JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2017;13(1):47-54 / https://doi.org/10.3988/jcn.2017.13.1.47

Desensitization to Oxcarbazepine: Long-Term Efficacy and Tolerability

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Background and Purpose Antiepileptic drug (AED)-associated cutaneous adverse drug reactions can lead to the discontinuation of medications. The aim of this study was to determine the long-term efficacy and safety of performing desensitization to oxcarbazepine.

Methods This study involved 20 patients who exhibited cutaneous adverse drug reactions associated with oxcarbazepine use between July 2009 and March 2016 at Samsung Medical Center. All of the participants had to discontinue oxcarbazepine despite presenting initially positive responses. Human leukocyte antigen genotyping was performed to detect the genetic predisposition to Stevens-Johnson syndrome. The desensitization to oxcarbazepine was performed with a starting dosage of 0.1 mg/day. Efficacy was evaluated by comparing the frequency of seizures before and at 1 and 3 years after desensitization. Adverse events occurring during desensitization and the retention rate after desensitization were also investigated.

Results Nineteen patients (95%) safely completed the desensitization protocol. One withdrew owing to emotional problems that appeared to be associated with oxcarbazepine. The follow-up period was 4.6±1.2 years (mean±SD), and oxcarbazepine was maintained for more than 3 years after desensitization in 15 patients (83.3%). The response rates were 84.2% and 77.8% at 1 and 3 years after desensitization, respectively. Eight patients remained seizure-free for 3 years, and two discontinued all AEDs. Transient adverse reactions such as mild rash and itching were reported by five patients during desensitization.

Conclusions This study has demonstrated the long-term efficacy and safety of desensitization to oxcarbazepine in patients exhibiting cutaneous adverse drug reactions. This favorable outcome should encourage the implementation of desensitization in patients presenting with hypersensitivity to oxcarbazepine as an alternative strategy in clinical practice.

Key Words desensitization, oxcarbazepine, intractable epilepsy, cutaneous adverse drug reactions, efficacy.

INTRODUCTION

Cutaneous adverse drug reactions to antiepileptic drugs (AEDs) are a common major problem in the treatment of epilepsy.[1,2] When an adverse reaction occurs, the drug in question needs to be withdrawn immediately in order to minimize its effects. Reintroducing the sensitized drug should be avoided because more-severe hypersensitivity reactions or even life-threatening conditions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) may occur.[3] In addition, the development of cross-reactivity to other AEDs reportedly occurs in 40−58% of cases.[4-6] Cutaneous adverse drug reactions may therefore have a decisive impact on the course of treatment. Applying a desensitization protocol to the causative drug may be an option, especially if the patients have previously shown a favorable response to the AED and subsequently show resistance or cross-reactivity to other AEDs.[7,8]

Received April 26, 2016
Revised June 19, 2016
Accepted June 20, 2016

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The desensitization protocol aims at inducing pharmacological tolerance to the compound responsible for the hypersensitivity reaction.[8] The causative drug is initially administered at a low dosage, and then the dosage is gradually increased. Successful desensitization is defined as reaching a therapeutic dosage and achieving toleration of repeated administration of the drug at that dosage without severe adverse reactions.[7,9] Desensitization has classically been employed for IgE-mediated type-I hypersensitivity reactions, and most studies of desensitization have investigated drugs associated with such reactions, including β-lactam antibiotics, chemotherapeutic agents, and monoclonal antibodies.[10]

AED-induced cutaneous adverse reactions reportedly occur in 5–17% of epilepsy patients,[11] but there is a lack of literature describing desensitization to AEDs, with most of the existing literature consisting of case reports.[12-14] We have previously reported on a pilot study of the efficacy of desensitization to oxcarbazepine,[15] but no previous study has demonstrated the ongoing effectiveness and safety of desensitization to oxcarbazepine. The aim of this study was to determine the long-term efficacy, tolerability, and maintenance of the therapeutic effect in seizure control of oxcarbazepine desensitization.

