

# Systemic allergy to human insulin and its rapid and long acting analogs: successful treatment by continuous subcutaneous insulin lispro infusion

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## SUMMARY

Since the introduction of highly purified human recombinant insulin, allergy to insulin has become a very rare clinical situation, encountered in less than 1% of patients. It results in potentially life-threatening immediate or delayed, local and general manifestations. Different treatments of unequal efficiency have been proposed, the use of insulin analogs showing benefits in certain situations. We report the case of a type 2 diabetic patient who presented local reactions and then an anaphylactic shock after the introduction of insulin analog premixes. Intra-dermal reactions performed with porcine, human and insulin analogs preparations (aspart, lispro, glargine) were all positive, as well as the specific anti-insulin IgE measurement. Because we could not achieve normoglycaemia with maximal oral treatment and low caloric diet, we decided to attempt a desensitisation by continuous subcutaneous infusion of insulin lispro, since the lowest skin reaction was obtained with this insulin. We were able to induce a tolerance, by means of very low basal rate, very slowly increased, without any boluses, and maintaining antihistamine therapy. Six months later, the patient remains free of any symptom and has achieved a quite good glycaemic control. We describe for the first time a case of allergy to human insulin and to all available rapid and long acting analogs. We show the interest of a treatment with CSII of analogs in order to induce tolerance.

**Key-words:** Allergy to insulin · Insulin analogs · IgE detection · Tolerance induction.

Castéra V, Dutour-Meyer A, Koeppel MC, Petitjean C, Darmon P. Allergy to insulin treated by lispro pump. *Diabetes Metab* 2005;31:391-400

## RÉSUMÉ

**Allergie systémique à l'insuline humaine et à ses analogues de courte et longue durée d'action : efficacité de l'administration sous-cutanée continue d'insuline lispro**

Depuis l'avènement de l'insuline humaine recombinante hautement purifiée, l'allergie à l'insuline est devenue un phénomène très rare, survenant chez moins de 1 % des patients. Elle peut se traduire par des manifestations immédiates ou retardées, locales ou générales, potentiellement graves. Différentes méthodes de traitement ont été proposées, d'efficacité variable, l'utilisation des analogues de l'insuline s'étant révélée bénéfique dans certaines situations. Nous rapportons le cas d'un patient de 50 ans diabétique de type 2 qui a présenté des réactions allergiques d'abord locales puis générales, allant jusqu'au choc anaphylactique à la suite de l'introduction d'une insulinothérapie avec des mélanges fixes d'analogues rapides. Les intra-dermo-réactions (IDR) réalisées avec l'insuline porcine, humaine et différents analogues (lispro, aspart, glargine) étaient toutes positives, tout comme les IgE spécifiques anti-insuline. Devant l'impossibilité d'obtenir une normoglycémie avec un traitement oral maximal et un régime hypocalorique, nous avons décidé de réaliser une désensibilisation par pompe sous cutanée avec l'analogue lispro, car c'est avec cette insuline qu'était observée la plus faible réaction lors des IDR. Nous avons ainsi pu induire une tolérance, grâce à des débits très faibles et augmentés très progressivement, sans bolus, sous couverture antihistaminique. Six mois plus tard, le patient ne présentait plus aucune réaction, et son équilibre glycémique était satisfaisant. Nous décrivons ainsi un premier cas d'allergie à l'insuline humaine et à tous les analogues rapides et lents disponibles. Nous montrons l'intérêt du traitement par pompe externe avec analogues pour l'induction de tolérance.

**Mots-clés :** Allergie à l'insuline · Analogues de l'insuline · Dosage des IgE · Induction de tolérance.

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Received: February 21st, 2005; revised: April 28th, 2005

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## Introduction

Insulin allergy has been a known complication of insulin therapy ever since this treatment has been used. With the introduction of highly purified recombinant human insulin, allergic reactions to this molecule have become rare but still persist, with an incidence estimated to be less than 1% [1]. This affection consists in a large array of clinical manifestations, from mild, local symptoms to potentially life-threatening general reactions. Several methods of treatment have been proposed, including the use of anti-histamines, the addition of glucocorticoids, or more specifically, the switch to a different insulin, for instance rapid acting insulin analogs. Indeed, these molecules have sometimes proven their efficiency in this situation, probably because of their decreased immunogenicity [2]. However, allergy or sensitisation to analogs have also been described [3-12]. We report below, for the first time, the case of a type 2 diabetic patient allergic to all kinds of tested insulins, including short and long acting analogs, who was successfully treated by continuous subcutaneous infusion of insulin lispro.

