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A retrospective evaluation of retigabine in patients with cognitive impairment with highly drug-resistant epilepsy

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ABSTRACT

Purpose: The purpose of this study was to evaluate retrospectively the efficacy and tolerability of retigabine (RTG) in residential patients of an epilepsy center.
Method: We used an industry-independent noninterventional retrospective evaluation on the basis of paper and electronic records plus interrogation of the treating neurologists. All patients (N = 20; 7 females; mean age: 31.8, range: 18–54 years) started on RTG between May 2011 and March 2012 were included. Evaluation was carried out after 6, 12, and 24 months. Changes in seizure frequency were measured as the number of seizures during three months on RTG compared with a three-month baseline period. The Clinical Global Impression scale was applied to include qualitative changes in seizure severity. All but one patient had symptomatic (structural; one patient: metabolic) or cryptogenic focal or multifocal epilepsy. All had grade III drug-resistant epilepsy and cognitive deficits of different degrees.
Results: The retention rates were 60% after 6 months, 35% after 12 months, and 20% after 24 months. At 12 months, there were 2 responders (10%): one had a >90% seizure reduction and the other had a >50% seizure reduction. Another 5 patients were still on RTG because of minor improvements. The reasons for discontinuation in 13 patients were adverse effects (6), lack of effect (6), and both (1). Cognitive or emotional changes were the side effects that most frequently led to discontinuation. Beyond the 12-month evaluation, 3 patients were discontinued as a consequence of the FDA warning regarding retinal pigmentation and discoloration of skin and nails in patients exposed to RTG. One patient had a moderate blue–gray finger coloring. Ophthalmological changes were not discovered.
Conclusion: Retigabine proved to be useful only for a small minority of patients in a sample of patients with particularly difficult-to-treat epilepsy.

1. Introduction

Our organization, the Bethel Epilepsy Center, provides care and medical treatment for a large number of persons with different types and degrees of handicap, many of whom have drug-resistant epilepsies. Hence, there is great interest in innovative antiepileptic drugs, like the novel potassium channel opener retigabine (RTG). Usually, new available drugs are first administered in those patients with the most difficult-to-treat epilepsies.

The purpose of this industry-independent work was to carry out a systematic retrospective evaluation of the initial experience (efficacy and tolerability) with RTG in inpatients of the residential department of our center. In general, patients with epilepsy with additional handicaps are often excluded from double-blind placebo-controlled trials especially if they are unable to give informed consent. Therefore, published data on RTG in this patient group are very rare. The purely observational and noninterventional character of this work allowed us to include this group of patients.

2. Method

All residential patients (N = 20; 7 females; mean age: 31.8, age range: 18–54 years) who were started on RTG in our center between its introduction to the market in May 2011 and March 31st, 2012 were included. There were no exclusions. Patient data (age at starting RTG, seizure types, epilepsy syndrome, pretreatment) were taken from the conventional and electronic documentation.

Evaluation was carried out after 6, 12, and 24 months of RTG treatment. Information on seizure frequency – per seizure type – was extracted from the current patient case records and entered in a data sheet. Seizure documentation about a three-month baseline period before RTG was started was available in all patients. In general, seizure documentation (date, time, and seizure description or classification based on seizure observation by trained staff and also on information given by the patient himself, whenever appropriate) is a regular part

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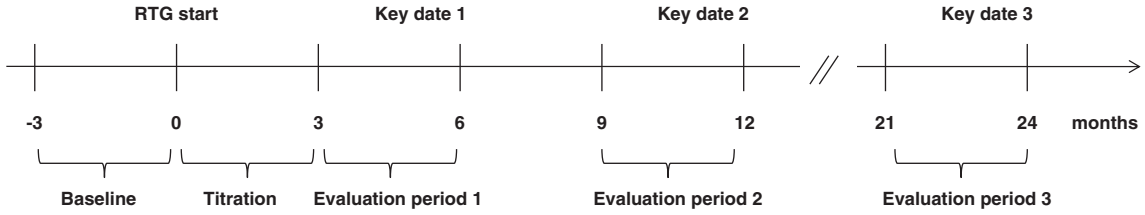

Fig. 1. Course of the study.

of every patient's electronic clinical record in our center. Changes in seizure frequency were calculated as the number of seizures during three months on RTG (evaluation period) compared with the three-month baseline period (Fig. 1). As usual, a 50% seizure reduction was defined as response. Additionally, efficacy was individually judged by the treating neurologists using the Clinical Global Impression (CGI) scale. This straightforward instrument allows including aspects of seizure severity (like seizure duration and time to complete recovery) and impact on daily life into the assessment.