METHODS

Patients

Patients who experienced cutaneous adverse drug reactions to oxcarbazepine between July 2009 and March 2016 at Samsung Medical Center (Seoul, Korea) were enrolled in this study. We reviewed their medical records for clinical features that confirmed the degree of allergic reactions to oxcarbazepine. Cutaneous adverse drug reactions to oxcarbazepine were defined as erythematous skin rash with or without systemic symptoms that developed within 3 weeks of the offending drug being administered, without modification by other drugs. It was also stipulated that the skin rash had to disappear after discontinuing oxcarbazepine. The extent of skin rash was assessed visually by a physician. The systemic symptoms included fever, lymphadenopathy, hematologic laboratory abnormalities, or life-threatening cutaneous reactions without evidence of a microbiologic infection. Clinical data included demographic characteristics, age at seizure onset, cause of epilepsy, type and frequency of seizure, type and dosage of AEDs, and cross-reaction with other AEDs.

The following inclusion criteria for patients were applied: 1) previously shown a positive response, with a decrease in the frequency of seizures induced by oxcarbazepine of more than 50%, 2) exhibited cutaneous adverse drug reactions to oxcarbazepine as defined above, 3) discontinued oxcarbazepine owing to cutaneous adverse drug reactions, and 4) seizures not controlled by more than two other AEDs following the discontinuation of oxcarbazepine. Patients who showed severe hypersensitivity reactions such as SJS, TEN, or drug reaction with eosinophilia and systemic symptoms (DRESS) were excluded for safety reasons.[8]

Desensitization protocol

The desensitization protocol for oxcarbazepine in this study has been described in a previous report of oxcarbazepine desensitization.[15] We diluted the original solution of oxcarbazepine with normal saline to obtain three diluted solutions of oxcarbazepine at different concentrations (Table 1). The administered daily dose of oxcarbazepine was increased using these solutions until seizure control became apparent or the maximum dosage was reached. All patients were warned about possible cutaneous adverse drug reactions, and advised to discontinue taking oxcarbazepine and to consult us if they experienced any adverse reactions during the desensitization protocol. When a patient showed an erythematous skin rash or complained of an itching sensation without generalized symptoms, desensitization was discontinued or the oxcarbazepine dosage was reduced. In addition, antihistamine medications were administered for symptom control.

Table 1. Desensitization protocol

Days	Type of solution	Daily dose increment	Dosage (mg/day)
1–12	A*	Increment by 1 mL on each day	0.1–3.2
13–20	B†	Increment by 4 mL on each day	4–32
21–32	C†	Increment by 2 mL on each day (to ≤10 mL)	60–120
33–42	O§ (2 mL/day)+C	Increment solution C by 2 mL on each day	132
43–52	O (4 mL/day)+C	Increment solution C by 2 mL on each day	252
53–62	O (6 mL/day)+C	Increment solution C by 2 mL on each day	372
63–72	O (8 mL/day)+C	Increment solution C by 2 mL on each day	492
73–82	O (10 mL/day)+C	Increment solution C by 2 mL on each day	612

We increased the dose on each day by adding an increment of 2 mL of solution C, from 2 to 20 mL on a 10-day cycle, which implied an oxcarbazepine daily dose increment of 12 mg.
*Solution A: 1 mL=0.1 mg, †Solution B: 1 mL=1 mg, ‡Solution C: 1 mL=6 mg, §Solution O: original solution, 1 mL=60 mg.

The desensitization protocol was continued after we had confirmed that the symptoms had improved as a result of these measures. During the desensitization protocol, the dosage of other concomitant AEDs was not modified and no new AEDs were introduced.

Human leukocyte antigen genotyping

Complete human leukocyte antigen (HLA) genotyping (of *HLA-A* and *HLA-B*) was performed on all but one patient to determine the genetic propensity for AED-induced SJS or TEN. The HLA genotyping followed the method used in a previous study of HLA genotypes and desensitization to oxcarbazepine in pediatric patients.[15]

Outcome assessment

Desensitization was defined as complete when the patient could tolerate oxcarbazepine at a dosage of 10 mg/kg/day without any cutaneous adverse drug reactions. The seizure outcome was evaluated based on the frequencies of seizures at baseline (during a period of 3 months before desensitization), at 1 and 3 years after desensitization, and at the last follow-up. Responders were defined as those who exhibited a reduction in seizure frequency of more than 50% relative to baseline. We assessed the retention rate in order to evaluate efficacy as well as tolerability. Tolerability was assessed by recording adverse reactions such as rash, fever, itching, or lymphadenopathy during desensitization, and cross-reactions with other AEDs were investigated. In addition, the numbers of AEDs administered to patients were compared.