## Case report

### First admission: insulin introduction

A 50-year-old man was admitted to our hospital in January 2003 for uncontrolled type 2 diabetes treated since 1999 with oral hypoglycaemic agents (repaglinide, Novonorm®, 2 mg three times a day; and acarbose, Glucor®, 100 mg three times a day). His past medical history consisted in a myocardial infarction two years before, dyslipidemia and arterial hypertension. He had no history of any allergy. At first admission, he reported a 16 kg weight loss over the last four months (weight 82 kg, BMI 27.4 kg/m<sup>2</sup>), with polyuria and polydipsia. Physical examination was normal. Glycaemic control was very poor, with an average capillary blood glucose around 20.0 mmol/l and HbA<sub>1c</sub> was 11.2% (normal range 4-6%). We then started a transient treatment by continuous subcutaneous insulin infusion with insulin lispro (Humalog®) via an external pump during five days, in order to restore euglycaemia. At cessation, we could not achieve normoglycemia with oral hypoglycaemic agents alone. Insulin therapy was then initiated, with three injections of premixes a day (Humalog Mix 50® 12 U before breakfast and 14 U before lunch, Humalog Mix 25® 20 U before dinner).

### Second admission: diagnosis of insulin allergy

Six months later, in July 2003, this patient came back to our unit for suspected insulin allergy. Actually, two weeks after insulin introduction in January, he presented red blotches, pruritus and burning sensation at the injection site immediately after the injection, lasting approximately for

half an hour. His general practitioner prescribed an oral antihistaminic agent and local dermocorticoids that did not provide any relief of his symptoms. A few weeks later, he developed generalised urticaria and, in July, he finally went to emergency medical department after he presented an anaphylactic reaction following Humalog Mix 25® injection, requiring intravenous methylprednisolone injection. Consequently, we decided to stop insulin, and to re-introduce oral hypoglycaemic agents (metformine, Glucophage® 1000 mg three times a day; glipizide, Ozidia® 20 mg once a day; acarbose, Glucor® 100 mg three times a day), in association with a low caloric diet. Two months after insulin cessation, glycaemic control was still very poor as HbA<sub>1c</sub> was 10.7%.

To assess the diagnosis of insulin allergy and to test the future possibilities of treatment, we examined skin reactions by intradermal (ID) testing with the Novo® insulin allergy kit (NovoNordisk®). This consists in injecting 0.05 ml of 5 U/ml of human recombinant insulin (HRI) and porcine insulin preparations, as well as 0.05 ml of the various additives, including protamine (350 σg/ml), metacresol (3 mg/ml), zinc (50 σg/ml), paraben (1 mg/ml), phenol (2 mg/ml) and isophane (2.4 mg/ml). Saline solution and histamine were respectively used as negative and positive references. These tests were positive for both porcine and human insulin as well as for protamine. They all produced immediate wheal and flare local reaction and a laryngeal tickling. Therefore, we performed the same ID tests with rapid analogs (lispro, Humalog® and aspart, Novorapid®), and with a long acting analog (glargine, Lantus®). Unfortunately, all of them were also positive. Aspart and glargine resulted in local reaction and laryngeal tickling, whereas lispro lead to local reaction only.

The relevant laboratory data found a total IgE rate at 222 kU/l (N < 100), insulin-specific IgE antibodies were positive at 0.50 kU/l (Class 1; N < 0.35) while protamine-specific IgE were negative (CAP system/Pharmacia Diagnostics®). Eosinophils were at 0.4 Giga/l (N < 0.7). Complement was within the normal range. HLA determination was DRB1/DQB1.

### Third admission: insulin tolerance induction

Because of the patients very poor glycaemic control with tendency to ketosis with oral hypoglycemic agents, and based on the few literature reports available, we initiated a gradual treatment with continuous subcutaneous infusion of lispro, since the lowest skin reaction was obtained with this insulin. The initial basal rate was very low, and was very slowly increased: 0.01 U/h the first day, 0.02 U/h the second day, 0.05 U/h the third day, then doubling the dose every day, until 0.8 U/h after 7 days, and finally, 1 U/h the eighth day and 1.3 U/h the ninth day. We did not administer any boluses to avoid potential allergy reactivation by the large pre meal dose of insulin. The Quickset® infusion set (Medtronic®) was chosen because there was no need for additional adhesive. Oral antihistamine treatment was

maintained. Clinical monitoring was intensive because of the potential risk of anaphylactic reaction. Glucose control gradually improved, and no local reaction was observed.

