

Brief communications

Cutaneous allergy to recombinant human type I IL-1 receptor (rhu IL-1RI)

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IL-1 is a cytokine that has been reported to be important in mediating a variety of inflammatory processes such as rhinitis¹ and rheumatoid arthritis.² The IL-1 receptor (IL-1R) exists in both membrane-bound and soluble forms, each with similar binding affinity for IL-1.³ Recombinant human (rhu) IL-1R in soluble form has the potential to suppress inflammatory processes by inactivating IL-1 and may therefore be a useful antiinflammatory therapeutic agent.

IgE-mediated hypersensitivity reactions have been described to occur in response to administration of other recombinant human proteins such as recombinant (rDNA) human insulin.⁴ It is speculated that this is due to alterations in tertiary protein structure because the primary amino acid sequence of rDNA insulin is identical to endogenously produced human insulin. Because IgE-mediated hypersensitivity reactions to one recombinant human protein have been described, it would not be surprising that other recombinant human proteins could also cause similar reactions.

We report positive skin test results with type I rhu IL-1R in a patient who had experienced large immediate reactions followed by delayed reactions. Results of ELISA for IgE against rhu IL-1RI, including inhibition, corroborated the presence of IgE antibody to rhu IL-1RI and the specificity of its binding.

CASE REPORT

A 26-year-old woman with severe rheumatoid arthritis received several weeks of injections of rhu IL-1RI. After receiving several injections, she noticed that she had erythema and pruritus at the injection site within 15 minutes. After it was initially recognized, the reaction occurred after every injection. There were no systemic symptoms.

She also reported that the day after an injection she experienced swelling, erythema, and pruritus at the injection site; these symptoms persisted for a day or two. She was skin tested with bacteriostatic water, histamine, and rhu IL-1RI several months after her last injection. At that time, blood was drawn, serum was separated from cells, and serum aliquots were stored at -20° C until ELISAs were performed.

Abbreviations used

rDNA:	Recombinant DNA
rhu IL-1R:	Recombinant human interleukin-1 receptor
rhu IL-1RI:	Type I recombinant human interleukin-1 receptor

METHODS

Skin tests were performed by using standard prick test and intracutaneous test methods. Skin tests were initially read at 20 minutes. Positive histamine and negative bacteriostatic water controls were also applied. Patients received 0.05 ml of 500 µg/ml rhu IL-1RI (25 µg) on one forearm and 0.05 ml of 2500 µg/ml rhu IL-1RI (125 µg) on the other forearm (Immunex Corp., Seattle, Wash.). These injections did not produce positive reactions in five healthy volunteers who had not received rhu IL-1RI.

IgE antibody against rhu IL-1RI was demonstrated by a double-antibody ELISA method.⁵ All incubations were performed at 37° C. Phosphate-buffered saline with 0.05% Tween-20 was used as the washing buffer between all steps of the assay. Immulon microELISA plates (Greiner and Sons, Nürtingen, W. Germany) were filled with 200 µl of appropriate reagent or serum dilution. The following were added sequentially: 100 µg/ml rhu IL-1RI (Immunex Corp.); serum dilutions; ϵ -chain-specific goat anti-human IgE (1:500; Sigma Chemical Co., St. Louis, Mo.); rabbit anti-goat-alkaline phosphatase-conjugated IgE (1:4000); p-nitrophenyl phosphate (Sigma Chemical Co.), 1 mg/ml in diethanolamine buffer (pH 9.8). Optical density was read at 405 nm in a Biotek Automatic Reader (Winooski, Vt.).

Inhibition assays were performed by incubating a 1:2 serum dilution with rhu IL-1RI or bovine insulin (Eli Lilly, Indianapolis, Ind.) at concentrations of 0, 10, 100, or 1000 µg/ml serum for 30 minutes at 37° C. Incubation with bovine insulin was used to evaluate nonspecific inhibition. The assay was performed in an identical fashion to that described above, except that the serum was preincubated with an inhibitor.

