and clobazam (n = 5). Four patients (one

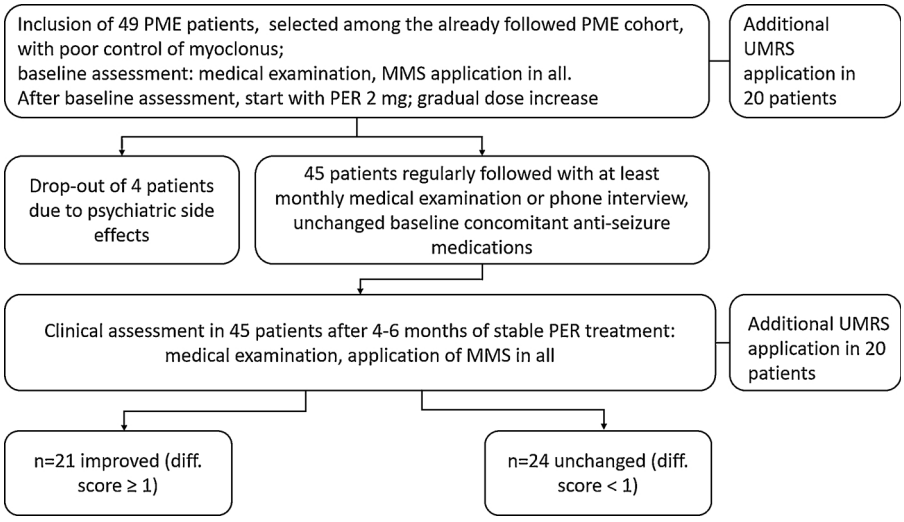

Fig. 1. Consort diagram illustrating the study procedures.

Table 1
Patient groups.

	Enrolled	EPM1	EPM2	Sialidosis	Kufs[a]	EPM7[a]	UND[a]
Patient number	49	18	12	5	1	1	12
Age at observation (ys)	36.6 ± 15.6	39.6 ± 14.8	25.7 ± 10.8	40.0 ± 6.1	16	19	44.8 ± 17.5
Sex (female)	27	7	6	4	1	0	9
Disease duration (ys)	22.8 ± 15.3	29.7 ± 12.8	11.2 ± 9.1	24 ± 7.4	3	7	24.2 ± 18.6
Recurrent seizures	17	4	11	0	1	0	1
PER daily dose (mg)	5.3 ± 2.5	4.7 ± 1.7	7 ± 3.0	4.4 ± 2.2		12	4.2 ± 1.6
Ongoing therapy (median of ASM)	3	3	3	3	3	3	2
Drop out	4	1	1	0	1	0	2
Differential Score ≥1	21	7	1	2	1	0	7
Patients evaluated by MMS	3.5 ± 1.1	3.5 ± 1.1	3.3 ± 1.3	4.4 ± 0.5	4	4	3.1 ± 1.0
Patients evaluated by UMRS	20	9	2	3	1	1	4

[a] Unverricht-like phenotype: one Kufs with adolescent onset, one EPM7 and two UND patients; UND = unclassified PMEs; ys = years.

EPM1, one EPM2, and two undetermined) were excluded from the efficacy analysis because they stopped treatment because of side effects (irritability, confusion, subjectively worsening myoclonus, hallucinations) within the first two months.

The MMS scores of the remaining 45 patients decreased from 3.5 ± 1.1 to 3.1 ± 1.1 (Wilcoxon's test; $z = -4.47$, $p < 0.001$), and the total UMRS score (n = 20) decreased from 116.2 ± 52.6 to 86.5 ± 45.7 ($z = -3.80$; $p < 0.001$) (Fig. 2**A** and **B**). Separate evaluations of the UMRS subtests showed decreases in the scores for "action myoclonus" from 53.1 ± 27.3 to 38.3 ± 27.4 ($z = -3.37$; $p = 0.001$), "functional tests" from 11.7 ± 6.2 to 9.2 ± 6.2 ($z = -2.93$; $p < 0.01$), "myoclonus at rest" from 13.5 ± 20.5 to 8.3 ± 14.8 ($z = -2.68$;p $p < 0.01$), and "patient questionnaire" from 29.7 ± 11.3 to 24.3 ± 10.6 ($z = -3.90$; $p < 0.001$). After 4–6 months of PER treatment, twenty-one patients showed a reduction of at least 1 point at MMS. Logistic analysis did not reveal any influence of disease duration, age at the time of observation, or the number of concomitant ASMs. Myoclonus was more likely to improve in the patents with EPM1 (n = 18) or an EPM1-like phenotype (n = 1 EPM7, n = 1 Kufs and two undetermined PMEs) ($p = 0.011$, Exp B 17.33) (Fig. 2**C**, Table 1).