Six months later, the patient still reports no reaction, and glucose control has improved as HbA<sub>1c</sub> is now 7.5%. The actual basal rate is 2.0 U/h. We have substituted boluses by administration of repaglinide (Novonorm®, 2 mg three times a day). Specific anti-insulin IgE are however still elevated (8.98 kU/l, class 3).

## Discussion

We have reported the case of a type 2 diabetic patient who presented immediate local and general allergy to pre-mixes of insulin rapid analogs. The ID testing was positive for all insulin commercially available so that we chose to induce a tolerance with CSII of lispro, which has been successful.

## Pathophysiology

Insulin injected in the subcutaneous tissue may elicit various reactions from the immune system [13]. Our patient presented a typical type I allergic reaction according to the Gell and Coombs classification [14], which is the most common type in insulin allergy. It involves IgE antibodies that are produced after an antigenic stimulation of B-lymphocytes. The insulin-IgE complex acting on basophils and mast cells stimulates the release of inflammation mediators as histamine, inducing the allergic reaction. Rarely, insulin may also be responsible for a type III antigen-antibody-complex reaction [15-17] or, as well, for a type IV T-lymphocyte-mediated delayed reaction [18]. Cytotoxic-type II reactions have not been described for insulin allergy.

Several factors, determined by both insulin and individual factors are known to influence the immune response to insulin. First of all, it has been shown that patients with type 1 diabetes are more disposed to form anti-insulin antibodies than patients with type 2 diabetes [19]. Besides, immunogenetic background might influence the development of insulin allergy since HLA DR3 is significantly associated with low or non-insulin-antibody response [13], whereas HLA groups B7, DR2 et DR4 seem to promote insulin allergy [20]. The association with other allergies has been discussed [21, 22]. Our patient did not present any of these characteristics.

The nature of insulin preparations is also a crucial determinant of immune response. In the history of exogenous insulin therapy, patients were treated with impure bovine, porcine and human insulin preparations, containing various contaminants. These differences in the purity or primary structure – bovine and porcine insulins differ from human insulin by three and one amino-acids, respectively – resulted in a very high rate of local reactions. This rate has been considerably reduced, but did not totally dis-

appear with the advent of highly purified human recombinant insulin, with an allergy incidence between 5 and 10% for local reactions and between 0.1 and 2% for systemic reactions [23]. Its antigenicity might be due to either a tertiary structural change before or during injection, as insulin self-aggregation into high molecular weight aggregates is thought to promote the formation of anti-insulin antibodies [15, 22], or to a cross-reactivity with animal insulins, when a patient has received it before [13], or, lastly, to the route of administration itself, as subcutaneous tissue is rich in mast cells [13].

Nowadays, insulin-dependent patients are mainly treated with HRI or its analogs, and allergy is encountered in less than 1% of patients [1]. The latter molecules have been created by recombinant technologies, involving a modification in the amino-acid sequence of native insulin, so they might represent new epitopes for recognition by the immune system. However, it has been demonstrated that they could be more or less immunogenic than HRI, both in man [24-26] and animals [27, 28]. The short acting analogs lispro and aspart are modified in the dimerisation site, reducing their tendency to form hexamers by self-association, thus enhancing absorption from the subcutaneous tissue. This feature seems to largely explain their low immunogenicity, which is suggested to be correlated with their contact in the subcutaneous tissue and exposure time to cutaneous mast cells. Moreover, it is very likely that the main immunogenic epitopes remain unchanged in rapid analogs [2]. Consequently, they have been efficient in the treatment of insulin allergy, as described below.

Modes of administration also influence immunologic response. Firstly, intravenous injections are considered to be less immunogenic than subcutaneous injections. Besides, an old report demonstrated an increase in insulin antibody titer during intensive treatment with a pump containing highly purified porcine insulin [29]. At that time, some technical problems due to the delivery systems, such as polymer formation, aggregation or insulin precipitation were not resolved and could explain this complication. Today, continuous subcutaneous infusion of rapid analogs seems to be, inversely, an efficient desensitisation method for insulin allergy, as discussed below. Finally, intermittent insulin therapy seems to be a potent stimulus for allergenicity [13,15]. In the case of our patient, we may suppose that the first insulin administration by pump could have constituted a sensitisation, reactivated at the time of insulin injection introduction. However, it has been recently demonstrated with lispro that an intermittent treatment does not exaggerate the specific or cross-reactive antibody response [24].