Information on tolerability was gained by scrutinizing doctors' notes (which included information provided by staff and complaints expressed by the patient himself or herself) and by personally interrogating the neurologists in charge.

With intent to enable comparisons, the method of this retrospective study was similar to evaluations carried out earlier in our center.

Given the relatively low case number, we abstained from a statistical analysis with respect to potential correlations between retention or response and seizure type, RTG daily dosage, comedication, or other variables. Because of the strictly noninterventional character of the study no ethics committee approval was obtained.

3. Results

Retigabine was added to the preexisting antiepileptic medication. According to the character of a noninterventional evaluation, the titration rate was not fixed. A typical schedule used by the treating neurologists (all with a special interest and long experience in epileptology) of the Bethel Medical Service would be 50 mg/day as starting dose followed by dose increases of 50–100 mg not faster than once a week (but every two to four weeks in most cases) until sufficient seizure control was reached or intolerable adverse effects emerged. The aim was to achieve the maximum clinical benefit. Changes to the baseline antiepileptic medication would normally be avoided or restricted to minor dosage adaptations. In some cases, an earlier unsuccessful therapeutic trial was terminated. Patients were seen by their treating neurologists in regular intervals (typically every two to six weeks). Additional visits could be arranged if problems occurred.

All but one patient had symptomatic (structural; one patient: metabolic) or cryptogenic focal or multifocal epilepsy. All patients had highly difficult-to-treat epilepsy, namely grade III drug-resistant epilepsy (history of >6 unsuccessful therapy trials; [1]). All had cognitive deficits of different degrees (Table 1).

Table 1
The cognitive level of patients (N = 20).

Intelligence (ICD 10)	N (%)
Borderline intelligence/neuropsychological deficits	10 (50%)
Mild intellectual disability	5 (25%)
Moderate intellectual disability	4 (20%)
Severe/profound intellectual disability	0 (0%)
Encephalopathy undetermined	1 (5%)

As is frequently the case in patients with treatment-refractory epilepsy, all were on combination therapy, many of them on a combination of 3 AEDs (Table 2).

After 6 months (evaluation period 1), the retention rate was 60% (12 patients).

At the 12-month evaluation (evaluation period 2), the retention rate was 35% (7 patients). There were only 2 responders (10%) according to the classical definition of a greater than 50% seizure reduction. One of them had a >90% seizure reduction. No patient was completely seizure-free. However, the CGI scale revealed some clinically relevant improvement in another 5 patients (Table 3).

3.1. Tolerability

The reasons for discontinuation up to the 12-month key date were adverse effects (6), lack of effect (6), and both (1). The most frequent side effects that required discontinuation were cognitive or emotional changes or even psychiatric symptoms (Table 4). The most striking case was a 21-year old male who had, besides compulsive gambling, no history of psychiatric disorder. One week after his RTG dosage (well tolerated up to then) was increased from 600 to 700 mg/day, he developed the feeling that the cupboard and other furniture of his apartment were moving. In an attempt to counteract against this, he jumped around wildly. He also had the feeling of small stones entering his mouth (coenesthesia). To avoid this, he made turning movements with his arms and a towel. He could be distracted from his strange behaviors for not more than a few minutes. He had to be admitted on an emergency basis into a psychiatric hospital. The symptoms resolved within a few days after RTG was reduced significantly.

Other adverse effects (not leading to discontinuation) were dizziness (5), gait disturbance (2), reduced concentration, reduced memory, reduced understanding (2), headache, diplopia, tremor, somnolence, floppiness, weight gain (2), mild paranoid thinking, mild aggression, and reduced urinary stream.

One patient reported positive side effects: he felt more quiet and relaxed (however, sometimes up to the point of indifference).

In summer 2013, a red-hand (dear doctor) letter by the manufacturer informed about the safety warning by the US Food and Drug Administration regarding retinal pigmentation and discoloration of skin and nails in patients exposed to RTG. Thereupon, the 7 patients still on RTG were reexamined by their neurologists and referred to an

Table 2
Baseline antiepileptic medication.

Number of baseline AEDs	N (number of patients)	AEDs at baseline	N
1	0	LTG	15
2	5	VPA	12
3	13	OCBZ	5
4	2	PGB, TPM	4 each
5	0	ZNS, PB/PRM	3 each

Baseline AEDs used in <3 patients: bromide, eslicarbazepine, lacosamide, levetiracetam, methsuximide, rufinamide, and sultiame.
LTG: lamotrigine, PB: phenobarbital, PGB: pregabalin, PRM: primidone, OCBZ: oxcarbazepine, TPM: topiramate, VPA: valproate, and ZNS: zonisamide.