

Continuous Subcutaneous Insulin Infusion as an Effective Method of Desensitization Therapy for Diabetic Patients with Insulin Allergy: A 4-year Single-Center Experience

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ABSTRACT

Purpose: This article summarizes our experiences in the application of continuous subcutaneous insulin infusion (CSII) as a method of rapid desensitization therapy for diabetic patients with insulin allergy that was subsequently switched to a regimen of multiple-dose injections for long-term insulin therapy.

Methods: The clinical data of 11 diabetic patients with insulin allergy in Peking Union Medical College Hospital from April 1, 2008, through December 31, 2011, were retrospectively analyzed.

Findings: All 11 conditions were diagnosed by case history, skin testing, determination of serum specific anti-insulin IgE, and reaction to withdrawal of insulin. Seven patients accepted the traditional injection method of desensitization, and 5 patients accepted CSII with the protocol designed for this study (1 patient accepted CSII after failure by the formal method). Six of the 7 patients who accepted the traditional method and all 5 patients who accepted CSII had successful results. All 5 patients in the CSII group switched to a regimen of multiple dosage injections. In a survey of 28 nurses, both experienced nurses and practical nurses preferred to use CSII as the method of desensitization.

Implications: It is feasible and effective for diabetic patients with insulin allergy to use CSII as a method of rapid desensitization with subsequent switching to a regimen of multiple-dose injections for long-term insulin therapy. (*Clin Ther.* 2016;■:■■■-■■■) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: continuous subcutaneous insulin infusion, desensitization, insulin allergy, diabetes mellitus, multiple dosage injection.

INTRODUCTION

Patients with poor control of type 2 diabetes mellitus who are undergoing maximum oral hypoglycemic therapy invariably need insulin therapy. In addition to common adverse reactions to insulin therapy, insulin allergy is a difficult problem to treat, although its prevalence has decreased to <1% of diabetic patients receiving insulin therapy since the introduction of recombinant human insulin.¹ However, insulin allergy results in potentially life-threatening, immediate or delayed, local and general manifestations.² Although some patients react to protamine³ or zinc⁴ in the insulin preparations, it is usually a persistent IgE-mediated insulin allergy (type 1 allergy)⁵ that necessitates desensitization.^{1,5} Different treatments of unequal efficiency have been proposed; a number of case reports and recent reviews have revealed that diabetic patients with insulin allergy have tolerated continuous subcutaneous insulin infusion (CSII) since 1987.⁶⁻⁹ Nearly all those patients successfully treated with CSII accepted this type of therapy as an option for long-term insulin therapy. Unfortunately, according to insurance policies in China, this expensive treatment is not covered for type 2 diabetic patients with insulin allergy. Therefore, we attempted to use CSII as a method of desensitization instead of a long-term regimen of insulin therapy so that patients with insulin allergy could spend as little money as possible. We retrospectively analyzed

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11 patients with diabetes mellitus; all presented with local skin reactions after subcutaneous injections of different types of insulin preparations. The aim of this study was to investigate the possibility of using CSII as a method of rapid desensitization and then switching to a multiple-dose injection regimen for long-term insulin therapy.

MATERIALS AND METHODS

We retrospectively analyzed medical records of 11 diabetic patients who presented with local skin reactions after subcutaneous injections of different types of insulin preparations from endocrinology clinical wards at the Peking Union Medical College Hospital from April 1, 2008, through December 31, 2011. The patients were treated with rapid insulin desensitization (5 patients with CSII and 7 patients with traditional rapid insulin desensitization; among them, 1 patient underwent both methods). Data from these patients are given in [Table I](#). The protocol of therapy was approved by the appropriate ethical committees related to the PUMC Hospital, and the insulin desensitization therapy was performed after obtaining patients' written informed consent.

Before starting the insulin desensitization therapy, the patients were evaluated to determine whether insulin was the only therapeutic method to control their blood glucose.

We designed a protocol of CSII application as a desensitization therapy according to the principle that immune tolerance may be induced by gradually increasing dosage from an extremely small amount. The first pilot case was successful.¹⁰ The protocol is listed in detail as follows. The short-action insulin preparation was diluted 10 times (from U100 to U10 by saline). insulin pumps (MiniMed; Medtronic, Fridley, Minnesota) were used in all patients (the first 2 patients with the Minimed 508C, and the other 3 patients with the Minimed 712 pump). The basal rate of diluted insulin began with 0.01 IU/h of insulin and then increased to where the basal infusion rate had a speed of 0.01 IU/h on the first day of desensitization. At the end of the first day, the basal rate increased to 0.24 IU/h. If the patient was free of any allergy symptoms, we started the basal rate from 0.25 IU/h on the second day (using the U100 insulin without saline dilution) and increased the rate by 0.05 IU/h

until it reached 1.4 IU/h at the end of the second day. On the third day of desensitization, we kept the basal rate as 1.0 IU/h or decreased it to 0.5 IU/h at night to avoid hypoglycemia in older patients. We added 4 to 6 IU to the bolus insulin infusion before each meal with the insulin pump. After that, we gave the bolus insulin by subcutaneous injection using a syringe, with a CSII basal insulin infusion administered at the same time on the fourth day. Finally, we stopped using CSII and gave the patient insulin therapy by alternative multiple subcutaneous injections.