Retarding agents, as protamine or zinc, added to enhance stability or alter duration of pharmacological effect can also be involved in allergic reaction after insulin injection preparation. Specific allergy to protamine itself has been widely described, isolated [30] or associated with insulin-molecule allergy [31-33]. A possible explanation for this

immunologic response after subcutaneous administration could be an interaction with insulin to become a complete or multivalent antigen [30].

In addition, there has been only one publication reporting two cases of insulin allergy due specifically to zinc, assessed by the absence of reaction after zinc-free insulin injection preparations [34]. Finally, insulin preparation conservatives, such as paraben, metacresol, phenol or isophane are sometimes responsible for allergic reactions [20].

## Diagnosis

Our patient presented with typical type I allergy, characterised by immediate local and general symptoms, associated with positive ID testing and the presence of specific anti-insulin IgE; however, insulin allergy can consist in a large spectrum of clinical manifestations [20].

## Symptoms

Diagnosis begins with a thorough clinical history and physical examination. The date of onset, nature, severity and frequency of symptoms, temporal association with allergen exposure, type of insulin used and existence of other allergies have to be precisely assessed.

Immediate type I reactions consist in local wheal-and-flare eruption at injection site, with induration, pruritus and burning sensation that appear a few minutes after the administration and last for one to two hours. This reaction is sometimes systemic, as in our patient, consisting in urticaria, angioedema or even anaphylactic shock, that appear straightaway or following the local manifestation. Type III reaction develops at the injection site from 2 to 6 hours after injection and last 12 to 48 hours. It is characterised by small subcutaneous, localised, tender and painful non-erythematous nodules with central hematomas at injection site [16]. Generalised symptoms can appear subsequently resulting in serum-sickness [15]. Delayed type IV cell mediated reactions develop 8-12 hours after administration, peak at 24 hours and last several days. Symptoms are always local, materialised by well defined, painful, itchy local mononuclear infiltration. Types III and IV reactions are sometimes associated with a type I immediate reaction [3, 18, 35] then called "biphasic" reactions.

## Skin testing and antibody measurement

To assess the diagnosis of type I IgE-mediated allergy, the traditional wheal-and-flare skin test remains the gold standard. Standardised extracts and methods should be used. These tests are performed during a short hospitalisation, under intensive medical surveillance, with an emergency kit at our disposal. The skin must be healthy, without any local treatment by steroids or immunosuppressive creams. Antihistaminic agents must be avoided for at least

3 days before testing. Reactions should be read 20 minutes after injection for immediate type allergy. They are considered to be positive if the reaction diameter is 3 mm wider than the one of the positive control. Appearance of systemic symptoms, as for our patient, validate the relevance of the test. Two types of skin tests may be performed. Skin prick tests (SPT), using undiluted commercial insulin preparations (100 U/ml), are less painful and induce less systemic reactions than ID testing. However, in one study, they were found to be insufficient for the diagnosis of insulin allergy because of their low sensitivity and false-negative reactions [36]. Intradermal reactions can be performed with the Novo<sup>®</sup> insulin allergy kit (NovoNordisk<sup>®</sup>), that simplifies the procedure, but that will no longer be available within a few months. Therefore, "manual" IDR should be performed, with a 0.02 ml injection of increasing dilutions of commercial preparations, ranging from a 1/100000 to a 1/10 dilution [20, 36]. Actually, most patients receiving insulin daily for a long time develop antibodies to it, and it has been estimated that 40% of patients without clinical allergy show positive immediate skin tests to the insulin being used for treatment [13]. With the use of highly purified preparations, this frequency would be closer to 15% [36]. Therefore, negative insulin cutaneous testing could help in excluding insulin allergy, but positive skin tests may also have no diagnostic relevance [23]. ID testing read at 6, 24 and 48 hours can be useful to establish the diagnosis of type III or type IV allergy [35].

