Treatment of Allergy to Heterologous Monocomponent Insulin With Human Semisynthetic Insulin
Long-Term Study

Bruno Bruni, MD
Patrizia Barolo, MD
Alberto Blatto, MD
Maurizio Carlini, MD
Silvia Gamba Ansaldi, MD
Giorgio Grassi, MD

Eight type II (non-insulin-dependent) diabetic subjects (7 women, 1 man, aged 42–61 yr), initially treated with oral hypoglycemic agents and intermittently treated with conventional insulins, were identified as developing allergic reactions to porcine and mixed-species monocomponent insulin. Allergy was systemic (urticaria and nonthrombocytopenic purpura) and local delayed in two subjects and local immediate or biphasic in six subjects. Lipoatrophy was present in two subjects. After treatment with human semisynthetic insulin (Monotard HM and Actrapid HM), systemic allergy disappeared. Local allergy disappeared in five subjects and was reduced in three subjects. No lipoatrophy occurred in new injection areas. The clinical results were accompanied by a significant decrease in serum insulin-specific IgE after 6, 12, 18, 24, 30, and 36 mo. Insulin-specific IgG showed an evident decrease in five of eight patients, but the difference in mean values was not significant after 6, 18, 24, 30, and 36 mo. With one exception, intradermal skin tests were positive to human, bovine, and porcine insulin before and after human insulin treatment. *Diabetes Care* 11:59–62, 1988

Since the introduction of highly purified [monocomponent (MC)] insulin preparations, true insulin allergy (systemic and local immediate or delayed reactions), as well as lipoatrophy, has been considered a rare phenomenon, although its frequency has not been established (1). Human insulin (semi- or biosynthetic) has been used to treat insulin allergy in recent years, because it is assumed that this insulin elicits the lowest possible immunogenic response (2,3). However, there have been only a few clinical studies of this treatment of MC animal insulin allergy. Some authors have reported striking improvement (4), but others have reported no alleviation at all or even deterioration (5,6). Moreover, a case of generalized allergic reaction to human semisynthetic insulin (Monotard HM) that did not recur when the patient was transferred to MC bovine insulin has recently been published (7). On the basis of 3 yr of personal experience, we report herein the successful treatment of insulin allergy and lipoatrophy with human semisynthetic insulin.

From the Karen Bruni Diabetes Center, Torino, Italy.
Address correspondence and reprint requests to Dr. B. Bruni, Centro di Diabetologia Karen Bruni, Ospedale Maria Vittoria, Corso Tassoni 44, 10144 Torino, Italy.

SUBJECTS AND METHODS

Of a population of 2150 diabetic patients undergoing treatment with porcine or mixed-species MC insulins (Lente MC, Rapitard MC, Monotard MC, or Actrapid MC; Novo, Bagsvaerd, Denmark) over the last 10 yr, we identified 8 subjects (7 women, 1 man, aged 42–61 yr) in whom allergy to insulin was documented in the hospital.

Demographic and clinical features of the patients are summarized in Table 1. All patients had been initially diagnosed as having type II (non-insulin-dependent) diabetes and were first treated with oral hypoglycemic agents and then transferred to insulin because of secondary drug failure. Six subjects had previously been treated with insulin of conventional purity, including NPH preparations. The patients were free from relevant clinical complications and were not receiving other drugs.

As indicated in Table 2, allergy was systemic in two subjects, with generalized urticaria and nonthrombo-

TABLE 1
Demographic and clinical features of 8 patients treated with monocomponent insulin

	Subjects				Insulin treatment		
	Sex	Age (yr)	BMI (kg/m²)	Diabetes duration (yr)	Insulin	Amount (U/day)	Duration (yr)
1	F	54	29	15	Rapitard MC	68	5*
2	M	52	23	10	Rapitard MC	34	3
3	F	55	24	12	Monotard MC	28	10*
4	F	61	24	13	Rapitard MC	72	2*
5	F	61	22	12	Lente MC	32	3*
6	F	49	21	10	Lente MC	36	4*
7	F	42	29	11	Lente MC, Actrapid MC	40	4
8	F	49	27	10	Lente MC, Actrapid MC	36	4*

BMI, body mass index.
*Previous intermittent insulin treatment with lente or NPH insulin.

cytopenic purpura noted at the volar surface of the arms, accompanied by local-delayed allergic reaction. In the other subjects, allergic reaction was immediate or biphasic, with or without lipoatrophy. Only one patient was atopic for certain. The allergic manifestations persisted for 3–8 mo and were not severe enough to require desensitization.