This study was approved by the Institutional Review Board (IRB) of Samsung Seoul Hospital (IRB number 2012-11-093).

RESULTS

Clinical characteristics of participants

Twenty patients were enrolled in this study. Nineteen patients with epilepsy had intractable seizures that had been inadequately controlled with multiple AEDs. The age at seizure onset was 8.13±4.33 years (mean±SD), and the age at desensitization was 10.63±3.43 years. The seizures had various etiologies, and they were unknown in 65.0% of the patients. All 19 patients with epilepsy were diagnosed with localization-related epilepsy with various semiologies: simple motor, dialeptic, and hypermotor seizures. All patients showed cutaneous adverse drug reactions to oxcarbazepine, with one-third of them (n=7) also exhibiting accompanying systemic symptoms such as fever, lymphadenopathy, or thrombocytopenia. None of the patients showed severe skin reactions or the involvement of other internal organs. Skin rash in response to oxcarbazepine developed within 2 weeks of drug administration (at 12.4±7.8 days), and this symptom disappeared after discontinuing oxcarbazepine in all cases. Cross-reactivity leading to skin rash was observed in 12 patients (60.0%), and half of these reacted with allergic skin rashes to more than 3 AEDs. One patient with paroxysmal kinesigenic dyskinesia (PKD) had been controlled with oxcarbazepine, but had to discontinue this medication owing to the development of a drug-related skin rash. The parents of this PKD patient wanted to participation in the desensitization to oxcarbazepine because of its excellent effect.

The demographic and clinical characteristics of all patients are summarized in Table 2. None of the patients carried ei-

Table 2. Demographic and clinical characteristics of all patients

Characteristic	Value
Sex (male:female), *n*	13:7
Age at seizure onset, years	8.13±4.33 (range 3 days to 16.1 years)
Age at desensitization, years	10.63±3.43 (4.8–16.2)
Etiology	
Cryptogenic	13 (65)
Symptomatic	7 (35)
Encephalitis	4 (20)
Focal cortical dysplasia	1 (5)
Hypoxic ischemic encephalopathy	1 (5)
Brain tumor	1 (5)
Seizure semiology[41]	
Simple motor seizure	3 (15.8)
Dialeptic seizure	13 (68.4)
Hypermotor	1 (5.3)
Secondary generalized seizure	11 (57.9)
AEDs inducing rash, *n*/total *n**	
Oxcarbazepine	20/20
CBZ	5/5
LTG	7/14
PHT	4/10
PB	3/8
GBP	1/3
LEV	2/17
Patients with rash to two AEDs	12 (60)
Patients with rash to more than three AEDs	6 (30)
Allergic reaction to oxcarbazepine	
Skin rash	20 (100)
Fever or lymphadenopathy	7 (35)
Thrombocytopenia	2 (10)

Data are mean±SD or *n* (%) values except where indicated otherwise.
*Number of patients who showed AED-induced rash/total number of patients who used the AED.
AED: antiepileptic drug, CBZ: carbamazepine, GBP: gabapentin, LEV: levetiracetam, LTG: lamotrigine, PB: phenobarbital, PHT: phenytoin.