Direct anti-insulin IgE evaluation by the CAP-system (Pharmacia Diagnostics<sup>®</sup>) helps reinforce the diagnosis. This is a valid technique that provides highly reliable quantitative results. However, it has been found that 44% of patients treated with human recombinant insulin without any clinical symptoms develop these antibodies [20]. This simple measurement is relevant for following the efficiency of desensitisation [20].

## Protamine allergy

We concluded that our patient was not allergic to protamine because, although he presented a positive IDR to protamine-sulphate, the specific IgE measurement was negative.

As for insulin itself, symptoms of protamine allergy are variable, from local immediate reactions to general manifestations, or exceptionally, delayed reactions [30-34]. It has been suggested that SPT should be achieved with a protamine-sulphate concentration of 10 mg/ml, and ID test with concentrations less than 10  $\sigma$ g/ml [30, 32]. Protamine-specific IgE measurements, when negative, are especially helpful to exclude this diagnosis since they are positive in approximately 50% of patients treated with protamine-containing insulin, without any clinical symptoms [31]. In any case, if skin tests or IgE are positive, patients should be informed of the high risk of severe reaction to intravenous injections [32]. The absence of reaction with protamine-free

insulin is another element in favor of protamine allergy [30].

## Other investigations

Some have proposed drug-induced lymphocyte stimulation tests [22,34,38], others have performed *in vitro* basophil histamine release to confirm the result of SPT [37] or a skin biopsy [3, 15]. However, these techniques are not recommended routinely. To note, hypereosinophilia is far from being specific of an allergic state.

## Treatment

Different treatments have been proposed in cases of established insulin allergy.

First of all, an emergent and absolute need of insulin in a diabetic patient who is known to be allergic to insulin, and who could not have been desensitised before, must require an intravenous administration.

In the absence of an emergency, absolute necessity of insulin therapy has to be firmly assessed. Of course, a type 1 diabetic patient undoubtedly needs this treatment. But, in type 2 patients, the possibility of treating with oral hypoglycemic agents associated with strict lifestyle intervention has to be considered first.

Local and mild symptoms can be dealt with by simple methods: dose division, variation of the injection site, antihistamines and local corticosteroids. Based on the knowledge that corticosteroids can prevent cellular lymphokine production, an association with local corticosteroid injection has been proposed for type III and type IV reactions, more or less successfully [4, 15, 16, 18]. This procedure failed in type I reaction [39]. Exceptionally, general corticosteroids can be provided [15, 16].

If these measures fail or if general serious and invalidating symptoms occur, other methods can be used to manage insulin allergy. First, one can propose the switch to a different insulin, preferentially to one with negative intra-dermal testing. In particular, rapid analogs have shown to be sometimes, but not always, efficient in this situation. Lispro and aspart present reduced antigenicity, supposedly due mainly to an increased clearance of monomeric analogs at injection sites and therefore reducing the exposition time to mast cells [2]. Several case-reports and a recent clinical trial indicate that lispro or aspart injections have been successfully used to manage insulin allergy (*tables I, II, IV*). However, as in our patient, allergy to these molecules exists as well (*table III*), frequently, but not always associated with regular insulin allergy [11]. Allergy to both HRI and analogs might be partly due to the existence of cross-reactivity between antibodies [24, 25, 27]. At any rate, it seems necessary to further evaluate their usefulness as a treatment of insulin allergy and to determine how their structure precisely affects the immune response.

Our patient presented positive local and general reaction after intradermal testing of the long acting analog glargine, therefore we decided not to use it as treatment. It has been shown that glargine injection did not elicit an increase of antibody titer compared with recombinant human insulin [26]. In the literature, three cases are reported concerning glargine and insulin allergy. The first one describes the case of a 45-year-old type 1 diabetic patient, allergic to animal and human recombinant insulins, but with a negative prick-test to glargine. The use of this insulin allowed tolerance induction to regular human insulin, although the mechanism involved remains unclear, maybe by anergic epitope spreading [43]. The second case describes a positive skin prick test to glargine in a patient allergic to all insulins, aspart excepted [10]. The third one concerns a 20-year-old diabetic woman, who presented delayed local manifestations after glargine injection, with negative IDR to all insulins tested, except for a weak response for glargine [12]. Consequently, we describe here the first case of allergy to all kinds of insulin commercially available in France, rapid and long acting analogs included. We did not test the new rapid analog glulisine and the new long acting analog detemir but, to our knowledge, no information is available in literature concerning their allergenicity, or their use in the treatment of insulin allergy.

