

are well described. In Fradin et al.'s seminal work, a 6-mg/kg dose was administered for a period of 3–9 weeks to three patients suffering from CU. Despite its beneficial effects, CsA was discontinued in all the three patients because of its undesirable side-effects (1). Barlow et al. reported the beneficial effect of 3 mg/kg CsA for a period of 1 month to 10 patients (2). This group described a modified protocol administration of CsA over a 3-month period, with the initial dose at 3 mg/kg which was gradually reduced (3). One-third of the CU patients were cured, with another third experiencing reduced symptom severity. Notably, in one-third of the patients in remission, urticaria relapsed 3–6 months after CsA discontinuation (4). Furthermore, those who relapsed developed CsA unresponsiveness (escape of therapy) following a second course of CsA, even when higher doses of CsA were administered (E. Toubi, personal observation).

In the present study, the administration of CsA for prolonged periods to patients who experienced a severe urticarial relapse following the tapering of CsA has been studied.

Case I. A 54-year-old male patient in whom severe CU could be controlled only with repeated courses of prednisolone administered over 2 years, was studied. CsA, at 3 mg/kg/day induced a full remission, yet each tapering attempt below 2.0 mg/kg/day was followed by a severe relapse, necessitating the return to the starting dose. This regimen was continued for 8 months, without any side-effects, and ultimately resulted in full cure during a 1-year follow-up.

Case II. The patient was a 51-year-old steroid-dependent female with severe CU lasting 14 months. Gradual tapering of CsA dosage after 3 months resulted in a severe relapse. Despite diarrhea and mild peripheral neuropathy, she insisted on continuing a dosage of 2 mg/kg/day. After 6 months the CsA dose was gradually tapered and patient remained asymptomatic during a 5-month follow-up.

More prolonged therapy may reduce the relapse often accompanying the typically short cyclosporin-A (CsA) treatment regimens for chronic urticaria.

Case III. The patient was a 51-year-old female with severe CU lasting 3 years that was successfully treated with CsA. As previously described in the aforementioned cases, we were unable to taper the dose below 2 mg/kg/day because of subsequent relapse. Moreover, corticosteroids were contraindicated because of the patient's comorbidity to diabetes mellitus. Six months after the initiation of treatment (with six more months of treatment planned), the patient continues to be asymptomatic.

As most reports on CsA treatment suggest this regimen for a limited period of time, and urticaria relapses follow CsA discontinuation in many, caregivers are urged to consider a more prolonged therapy with CsA. The notion of allowing an extended treatment period is especially attractive in those patients in whom 'escape of therapy' may ensue with the discontinuation of CsA.

We propose that, as is customary in the management of autoimmune diseases, CsA should be considered as a possible treatment option early in the course of severe CU. When prolonged treatment with prednisolone is inadvisable, the use of CsA may have added value. Further experience with prolonged CsA treatment is needed in order to determine the extent to which this regimen might reduce the incidence of relapse upon CsA discontinuation and thus provide enhanced treatment efficacy.

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Systemic allergic reaction by a human insulin analog

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Key words: anaphylaxis; desensitization; human insulin; lispro; local reactions.

Human insulin varies from bovine and porcine insulin in three and one amino acids, respectively. Insulin lispro is a new rapid-acting analog of human insulin identical to the human species except for the location of two amino acids B28 (proline) and B29 (lysine). It is considered less immunogenic than human insulin itself.

A 62-year-old diabetic man with stable ischaemic heart, peripheral vascular disease, extrinsic asthma, and urticaria by pirazolones, had been treated for 10 years with oral hypoglycemic agents. Treatment with human insulin was required. He received daily doses of insulin lispro with protamine with good tolerance for the first 4 months. During the following 2 months, he occasionally developed self-limited local 10 mm immediate reactions. Due to a persistent bad metabolic control, insulin was increased. One week later, minutes after the subcutaneous injection of lispro (34 IU) he suffered a generalized urticaria with severe bronchospasm that required treatment with adrenalin. Insulin was discontinued.

Skin prick test (SPT) with regular and lispro insulin 100 IU/ml were positive. SPT (10 mg/ml) and intradermal tests (0.1 and 1 mcg/ml) to protamine were negative.