Table 3. Efficacy of desensitization in seizure control

Patient no.	Bwt* (kg)/ dosage† (mg/day)	Time‡ (days)	Seizure outcome			Number of concomitant AEDs			AEDs developing cross-reactivity	Follow-up§ (years)
			After 1 year	After 3 years	Last follow-up	After 1 year	After 3 years	Last follow-up		
1	90/None‖	72	>90% reduction	No effect	N/A	3	1	1¶		4.6
2	71/1,800	72	No effect	No effect	>50% reduction	5	4	6	LTG	5.8
3	70/1,800	52	>90% reduction	>90% reduction	No effect	6	4	4		6.7
4	58/none**	57	No effect	N/A	N/A	4	4¶	4¶	LTG	5.4
5	68/1,200	72	No effect	>50% reduction	No effect	3	4	5	PHT	5.3
6	34/none‖	42	>50% reduction	N/A	N/A	4	3¶	3¶	CBZ, PHT	3.3
7	85/none	120	>90% reduction	Seizure-free	Seizure-free	3	0	0	CBZ, LEV	5.0
8	60/1,200	72	>90% reduction	>90% reduction	>90% reduction	2	2	2	LTG	5.1
9	40/900	42	>90% reduction	>90% reduction	>90% reduction	2	2	2	CBZ, PB	4.9
10	41/900	37	Seizure-free	Seizure-free	Seizure-free	3	1	1	LEV	4.4
11	67/750	124	>90% reduction	Seizure-free	Seizure-free	6	3	2	CBZ, GBP, LTG, PB	5.4
12	55/none	42	Seizure-free	Seizure-free	Seizure-free	1	1	0		4.3
14	57/1,650	57	>50% reduction	>90% reduction	>90% reduction	2	3	3		4.0
15	67/1,600	72	Seizure-free	Seizure-free	>50% reduction	2	2	2	LTG	4.1
16	69/900	72	Seizure-free	Seizure-free	Seizure-free	2	2	1		3.8
17	45/none††	Failed	Failed	N/A	N/A	N/A	N/A	N/A	LTG, PHT	3.8
18	60/750	52	Seizure-free	Seizure-free	Seizure-free	2	2	2	PHT	5.1
19	75/1,350	62	Seizure-free	>90% reduction	Seizure-free	1	1	1		4.6
20††	27/960	42	Seizure-free	N/A	Seizure-free	1	N/A	1	CBZ, LTG, PB	1.0

Patient no. 13, who had paroxysmal kinesigenic dyskinesia, was not included in this table.
*Bwt, current body weight of patient, †Current oxcarbazepine dosage, ‡Time taken to reach the optimal oxcarbazepine dosage of 10 mg/kg/day, §Follow-up period after desensitization, ‖Discontinuation of oxcarbazepine owing to no seizure control, ¶Not including oxcarbazepine, **Discontinuation of oxcarbazepine owing to skin rash at high dosage (1,080 mg/day for a body weight of 31 kg), ††Withdrew from desensitization protocol, ††Followed up for 1 year from desensitization.
AEDs: antiepileptic drugs, CBZ: carbamazepine, GBP: gabapentin, LEV: levetiracetam, LTG: lamotrigine, N/A: not available, PB: phenobarbital, PHT: phenytoin.

ther the *HLA-A**3101 or *HLA-B**1502 allele, which have been found to be strongly associated with AEDs-induced SJS or TEN.

Efficacy of desensitization

Nineteen patients (95.0%) completed the desensitization protocol without severe allergic reactions. The remaining patient could not complete this protocol due to exhibiting a depressive mood at a dosage of 216 mg/day (7.4 mg/kg/day), although no cutaneous adverse drug reaction occurred. The time taken to reach the optimal dosage of 10 mg/kg/day and the maximum therapeutic dosage were 63.6±24.1 days (range 37–124 days) and 116.0±58.2 days (range 47–300 days), respectively. The maintenance dosage was 20.9±7.3 mg/kg/day (range 8.3–35.6 mg/kg/day).

Patients were followed up for 4.6±1.2 years (range 1–6.7 years). At 1 year after starting desensitization, the seizure frequency had reduced by more than 50% in 16 patients (84.2%), and the retention rate was 94.7% (18 patients). Nineteen patients were followed up for more than 3 years after desensitization, and the rate of responses (corresponding to a reduction in seizure frequency of ≥50%) was 77.8% (*n*=14). The retention rate was 83.3% (*n*=15) at 3 years. Eight patients were seizure-free after 3 years of follow-up. At the last follow-up, nine patients (47.4%) were seizure-free, and two remained seizure-free without any AEDs for 13 and 6 months.