Analogues are not necessarily an alternative in the management of insulin allergy. Therefore, desensitisation or tolerance induction should be attempted, when other techniques failed, if systemic reactions are severe and persistent or in case of positive skin test to all insulins, as for our patient. It has to be performed in a hospital setting and informed consent should be obtained. The mechanism by which desensitisation works is uncertain; it probably involves the depletion of mediators, as mast cells remain chronically degranulated in insulin infusion areas, the induction of blockade of IgG antibodies [44, 45], and the generation of suppressive T-cells [20].

The first possibility is classic progressive desensitisation, consisting in frequent subcutaneous injection of small increasing doses of insulin, in order to obtain low constant blood levels until reaching therapeutic levels. Several protocols are suggested: for example, Galloway proposed a protocol in which the dose range begins at 1 U of 0.005 U/ml of human regular insulin, and ends at 8 U of 50 U/ml with a total of 15 steps. The injections are given intradermally at 30-minute intervals. Whenever a reaction is noted, the protocol is restarted two steps lower than the one that caused the reaction. This method is generally efficient for type I allergy since 90% of patients with systemic insulin allergy can be successfully desensitised [44]. In case of failure, more prolonged protocols or repeated desensitisation can be proposed [31]. Type III or type IV allergies have been reported to be partially or totally refractory to this procedure [16-18]. Therefore, failure of desensitisation could indirectly indicate an immune complex disease, and lispro has been effi-

**Table I**

Cases of insulin allergy successfully treated by lispro injections.

| Reference         | Patient                           | Symptoms                                                             | Diagnostic tests                                                                                                                                                              | Treatment                                                                                  |
|-------------------|-----------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Kumar (2)         | F, 34-yr-old, type 2 diabetes.    | Local and general immediate reaction to HRI.                         | Specific IgE: positive<br>IDR HRI: positive<br>IDR lispro: positive but less intense                                                                                          | Failure of desensitisation with HRI.<br>Successful desensitisation with lispro injections. |
| Frigerio (17)     | F, 22-yr-old, type 1 diabetes.    | Immediate local and general reaction to crystalline insulin in CSII. | Specific IgE : negative<br>SPT/IDR AI, HRI: negative<br>SPT protamine : weakly positive<br>SPT/IDR other additives : negative<br>Presumably type III hypersensitivity         | Failure of desensitisation with HRI.<br>Successful treatment with lispro injections.       |
| Hermoso (40)      | Girl, 11-yr-old, type 1 diabetes. | Local immediate reaction to HRI.                                     | Specific IgE: positive.<br>SPT AI, HRI: positive<br>SPT protamine: positive                                                                                                   | Lispro injections: no reaction.                                                            |
| Lluch-Bernal (35) | F, 28-yr-old, type 1 diabetes.    | Local immediate and delayed reaction to HRI.                         | Specific IgE: negative<br>IDR HRI: biphasic reaction<br>IDR lispro: negative<br>IDR additives: negative<br>Biphasic hypersensitivity                                          | Lispro injections: no reaction.                                                            |
| Abraham (41)      | F, 41-yr-old, type 2 diabetes.    | Local and general manifestations to AI and HRI.                      | Insulin antibodies (?) : negative                                                                                                                                             | Lispro injections: no reaction.                                                            |
| Panczel (33)      | F, 54-yr-old, type 2 diabetes.    | Local immediate and delayed reaction with protamine-containing HRI.  | Specific IgE: negative<br>DR HRI: immediate positivity<br>IDR protamine: delayed positivity<br>IDR lispro: negative<br>Simultaneous hypersensitivity to insulin and protamine | Lispro injections: no reaction.                                                            |

F: Female; SPT: Skin Prick Test; IDR: Intradermal Reaction; AI: Animal Insulin; HRI: Human Recombinant Insulin.