RESULTS

Diagnosis of insulin allergy

The standard diagnosis protocol of insulin allergy required an exclusion of poor injection technique and a reaction to alcohol wipes. Insulin allergy was diagnosed according to the following 4 conditions. First, case history was checked to ensure that the symptoms and signs were consistent with insulin allergy. Second, a description of whether the patient's reaction alleviated after insulin was retrieved and carefully reviewed; the clinical manifestations of all 11 cases disappeared after insulin therapy stopped. Third, serum specific anti-insulin IgE to porcine and bovine, human insulin, and specific antiprotamine IgE in all these patients were assessed. Last, intradermal skin tests were performed with several insulin preparations to assist diagnosis of insulin allergy. All 11 cases were consistent with those 4 diagnosis criteria of insulin allergy, and all cases inevitably needed insulin therapy ([Table I](#)). Porcine regular, human regular, and short-action human insulin analogs (including insulin aspart and insulin lispro) and NPH were used in the intradermal skin tests; the volume of these types of insulin preparations was 0.1 ml that contained 1 U of insulin each, and we used saline as a negative control (the volume was also 0.1 ml). After the intradermal skin tests were performed, occurrences of erythema and wheal were recorded immediately and carefully.

Selecting 1 insulin/ or insulin analog preparation for desensitization

Intradermal skin tests were performed with the types of insulin preparations listed above, and the volume of each skin test solution was 0.1 ml that

Table I. General characteristics of diabetic patients with allergy to insulin.*

Patient No.	Sex	Age, y	Course of Diabetes, y	Allergy Onset After Initiation of Insulin	Manifestation of Allergy	Insulin Selected in Therapy	Duration of Therapy, d	Serum Total IgE, kU/L	Specific IgE to Porcine Insulin (Grade)	Specific IgE to Bovine Insulin (Grade)	Specific IgE to Human Insulin (Grade)	Specific IgE to Protamine (Grade)	Allergy to Others
1	F	53	7	10 mo	Itching, wheal	Lispro	3	63.6	2	2	2	NA	No
							7 (failed)	NA	3	NA	3	NA	No
2	M	68	1	5 mo	Itching, wheal, induration, pain	Humulin R	3	127	3	3	3	NA	No
3	M	65	12	1 wk	Wheal, papule, itching	Lispro	3	535	3	3	3	0	Penicillin, cefepime, gliquidone
4	M	73	20	8 mo	Induration, itching	Lispro	3	266	0	0	0	0	Levofloxacin, fish, shrimp, green onion, sesame, mushroom
5	F	49	18	3 d	Itching, wheal, induration, rash	Lispro	4	18	1	0	1	NA	Penicillin Quinolones
6	F	74	11	1 mo	Itching, induration, rash	Humulin R	3	316	1	0	0	0	Penicillin
7	F	62	6	2 wk	Red, itching	Novolin R	3	273	0	1	0	0	no
8	F	18	0.5	1 mo	Pain, itching, rash	Lispro	5	510	3	3	3	0	penicillin
9	M	65	10	2 wk	Redness, induration, itching	Humulin R	5	NA	3	3	3	0	Phenemal, levofloxacin
10	F	54	11	5 d	Papule, pain, itching	Novolin R	6	NA	NA	NA	0	NA	Adhesive plaster
11	M	47	4	11 d	Induration, itching	Aspart	4	136	3	2	2	0	patulin

NA = not applicable.

*Patients 1 through 7 accepted continuous subcutaneous insulin infusion therapy for desensitization, whereas patients 8 through 11 accepted therapy of multiple subcutaneous insulin injection. Patient 1 was admitted in our hospital twice to accept these 2 methods of desensitization. The lower rows provide the data of the traditional regimen of multiple dose injection. Specific IgE levels for insulin grade are as follows: 0, <0.35 kUA/L; 1, ≥0.35 kUA/L (suspected or mild); 2, ≥0.70 kUA/L (moderate); 3, ≥3.5 kUA/L; 4, ≥17.5 kUA/L; 5, ≥50 kUA/L; 6, ≥100 kUA/L (grade 3 to 6: severe).

contained 1 U of insulin, with saline used as a negative control. On the basis of the local skin reactions, including the occurrence and disappearance time and the area size of erythema, wheal, induration, or pseudopodia, the insulin preparation with the weakest reaction was selected as the one for desensitization (usually the regular or short-action insulin analog).