The number of concomitant AEDs administered to patients with epilepsy decreased from 5.85±3.22 before desensitization to 2.33±1.53 after desensitization. One patient with PKD experienced no symptoms with oxcarbazepine monotherapy. Table 3 and 4 present the efficacy, oxcarbazepine dosage, and concomitant AEDs in each patient.

Three patients became resistant to oxcarbazepine after successful desensitization. The first patient (patient no. 3 in Table 3) had been treated for cryptogenic localization-related epilepsy from the age of 3.6 years. At the age of 12 years, focal cortical dysplasia in the right frontal lobe was found in follow-up brain magnetic resonance imaging, and the patient underwent epilepsy surgery. The second patient (patient no. 19 in Table 3) was seizure-free for 22 months after desensitization. His seizures recurred at the age of 18.3 years and were assumed to be associated with lifestyle, in particular with an irregular sleep schedule, alcohol consumption, or sleep deprivation. The third patient (patient no. 1 in Table 3) was eventually diagnosed with cryptogenic localization-related epilepsy. Her seizure frequency had decreased by more than 90% at 2.6 years after desensitization. She discontinued other AEDs, including oxcarbazepine, and had remained on just one AED (lamotrigine) until November 2015. The frequency of her seizures subsequently increased, and they could not be controlled with two AEDs.

Tolerability of desensitization

During desensitization, five patients (26.3%) transiently exhibited very mild and confined erythematous skin rash on their face and extremities, and two of them complained of a mild itching sensation with skin rash. In four of these patients, skin rash developed at 4–6 weeks after initiating desensitization, at an oxcarbazepine dosage of 3.0±4.6 mg/kg/day (range 1.0–10.6 mg/kg/day). An erythematous skin rash developed on the face of the fifth patient more than 2 months after reaching the dosage of 10 mg/kg/day. The symptoms of these patients improved almost immediately (within 3 days) upon ceasing increments or decreasing in the administered dosage. In addition, antihistamine was provided for symptomatic relief. After the skin reactions had manifestly disappeared, desensitization was resumed while being careful to detect any possible recurrence. All of the patients subsequently completed desensitization without further adverse safety events. No patient experienced severe life-threatening adverse reactions such as SJS or TEN.

One patient (patient no. 4 in Table 3) discontinued oxcarbazepine long after the desensitization protocol. This patient had completed the desensitization protocol in 42 days, and remained on oxcarbazepine for more than 1 year with a reduction in seizure frequency of more than 50%. Although the drug was well tolerated, a skin rash appeared and the patient complained of an itching sensation at 21 months after desensitization. Although the causal relationship between these symptoms and oxcarbazepine was not definitive, we decided to discontinue oxcarbazepine (1,080 mg/day, 34.8 mg/kg/day) for safety reasons; the rash then disappeared 3

Table 4. Outcomes at 1 and 3 years after desensitization and at the last follow-up

Outcome	After 1 year (*n*=19)	After 3 years* (*n*=18)	Last follow-up (*n*=19)
Seizure-free	8 (42.1)	8 (44.4)	9 (47.4)
>90% reduction	6 (31.6)	5 (27.8)	3 (15.8)
50–90% reduction	2 (10.5)	1 (5.6)	2 (10.5)
<50% reduction	3 (15.8)	3 (16.7)	4 (21.1)

Data are *n* (%) values.
*One patient not included due to starting desensitization in February 2015.

days after this discontinuation.

DISCUSSION

This study found that desensitization to oxcarbazepine could be successfully applied as an alternative management strategy for more than 3 years in epilepsy patients who experienced cutaneous adverse drug reactions to oxcarbazepine and whose seizures were refractory to other AEDs. The long-term efficacy of desensitization was good, as indicated by response and retention rates of more than 70% and 80%, respectively. In addition, desensitization was well tolerated by all patients without severe life-threatening adverse reactions, although one discontinued the medication for other reasons. Mild adverse events such as an erythematous skin rash on the face or extremities and itching sensations were observed in 26.3% of the patients, but these events were well controlled and did not make it necessary to discontinue the medication.