**Table II**

Cases of insulin allergy successfully treated by aspart injections.

| Reference    | Patient                        | Symptoms                                            | Diagnostic tests                                                                                   | Treatment                       |
|--------------|--------------------------------|-----------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------|
| Airaghi (37) | M, 45-yr-old, type 2 diabetes. | Immediate and prolonged local reaction to HRI.      | Specific IgE: positive<br>SPT HRI: positive<br>SPT lispro: weakly positive<br>SPT aspart: negative | Aspart injections: no reaction. |
| Yasuda (38)  | F, 59-yr-old, type 2 diabetes. | Immediate local and general reaction to AI and HRI. | Specific IgE: positive<br>IDR AI, HRI: positive<br>IDR lispro: positive<br>IDR aspart: negative    | Aspart injections: no reaction. |

M: Male; F: Female; SPT: Skin Prick Test; IDR: Intradermal Reaction; AI: Animal Insulin; HRI: Human Recombinant Insulin.

cient in this particular situation, since the formation of immune complexes might be profoundly affected [17].

Today, continuous subcutaneous insulin infusion therapy (CSII) seems the ideal method for desensitisation. Indeed, continuous delivery avoids repeated injections administered during classic protocols. Moreover, it is gener-

ally well accepted by patients and results in improved metabolic control, delaying or preventing diabetic complications. The first report of management of insulin allergy using CSII containing HRI was published in 1988 [46], with only one single case described in the literature afterwards [1]. Nowadays, several reports have shown the effi-

**Table III**  
Cases of lispro and aspart sensitization.

| Reference            | Patient                        | Symptoms                                                      | Diagnostic tests                                                                                                                       | Treatment                                                       |
|----------------------|--------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Gonzalo (3)          | F, 32-yr-old, type 1 diabetes. | Local biphasic reaction to HRI.                               | Specific IgE: positive<br>SPT HRI: positive<br>SPT lispro: positive<br>SPT/IDR protamine: negative<br>SPT additives: negative          | Antihistamine provided partial relief of symptoms.              |
| Pratt (4)            | M, 79-yr-old, type 2 diabetes. | Delayed local reaction to AI, HRI and lispro.                 | Specific IgE: positive                                                                                                                 | Successful treatment with lispro CSII.                          |
| Naf (5)              | M, 43-yr-old, type 1 diabetes. | Immediate local and systemic reaction to HRI and lispro.      | Specific IgE: positive<br>SPT HRI: positive<br>SPT lispro: positive<br>SPT additives: negative                                         | Successful treatment with lispro CSII.                          |
| Barranco (6)         | M, 62-yr-old, type 2 diabetes. | Local and systemic immediate reaction after lispro injection. | Specific IgE: positive<br>SPT HRI: positive<br>SPT lispro: positive<br>SPT/IDR protamine: negative                                     | Partially efficient desensitisation with HRI standard protocol. |
| Fernandez (7)        | M, 60-yr-old, type 2 diabetes. | Local and general immediate reaction to HRI.                  | Specific IgE: positive<br>IDR AI, HRI: positive<br>IDR lispro: positive<br>SPT/IDR additives: negative                                 | ?                                                               |
| Takata (8)           | F, 53-yr-old, type 2 diabetes. | Immediate local reaction to HRI and rapid analogs.            | Specific IgE: positive<br>SPT AI, HRI: positive<br>SPT lispro: positive<br>SPT aspart: positive<br>SPT protamine: positive             | Oral hypoglycemic agents, intensified diet and exercise.        |
| Imiela (9)           | F, 55-yr-old, type 1 diabetes. | Immediate local and general reaction to HRI.                  | Specific IgE: positive<br>IDR AI, HRI: positive<br>IDR lispro: positive<br>IDR aspart: positive                                        | Successful tolerance induction with lispro CSII.                |
| Durand-Gonzalez (10) | M, 81-yr-old, type 2 diabetes. | Immediate local and general reaction with HRI.                | SPT AI, HRI: positive<br>SPT lispro: positive<br>SPT aspart: negative<br>Skin tests glargine: very positive<br>SPT additives: negative | Successful treatment with aspart CSII.                          |
| JiXiong (11)         | F, 48-yr-old, type 2 diabetes. | Immediate local and systemic reaction to aspart.              | SPT HRI: negative                                                                                                                      | HRI injections.                                                 |
| JiXiong (11)         | M, 52-yr-old, type 2 diabetes. | Immediate local reaction to aspart.                           | Specific IgE: positive<br>SPT HRI: negative<br>SPT aspart: positive                                                                    | HRI injections.                                                 |
| Vernassière (12)     | F, 50-yr-old, type 2 diabetes. | Immediate general reaction to lispro.                         | IDR AI, HRI: negative<br>IDR lispro: highly positive<br>IDR aspart: negative                                                           | ?                                                               |

M: Male; F: Female; SPT: Skin Prick Test; IDR: Intradermal Reaction; AI: Animal Insulin; HRI: Human Recombinant Insulin.

ciency of CSII containing insulin analogs, even in children (*table IV*). Indeed, this technique combines two important parameters in the induction of tolerance: small continuous administration and the use of potentially less immunogenic molecules. Therefore, we think that this is a first-rate treatment in the management of insulin allergy.