Specific IgE (s-IgE) to human insulin (CAP-Pharmacia, Uppsala, Sweden)TM measured 10.4 kU/l. S-IgE by enzyme-

Local reactions after a successful desensitization in an anaphylaxis by insulin lispro.

linked immunosorbent assay and DOT-blott to lispro, lispro with protamine and regular insulin was positive. A single 6-kDa allergen was detected by IgE-immunoblot. Both tests were performed in two control subjects, and one of them, an insulin-dependent diabetic male, resulted negative.

Insulin again became necessary and a desensitization protocol to regular human insulin was conducted. The initial dose of 0.001 IU was progressively increased to 5 IU in 3 days (9 IU cumulative dose) without pre treatment. The patient did not experience adverse reactions. He later received 8 IU t.i.d. of lispro insulin with good tolerance.

When lispro was increased to 15 IU t.i.d. he occasionally suffered local immediate reactions. As he received 34 IU, local reactions appeared daily and he developed hives two times in every place after injection of the insulin. Urticaria was resolved with cetirizine 10 mg and for the following 10 days no local reaction appeared.

Six months after the desensitization protocol was performed, a new allergologic study was performed. SPT to regular and lispro insulin remained positive and s-IgE to human insulin decreased to 6.04 kU/l. Local reactions were successfully avoided with daily cetirizine administration since then.

As human insulin is being used, severe allergic reactions are rare (1), with the analog lispro which is considered an alternative treatment for local reactions to human insulin (2). As its molecular form has a rapid subcutaneous absorption the reduced exposure time to cutaneous mast cells may decrease its allergenicity (3, 4). Yet, cross-reactivity between lispro and human insulin has been reported (3).

After the desensitization protocol, our patient remained asymptomatic for several weeks, being able to receive lispro to control the diabetes and in 6 months a marked decrease (60%) of sIgE insulin levels was observed. The insulin desensitization was a success. Although cutaneous reactions reappeared, as it has been already reported (5), the use of antihistamines was enough to continue treatment with insulin.

We present an IgE-mediated anaphylaxis by a human insulin analog in a patient who had only received insulin

lispro and had never interrupted it. A clinical cross-reactivity between human insulin and lispro, in our patient, was observed. A successful desensitization protocol was carried out. Although mild local reactions were resumed, it was successfully avoided with daily administration of antihistamines.

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Type-I hypersensitivity to ceftriaxone and cross-reactivity with cefalexin and ampicillin

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Key words: adverse reaction; ampicillin; cephalexin; ceftriaxone; hypersensitivity.

Besides penicillins, cephalosporins represent the most commonly

Anaphylactic shock to ceftriaxone.

prescribed beta-lactams, capable of inducing IgE-mediated reactions. Ceftriaxone is a third-generation cephalosporin used for treating serious infections. There are three documented reports of IgE-mediated reaction to ceftriaxone, two with selective immediate hypersensitivity to ceftriaxone (1, 2), and one with cross-reactivity between ceftriaxone and cefotaxime (3).

A 3-year-old girl who had an anaphylactic reaction within 10 min after i.v. administration of the second dose of ceftriaxone (750 mg) for urinary infection is reported here. Symptoms included generalized urticaria, angioedema, rhinitis, dyspnea, shortness of breath, wheezing, tachycardia and hypotension. After treatment with anti-shock therapy, her symptoms were considerably reduced within 1 h and completely resolved after 12 h. She had no previous history of drug allergy or atopy and no family history of allergic disease. Six months later, the child was referred to this department in order to study the drug reactions and to determine safe alternative drugs for the future.

The child underwent prick and intradermal skin tests with standard concentration of penicilloyl-polylysine (Torlak, Yugoslavia), minor determinant mixture, penicillin G, penicillin V, ampicillin, amoxicillin, cephalexin, cefaclor, cefotaxime and ceftazidime diluted in 0.9% sodium chloride and administered at increasing concentrations, as previously described (3). Tests were considered positive when wheals larger than 3 mm in diameter for prick tests or greater than 5 mm in diameter for intradermal tests appeared 20 min later.

Commercially available assays for specific IgE (UniCAP System; Pharmacia, Uppsala, Sweden) were performed for penicilloyl G and penicilloyl V. Levels of specific IgE >0.35 kU/l were considered positive.

When both *in vivo* and *in vitro* tests were negative, single-blind, placebo-controlled challenges with progressively increasing amounts (0.01, 0.1 and 1.0) of the respective therapeutic doses of drugs