Thirty-two patients were free from tonic-clonic seizures at the time of starting PER, and 17 had shown at least monthly seizures (4 EPM1, 11 EPM2, one Kufs, one undetermined) in the last four month; among these, PER treatment led to a >50% reduction in seizure frequency in the same time period.

The adverse events occurring in 22 of the 49 enrolled patients (44.8%) were drowsiness (10, 20.4%), irritability or anxiety (13, 26.5%), aggressiveness (3, 6.1%), dizziness (1) and weight gain (1). At the last observation, 38 patients out of 49 have continued PER at a mean dose of 5.89 ± 2.20 mg for a period of 16.82 ± 5.89 months (retention rate: 77.5%); while 11 patients withdrew PER due to persistent side effects (anxiety and irritability). We did not find any significant relationship between the appearance of side effects and the concomitant ASM.

4. Discussion

Our findings indicate that PER can reduce the severity of myoclonus and the frequency of tonic-clonic seizures in patients with PME of various etiology. The use of standard quantitative scales clearly showed the effect of PER on EPM1 or EPM1-like phenotype with prominent action myoclonus. This is in line with the findings of Crespel et al. (2017) but, unlike Goldsmith and Minassian (2016) who used a customised severity scale, we could not confirm its effectiveness on myoclonus in EPM2 patients, who nevertheless showed a significant improvement in seizure control. Indeed, in EPM2 patients, it is difficult to make a quantitative assessment of action myoclonus because they generally present a mixture of positive and negative action myoclonus,

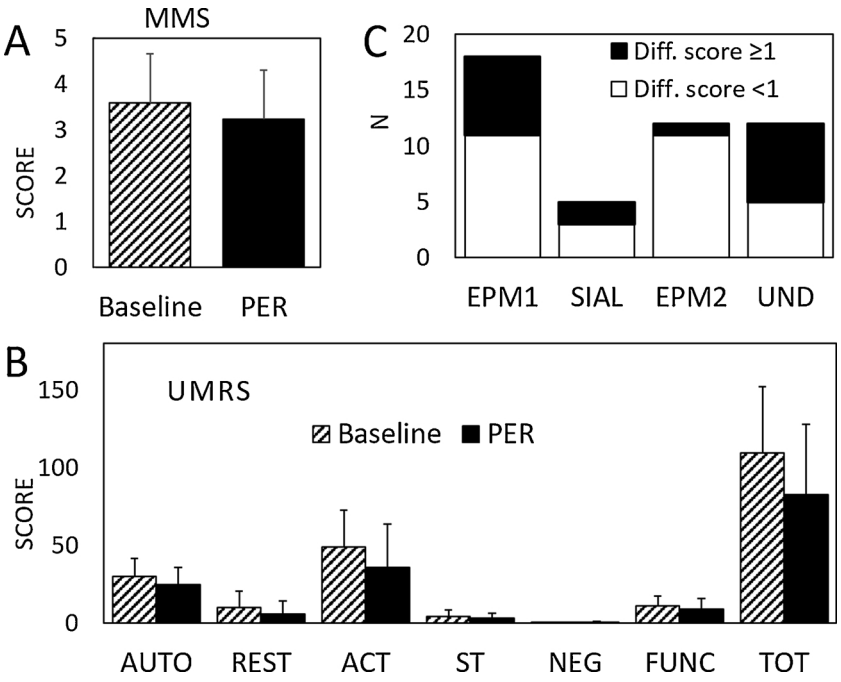

Fig. 2. A and **B:** Effect of PER on myoclonus as evaluated using the MMS (45 patients) and UMRS (20 patients) (MMS: minimal myoclonus scale; UMRS: unified myoclonus rating scale; REST: myoclonus at rest; AUTO: patient questionnaire; ACT: action myoclonus; ST: stimulus sensitivity; NEG: negative myoclonus; FUNC: functional tests). **C:** Effect of PER on myoclonus in PMEs with different genetic etiologies (SIAL: sialidosis; UND: undetermined). The number of patients who improved after starting PER is shown in black. The differential score (Diff. score) indicates the post-treatment change as assessed using the minimal myoclonus scale.

often indistinguishable from the myoclonic jerks associated with polyspikes and waves (Franceschetti et al., 2014).

At the onset of PER treatment, most of patients were seizure free from years, but had invalidating action myoclonus; therefore, the seizure reduction was obvious in EPM2 only, typically showing recurrent seizures. This anti-seizure effect is in line with the beneficial effect of PER on tonic-clonic and myoclonic seizures in patients with non-progressive generalised epilepsies (Villanueva et al., 2018; Gil-López et al., 2018), and in individual patients with EPM2 (Schorlemmer et al., 2013) or sialidosis (Hu et al., 2018).