RESULTS

Skin test results are listed in Table I. The patient had negative reactions to bacteriostatic water and positive reactions to histamine. The patient had negative prick test responses to rhu IL-1RI at 25 µg and 125 µg. She also had a negative intracutaneous reaction to rhu IL-1RI at 25 µg but a positive reaction to 125 µg rhu IL-1RI. Five normal control subjects had no reaction to this dose. Reactions remained positive at 30 minutes, 24 hours, and 48 hours.

IgE antibody to rhu IL-1RI was detected in the patient's serum by our ELISA technique (Fig. 1, A); however, the result of Immunex Corporation's ELISA for IgE antibody

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TABLE 1. Skin test results at 30 minutes in a patient who had previously experienced immediate and delayed local reactions to rhu IL-1R

	Bacteriostatic water control	Histamine	rhu IL-1RI	
			25 μ g	125 μ g
Prick test	0	7 mm wheal 15 mm erythema	0	0
Intracutaneous test	0	9 mm wheal 16 mm erythema	0	9 mm wheal 20 mm erythema

to rhu IL-1R was negative. Our antibody activity was completely inhibited by prior incubation of the patient's serum with rhu IL-1RI (Fig. 1, B). Preincubation of patient's serum with bovine insulin produced a minimal degree of inhibition of IgE binding to rhu IL-1RI.

DISCUSSION

There are no previous reports of skin reactions to rhu IL-1RI. However, other recombinant human proteins such as rDNA insulin have been reported to cause hypersensitivity reactions, and thus the occurrence of a hypersensitivity reaction to rhu IL-1RI is not unexpected.

The patient in this report described both immediate and delayed pruritic erythematous reactions at the site of rhu IL-1RI injection. She demonstrated both immediate and delayed cutaneous reactions after a 0.05 ml intracutaneous injection of 2.5 mg/ml rhu IL-1RI (125 μ g). Also, IgE antibody against rhu IL-1RI was demonstrated by ELISA. Inhibition ELISA studies confirmed the specificity of the IgE antibody binding to rhu IL-1RI.

Technical differences in assay performance probably explain the disparate results between Immunex and Northwestern assays.

In summary, recombinant human proteins, such as rhu IL-1RI and rDNA human insulin, may induce IgE antibody and hypersensitivity reactions. As new recombinant human proteins are introduced, other IgE-mediated hypersensitivity reactions are likely to be described.

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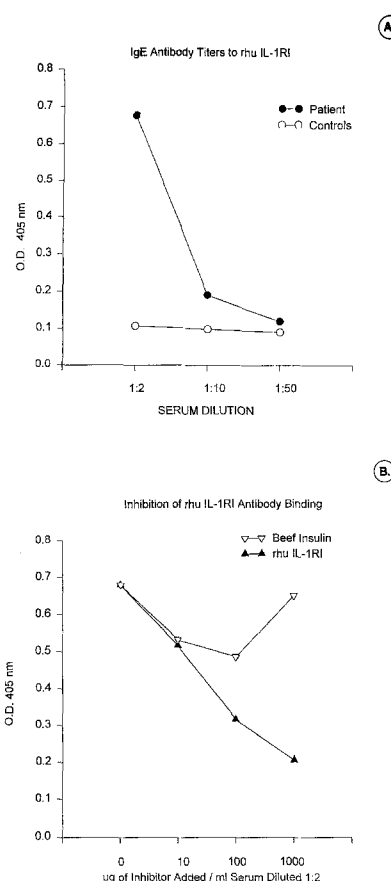


FIG. 1. A, IgE against rhu IL-1RI in serum of patient with local rhu IL-1RI reactions (filled circles) as determined by ELISA. Mean of three controls is also shown (open circles). B, IgE against rhu IL-1RI in serum of same patient with inhibition by rhu IL-1R (filled triangles) and bovine insulin (open triangles).

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