Processes of desensitization

According to the rules of desensitization, the process of insulin desensitization was performed with the patient under close monitoring, with preparations for emergency interventions in an inpatient setting.¹⁰ Five patients accepted CSII as the method of desensitization therapy, and 7 patients accepted traditional desensitization therapy (multiple dose injection), depending on the willingness of the patients. One patient accepted the former treatment after not tolerating insulin in the latter treatment. We used the pilot CSII desensitization protocol designed for this study for all 5 patients who accepted CSII for desensitization. With this protocol, used during a period of 3 days, all 5 patients who received CSII desensitization remained free of any insulin allergy symptoms. We gave the bolus insulin by subcutaneous injection using a syringe, with the CSII basal insulin infusion administered at the same time on the fourth day. Afterward, the patients were all successfully switched to insulin therapy by multiple subcutaneous injections with a syringe. For the other patients, the traditional desensitization protocol was applied according to the classic method.¹

Effect of 2 types of insulin desensitization therapy

All 5 patients using CSII for desensitization tolerated the multiple-dose insulin injection regimen, and 6 of 7 patients were successful using the traditional desensitization procedure. The unsuccessful case was in patient 1, who finally agreed to use the CSII protocol after the failure of the traditional treatment of desensitization. After 3 days, this patient was free of allergic symptoms, and on the fourth day, the regimen of insulin therapy was successfully switched from CSII to multiple subcutaneous injections by a syringe. After the first follow-up of 3 to 5 months, all 5 patients using CSII for desensitization were free of

any insulin allergic reactions brought on by multiple subcutaneous injection therapy.

Survey of the nurses' opinion of CSII as an insulin desensitization therapy

Nurses experienced with operating an insulin pump and inexperienced practical nurses were asked to fill out the questionnaire regarding the convenience and effectiveness of the CSII method. If they had not used an insulin pump before, they were asked the question, "If you had learned how to operate an insulin pump, which kind of desensitization therapy would you prefer?" The results indicate that 15 experienced nurses prefer the CSII desensitization therapy to multiple injections by syringe. The 13 inexperienced practical nurses who finished the questionnaire expressed interested in learning how to operate an insulin pump and would use this method for desensitization therapy. The reasons the nurses preferred CSII therapy for insulin allergic patients included mitigation of the workload, avoidance of the stimulation of a syringe needle, and decreased error rate.

DISCUSSION

In the present study, we investigated the possibility of using CSII as a method of rapid desensitization instead of a long-term regimen of insulin therapy for diabetic patients allergic to insulin. The fact that all 5 patients accepted this protocol and experienced a satisfactory effect suggests that CSII as a method of desensitization may be a good choice for these patients.

To use CSII as a method of rapid desensitization instead of a long-term regimen of insulin therapy may be a good choice in developing countries. Although CSII was introduced to treat insulin allergy as early as 1987,⁶ most cases accepted the CSII regimen as a lifelong therapy.⁸ In 2012, a patient with insulin allergy had been successfully treated by CSII when switching to a multiple-dosage injection 1 year later.¹¹ However, in many developing countries, CSII is still an expensive type of insulin therapy, and most patients cannot afford it. According to our procedure, it is unnecessary for those patients to use CSII as a lifelong therapy; patients will only need to rent an insulin pump for approximately 3 days.

Furthermore, it is also unnecessary for patients to learn how to operate the insulin pump because it can be managed by experienced nurses in the wards. Therefore, it is more practical to use CSII as a method of desensitization in developing countries.

CSII has been proposed to be an ideal method for treating insulin allergy in many published studies,^{8,9} but more convincing data are needed to support this opinion. We tried to compare the effects of CSII and the traditional regimen of desensitization, but the limited number of those rare cases restricted further statistical analysis. According to our data, CSII was at least as effective as the traditional regimen of desensitization. It is theoretically possible that CSII was superior to the traditional regimen because CSII involved increasing the dosage of insulin gradually and stably. In many case reports, CSII was always used after the traditional regimen fails to work. In the present study, 1 patient did not respond to the traditional regimen but had successful results with CSII regimen. Furthermore, we can conclude from the simple survey of nurses that CSII as a method of desensitization is widely accepted by nurses.