Allergic drug reactions are commonly divided into two types according to the time of symptom onset: 1) type-I immediate reactions, occurring within 1 hour of exposure, and 2) delayed reactions, occurring more than 1 hour after exposure.[16] Drugs that have been implicated in type-I hypersensitivity reactions include antibiotics, nonsteroidal anti-inflammatory drugs, and biologic modifiers. Desensitization to these drugs is common, and various studies of desensitization to antibiotics, monoclonal antibodies, and chemotherapeutic agents have been reported.[7,17,18] In contrast, studies of desensitization to AEDs are rare, though several case reports about desensitization to a small number of aromatic AEDs have been published. These reports include cases of successful desensitization to carbamazepine in patients who are intolerant to multiple AEDs, and to pentobarbital in an infant with Ohtahara syndrome.[13,19,20] Itomi et al.[21] reported the occurrence of desensitization to phenytoin in an 8-year-old boy with intractable complex partial seizures. He was started on phenytoin at a dosage of 1 mg/day, which was gradually increased over a period of 4 months until his seizures were controlled, which occurred at a dosage of 150 mg/day. Another recent study found desensitization in a patient with absence epilepsy, which was intractable with three other AEDs: levetiracetam, ethosuximide, and lamotrigine.[22] Valproic acid was the only effective drug for controlling the seizures in this patient, but he exhibited a hypersensitivity reaction and the drug had to be discontinued. An oral desensitization protocol was adopted and a few weeks later his seizures were completely controlled without significant adverse reactions. Only two studies of desensitization to oxcarbazepine have been reported. The first case report concerned an attempt in a 12-year-old male by Watts and Bird,[12] and the other was reported by our group and concerned a desensitization protocol in pediatric patients with epilepsy who were refractory to alternative AEDs.[15] In all of these desensitization subjects there was no choice but to withdraw the offending drug due to cutaneous adverse drug reactions, despite initial good responses, and their seizures were not controlled by alternative AEDs. After desensitization, these patients did not exhibit severe adverse effects, and the drugs to which they had been desensitized were effective in 89.5% of them.

Nineteen patients (95%) had intractable localization-related epilepsy in the present study. They had been taking more than five AEDs (5.85±3.22) before desensitization, yet their seizures were still not adequately controlled. Although their initial responses to oxcarbazepine were good, the medication had to be withdrawn after the development of skin rashes. Alternative drugs were administered, but two-thirds of the patients showed cross-reactivity to other AEDs and their seizures could not be controlled with the other medications. Desensitization was therefore considered as a therapeutic option in light of their intractable seizures. There was a risk of the previous allergic reactions recurring during the desensitization protocol, even when the dosages were minimal. The parents of the patients were educated about recognizing and reporting the potential adverse events, and it was recommended that the patients remained in the clinic for monitoring for at least 2 hours after applying the initial desensitization dosage. In addition, patients with potentially life-threatening drug-related conditions such as SJS, TEN, DRESS, and systemic vasculitis were excluded from the trial.[8]

We have previously reported on a prospective pilot study of oxcarbazepine desensitization, in which the mean follow-up period was 16.2 months.[15] The present study had a longer follow-up and so allowed us to evaluate the long-term efficacy and safety of oxcarbazepine desensitization—patients in this study were followed up for a mean of 4.6 years after desensitization. With respect to efficacy and tolerability, we found similar success rates and superior safety relative to previous reports of drug desensitization. For example, successful completion rates of 75−93% were found in aspirin desensitization studies, while 5−12% of the patients discontinued the protocol because of side effects.[23-25] Fam et al.[26] evaluated the long-term outcome of desensitization to allopurinol in patients with hyperuricemia. Thirty-two of their patients had withdrawn from allopurinol owing to allopurinol-related pruritic skin eruptions, and subsequently slow oral desensitization was applied. The desensitization protocol was completed by 28 (87.5%) of the patients over an average period of 1 month, with the remaining 4 patients (12.5%) withdrawing due to relapsed skin rashes. At a 3-year follow-up, three of the patients who had completed the de-

sensitization protocol showed late cutaneous adverse drug reactions and discontinued the treatment. As a result, Fam et al.[26] reported the final success rate of the desensitization as 78%, and transient mild cutaneous adverse drug reactions in confined regions were observed in 25% of the patients during desensitization. That study, like the present one, found that desensitization was safe, with no patients experiencing severe hypersensitivity reactions to the drug.