PER was sufficiently tolerated, and only a minority of the patients discontinued the drug because of side effects. The most frequent side effects were psychological and behavioural, as previously reported in PME (Goldsmith and Minassian, 2016; Crespel et al., 2017) and in focal epilepsy (Rohracher et al., 2018). Their incidence was higher than that observed in a cohort of patients with idiopathic generalised epilepsies using similar concomitant ASM (Villanueva et al., 2018), possibly because PER exacerbated the pre-existing psychological and behavioural problems of many PME patients (Ferlazzo et al., 2009; El Tahry et al., 2015).

Mainly due to the rarity of the disorder, the study has limitations due to lack of placebo, blinded outcome and blinded assessment. Moreover, the number of patients was small compared to studies performed on focal epilepsy.

5. Conclusions

The study was designed to enrol a quite large number of patients with rare PMEs through several centres, and to apply quantitative scales, already used in EPM1 series (Magaudda et al., 2006; Kälviäinen et al., 2016; Canafoglia et al., 2017). This allowed comparing the response to PER in several PME subgroups, and to detect the greater effectiveness on action myoclonus in EPM1. As well, it allowed noticing the effectiveness on seizure in EPM2.

The study can give information supporting the use of PER to treat PME patients with disabling action myoclonus. In agreement with a previous study that tested tolerability in a large population with epilepsy (Rohracher et al., 2018), the rather common occurrence of irritability suggests a careful monitoring, namely in those PME patients who already suffer from more or less overt psychiatric conditions (Ferlazzo et al., 2009; El Tahry et al., 2015).

Authors' contributions

L. Canafoglia: study design; data acquisition, analysis and interpretation; drafting and revision of the manuscript for intellectual content. G. Barbella: study design; data acquisition, analysis and interpretation; revision of the manuscript for intellectual content. E. Ferlazzo: study design; data acquisition, analysis and interpretation; revision of the manuscript for intellectual content. P. Striano: study design; data acquisition and revision of the manuscript for intellectual content. A. Magaudda: data acquisition, analysis and interpretation. G. d'Orsi: data acquisition, analysis and interpretation. T. Martino: data acquisition, analysis and interpretation. C. Avolio: data acquisition, analysis and interpretation. U. Aguglia: data acquisition, analysis and interpretation. C. Sueri: data acquisition, analysis and interpretation. L. Giuliano: data acquisition, analysis and interpretation. V. Sofia: data acquisition, analysis and interpretation. F. Zibordi: data acquisition, analysis and interpretation. F. Ragona: data acquisition, analysis and interpretation. E. Freri: data acquisition, analysis and interpretation. C. Costa: data acquisition, analysis and interpretation. E. Nardi Cesarini: data acquisition, analysis and interpretation. M. Fanella: data acquisition, analysis and interpretation. D. Rossi Sebastiano: data acquisition, analysis and interpretation. P. Riguzzi: data acquisition, analysis and interpretation. A. Gambardella: data acquisition, analysis and interpretation. C. Di Bonaventura: data acquisition, analysis and interpretation. R. Michelucci: data acquisition, analysis and interpretation. T. Granata: data acquisition, analysis and interpretation. F. Bisulli: data acquisition, analysis and interpretation. L. Licchetta: data acquisition, analysis and interpretation. P. Tinuper: data acquisition, analysis and interpretation; F. Beccaria: data acquisition, analysis and interpretation. E, Visani: data analysis and interpretation; revision of the manuscript for intellectual content. S. Franceschetti: study design; data acquisition, analysis and interpretation; revision of the manuscript for intellectual content.

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Declaration of Competing Interest

L. Canafoglia has served on the advisory board of EISAI; G. Barbella has no disclosure to make; E. Ferlazzo has served on the advisory boards of UCB pharma and EISAI; P. Striano has served on the advisory board of EISAI, GW pharma, Zogenix; A. Magaudda has no disclosure to make; G. d'Orsi has served on the advisory board of EISAI; T. Martino has no disclosure to make; C. Avolio has no disclosure to make; U. Aguglia has no disclosure to make; C. Sueri has no disclosure to make; L. Giuliano has no disclosure to make; V. Sofia has no disclosure to make; F. Zibordi has no disclosure to make; F. Ragona has no disclosure to make; E. Freri has no disclosure to make; C. Costa has served on the advisory board of EISAI; E. Nardi Cesarini has no disclosure to make; M. Fanella has no disclosure to make; D. Rossi Sebastiano has no disclosure to make; P. Riguzzi has no disclosure to make; A. Gambardella has no disclosure to make; C. Di Bonaventura has no disclosure to make; R. Michelucci has no disclosure to make; T. Granata has no disclosure to make; F. Bisulli has no disclosure to make; L. Licchetta has no disclosure to make; P. Tinuper has no disclosure to make; F. Beccaria has served on the advisory board of EISAI, GW pharma; E. Visani has no disclosure to make; S. Franceschetti has no disclosure to make in relation to this manuscript.

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