In the present study, we designed a detailed protocol of CSII desensitization according to the principle of desensitization because previous studies have not provided a standard protocol, and CSII was commonly used as a method of a long-term regimen of insulin therapy. The practice of this protocol in 5 cases certified its feasibility.

There were some shortcomings in our series of case analyses. First, it was a retrospectively observational study because this was the only ethical option for this type of intervention. Second, because the sample size was not large enough, we cannot statistically compare the effect of the 2 types of desensitization regimens, although it is the largest clinical study on CSII application in insulin allergy to date. Large sample, well-designed, multicenter clinical studies are needed to investigate whether CSII will be the first choice of desensitization.

In conclusion, it is possible and effective for diabetic patients to use CSII as a method of rapid desensitization and then switch to a multiple-dose injection regimen for long-term insulin therapy. CSII is preferred by clinical nurses because it helps to

decrease their workload and the error rate. Further studies are needed to investigate the status of CSII in insulin desensitization.

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AUTHOR CONTRIBUTIONS

N.L. set the concept of the study; T.Y. and N.L. designed the paper and performed analysis of the paper. T.Y. drafted the paper. T.Y. and N.L. drafted this research. Y.D. contributed to completing the survey of nurse. W.Z. and L.W. contributed in revising the draft and approval of the final version.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

SUPPLEMENTAL MATERIAL

Supplemental materials accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clinthera.2016.09.018>

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QUESTIONNAIRE FOR NURSES ABOUT INSULIN DESENSITIZATION REGIMENS

We are very glad to invite you to join this survey! Due to insulin desensitization of CSII regimen has been recently adopted in the endocrinology clinical ward, we design this survey in order to know the influence of this project on nurses' work load and opinion of nurses about both regimens. To ensure its objectiveness, this survey is anonymous and will not leak any personal information. Thank you for your participation!

No.	Questions	Answer
Q1	Your identity is: 1) practical nurse; 2) nurse rotated from Dept. of Internal Medicine ; 3) Senior nurse of endocrinology clinical ward (Working in endocrinology clinical ward for more than one year)	
Q2	Your gender: 1) male; 2) female	
Q3	Do you think which regimen brings more workload? 1) traditional regimen; 2) CSII regimen	
Q4	Do you think which regimen brings less pain for those patients? 1) traditional regimen; 2) CSII regimen	
Q5	Do you think which regimen is easy to perform for nurses? 1) traditional regimen; 2) CSII regimen	
Q6	Do you think which regimen is relatively difficult to master? 1) traditional regimen; 2) CSII regimen	
Q7	Do you think which regimen brings less error? 1) traditional regimen; 2) CSII regimen	
Q8	Do you think which regimen is preferred for patients to perform desensitization? 1) traditional regimen; 2) CSII regimen	
Q9	Do you think which regimen do you prefer? 1) traditional regimen; 2) CSII regimen	
Q10	If you have learned how to operate an insulin pump, which kind of desensitization therapy would you prefer? 1) traditional regimen; 2) CSII regimen	
Q11	Other comments about both regimen of insulin desensitization.	

关于护士对于脱敏治疗模式观点的问卷

您好! 非常高兴能邀请您参加这次调查! 鉴于近期病房开展 CSII 模式进行脱敏治疗, 为了解此项目对护士工作的影响和护士对于两种脱敏治疗模式的观点, 特开展此调查。为保证调查的客观性, 本调查为无记名方式, 且不会泄露任何个人信息。非常感谢您的参与!

序号	相关问题	问题答案
Q1	您的身份是: 1) 实习护士; 2) 内科轮转护士; 3) 内分泌科资深护士 (内分泌病房工作 1 年以上)	
Q2	您的性别是: 1) 男; 2) 女	
Q3	您认为哪种模式工作量大? 1) 传统模式 2) CSII 模式	
Q4	您认为哪种模式对于病人来说痛苦程度较低? 1) 传统模式 2) CSII 模式	
Q5	您认为哪种模式对护士操作更为简单? 1) 传统模式 2) CSII 模式	
Q6	您认为哪种模式操作相对难以掌握? 1) 传统模式 2) CSII 模式	
Q7	您认为哪种模式不易出错? 1) 传统模式 2) CSII 模式	
Q8	您认为病人更愿意采用哪种模式进行脱敏治疗? 1) 传统模式 2) CSII 模式	
Q9	您更愿意使用哪种脱敏治疗模式? 1) 传统模式 2) CSII 模式	
Q10	如果经过培训, 您更愿意使用哪种脱敏治疗模式? 1) 传统模式 2) CSII 模式	
Q11	对两种脱敏治疗模式的其它评论	