The desensitization protocol modifies the IgE-mediated hypersensitivity reaction by temporarily impairing sensitized mast cells. Considering that cutaneous adverse drug reactions in our patients were associated with delayed hypersensitivity, the protocol should be referred to as the 'induction of tolerance' rather than 'desensitization.' However, at present 'desensitization' is used when referring to various non-IgE-mediated hypersensitivity reactions, because the pathomechanism of desensitization is not fully understood and nonimmunologic mechanisms are thought to be involved.[9,27] In addition, numerous studies have found successful desensitization to non-IgE-mediated reactions, such as those involving sulfonamide, temozolomide, and allopurinol, and in doing so reflect the extended meaning of desensitization.[28-30] These results suggest that not only IgE-sensitized mast cells—which play a major role in type-I hypersensitivity—but also undefined immunologic mechanisms and genetic factors are involved in desensitization.8 Future research needs to clarify the pathomechanism of desensitization through immunologic evaluations involving large populations.

Five of the 19 patients who completed the desensitization protocol in this study experienced mild adverse reactions during desensitization. Their symptoms were limited to skin reactions, and they improved when the dosage was reduced or the escalation of the dosage was delayed until symptoms had improved. This points to the symptoms being associated with both the amount of allergen exposure and the rate of escalation. A similar relationship between lamotrigine and skin rash has been established in previous studies. Well-known risk factors for lamotrigine-related skin rash include a high initial dosage, rapid titration of dosage, and concurrent valproic acid administration.[31] Clinical trials aimed at reducing the incidence of lamotrigine-related skin rash found that slower titration and lowering of the starting dosage were effective in preventing the development of skin rash.[32-34] We similarly consider that it may be beneficial to initially apply a very low dosage and then only gradually escalate it in patients who have experienced adverse drug reactions.

Previous studies have revealed associations between genetic risk factors and cutaneous adverse drug reactions, in that the risk of developing allergic reactions was increased if the patient had a specific HLA genotype. In particular, *HLA-A**3101 and *HLA-B**1502 have been found to be associated with in carbamazepine-induced allergic skin reactions in Han Chinese and Southeast Asian populations.[35-38] However, associations of those HLA alleles with AEDs other than carbamazepine have not been reported, and one study found that Korean patients with AED-induced skin rash did not carry these two alleles.[39,40] Likewise, in the present study, no HLA allele was found to be associated with carbamazepine-induced SJS or TEN.

While this study has demonstrated the long-term efficacy and tolerability of desensitization to oxcarbazepine, the desensitization protocol is lengthy and it poses the risk of various degrees of hypersensitivity reactions. Therefore, the availability of an alternative medicine would subordinate the use of desensitization.

Desensitization to AEDs may be an effective and tolerable treatment approach for patients with AED-induced cutaneous adverse reactions over longer time frames. However, the desensitization protocol should be applied carefully and only in cases with a history of mild adverse reactions and without life-threatening conditions, since the reintroduction of sensitized drugs may trigger the same or even more-severe allergic reactions. In addition, performing a comprehensive clinical examination before desensitization and providing education about how to detect incipient adverse events are mandatory.

In conclusions, the desensitization protocol is aimed at inducing the tolerance to a drug associated with allergic reactions and may be an option for patients who experience cutaneous adverse drug reactions. This study has demonstrated that desensitization to oxcarbazepine is a safe and useful alternative management strategy for patients in whom the drug would otherwise inevitably have to be discontinued. We found high response and retention rates during a long-term follow-up. This favorable outcome should encourage the implementation of desensitization in clinical practice for patients exhibiting hypersensitivity to oxcarbazepine.

Conflicts of Interest

The authors have no financial conflicts of interest.

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