The assessment of real desensitisation should study negatiation of skin tests and decrease of IgE rate, the gold-standard being the possibility to re-introduce classic injections or boluses, even in the long term [2]. Concerning our patient, we cannot say that we achieved desensitisation, but rather tolerance induction. Indeed, although no clinical

**Table IV**

Cases of insulin allergy successfully treated by subcutaneous continuous infusion of insulin rapid analogs.

| Reference            | Patient                             | Symptoms                                                 | Diagnostic tests                                                                                                                                   | Treatment                                        |
|----------------------|-------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Eapen (39)           | Girl, 5-yr-old, type 1 diabetes.    | Immediate local and general reaction to HRI.             | SPT HRI: negative<br>IDR HRI: positive<br>SPT diluent: negative                                                                                    | Successful desensitisation with lispro CSII.     |
| Pratt (4)            | M, 79-yr-old, type 2 diabetes.      | Delayed local reaction to AI, HRI and lispro.            | Specific IgE: positive                                                                                                                             | Successful treatment with lispro CSII.           |
| Naf (5)              | M, 43-yr-old, type 1 diabetes.      | Immediate local and systemic reaction to HRI and lispro. | Specific IgE: positive<br>SPT HRI: positive<br>SPT lispro: positive<br>SPT additives: negative                                                     | Successful treatment with lispro CSII.           |
| Imiela (9)           | F, 55-yr-old, type 1 diabetes.      | Immediate local and general reaction to HRI.             | Specific IgE: positive<br>IDR AI, HRI: positive<br>IDR lispro: positive<br>IDR aspart: positive                                                    | Successful tolerance induction with lispro CSII. |
| Durand-Gonzalez (10) | M, 81-yr-old, type 2 diabetes.      | Immediate local and general reaction with HRI.           | SPT HRI, AI: positive<br>SPT lispro: positive<br>SPT aspart: negative<br>Skin tests glargine: very positive<br>SPT additives: negative             | Successful treatment with aspart CSII.           |
| Durand-Gonzalez (47) | F, 31-yr-old, gestational diabetes. | Immediate local reaction to HRI.                         | Specific IgE: positive<br>SPT HRI and AI: positive<br>SPT additives: negative                                                                      | Transient efficacy of lispro CSII. Caesarean.    |
| Sola-Gazagnes (48)   | F, 21-yr-old, type 1 diabetes.      | Local immediate reaction to HRI.                         | SPT ?: negative<br>IDR AI and HRI: positive<br>IDR protamine: positive<br>Analog not tested but immediate reaction after a single lispro injection | Successful treatment with lispro CSII.           |

M: Male; F: Female; SPT: Skin Prick Test; IDR: Intradermal Reaction; AI: Animal Insulin; HRI: Human Recombinant Insulin.

allergic reaction was noted, the IgE rate increased after six months of CSII treatment. Moreover, because of good glycaemic control with a constant basal rate, we did not take the risk of administering boluses, which we preferred to replace by repaglinide.

One case in the literature describes a dramatic life-threatening allergy to all available insulin preparations that failed three desensitisation attempts and thus required a pancreas transplantation [49].

### Protamine allergy

For protamine allergy alone, the easiest treatment is to use a protamine-free insulin preparation [30,32]. Another possibility is desensitisation with protamine-sulphate. If there is a dual sensitivity with insulin, one can try desensitisation with NPH or regular insulin, which are not always effective [31], or the switch to a rapid acting analog [33]. In any case, the patient has to be aware of the risk of systemic reaction in case of intravenous administration.

### Conclusion

Nowadays, insulin allergy remains a rare clinical situation, that might cause serious complications. Long and rapid acting analogs have sometimes been useful in these situations. For the first time, we described the case of a diabetic man allergic to all kinds of commercially available insulins. Therefore the only therapeutic choice was tolerance induction by means of subcutaneous insulin infusion of insulin lispro, which was successful. We believe that CSII of analogs has its place among first line treatments for management of insulin allergy.

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