Intradermal skin tests were performed with a Novo kit containing saline, zinc acetate, and protamine sulfate; diluting media for Actrapid, Monotard, and neutral insulins; and human, bovine, and porcine insulins (Actrapid). After dilution at 1:10, 0.1 ml of each solution was injected intradermally into the forearm; protamine sulfate was also diluted 1:10. Reactions were graded per Phillip and Wedner (8): −, same as saline control; +, flare (with saline control negative); ++, wheal of 3–5 mm diameter or twice as large as control and flare; +++, large wheal of >5 mm diameter or 3 times as large as control and flare; and ++++, wheal with pseudopods.

Reactions were checked after 20, 30, 60, and 120 min and 24 h by the same observer. Maximum intensity usually occurred within the first 60 min. All patients had positive reactions to human, porcine, and bovine insulins (Table 2). A control group, 20 subjects with type II diabetes aged 20–60 yr, was treated with the same animal insulins at similar dosages without signs of allergy, and all control subjects were negative to all allergens in the kit.

Sera of allergic patients were analyzed for insulin-specific IgE antibodies [by Falholt's solid-phase radioimmunoassay, (9); considered significant at >0.7 U IgE/ml] and insulin-specific IgG antibodies [Christiansen's radioimmunoelectrophoretic method, (10); detection limit, 0.05 mU insulin bound/ml]. The Sepharose-insulin used for binding of IgE was of porcine origin. The assays were performed at the Novo Research Institute. In control patients, IgE levels were below the level considered significant and IgG levels were <0.05 mU/ml.

The patients were then transferred to human semisynthetic monocomponent insulin (Monotard HM and Actrapid HM, Novo), virtually at the same dosage as before, in two daily injections and usually in mixtures. The patients were examined at 3- to 6-mo intervals for up to 36 mo. Insulin-specific IgE and IgG were assayed. The mean values of IgE and IgG before and 6, 12, 18, 24, 30, and 36 mo after human insulin treatment were compared statistically with the Wilcoxon sign-rank test (11). Intradermal skin tests were repeated 36 mo after the injection of human insulin with the same procedures. One patient died of myocardial infarction after 24 mo.

RESULTS

As shown in Table 3, systemic allergic reaction disappeared immediately after the insulin preparation was changed. Local allergic reaction disappeared in five subjects and was reduced (occasional hardening and reddening with slight itching) in three subjects within the 1st mo after transfer to human insulin. Lipoatrophy did not appear in new injection areas. Nevertheless, intradermal skin tests were persistently positive to hu-

TABLE 2
Characteristics of insulin allergy in 8 patients

		Insulin allergy		Insulin skin tests		
Patient	Allergy history	Type	Duration (mo)	Human	Porcine	Bovine
1	Doubtful	Systemic and local delayed	4	+	++	+++
2		Systemic and local delayed	4	+++	+++	+++
3*		Local immediate and delayed	4	+	+++	+++
4	Penicillin	Local immediate and delayed	3	+++	+++	+++
5*		Local immediate and delayed	4	+++	++	+++
6	Doubtful	Local immediate and delayed		+	+++	+++
7		Local immediate	8	+	++	+++
8		Local immediate	6	++	+++	+++

Allergic reactions: +, flare; ++, wheal and flare; +++, large wheal and flare.
*Lipoatrophy present.

TABLE 3
Effect of human insulin treatment on allergic manifestations in 8 patients

		Insulin skin tests		
	Allergy	Human	Porcine	Bovine
1	Systemic disappeared	+++	++	+++
2	local reduced	+++	++	+++
3*	Systemic disappeared	++	+++	+++
4	local reduced	+++	+++	+++
5*	Disappeared	+++	++	+++
6	Disappeared	++	+++	+++
7	Disappeared	+++	+++	++
8	Disappeared			+

Allergic reactions as defined in Table 2.
*Lipoatrophy disappeared.

man, porcine, and bovine insulins and even intensified for human insulin in four subjects by the end of the study. Only one subject became negative to human and porcine insulins.

In parallel with clinical improvements, Table 4 shows a progressive decrease in insulin-specific IgE that is statistically significant after 6, 12, 18, 24, 30, and 36 mo of human insulin treatment. As summarized in Table 5, insulin-specific IgG showed an evident decrease during the same period in five patients. However, the difference of the mean values was not statistically significant after 6, 18, 24, 30, and 36 mo. No evident modifications in metabolic control or insulin requirement were noted in long-term treatment after the change of insulin preparations.

DISCUSSION

Our data indicate that insulin allergy (and lipoatrophy) resulting from sensitizing humoral antibodies during treatment with highly purified MC porcine and mixed-species preparations may be a common clinical problem. Our data point to a 0.3% incidence of systemic and local-immediate (or biphasic) reactions. These manifestations were noted in elderly subjects (7 women, 1 man) previously treated with oral hypoglycemic agents on the basis of a diagnosis of type II diabetes. Six of eight patients had a history of discontinuous treatment with insulin of conventional purity before secondary drug failure and the start of permanent MC insulin treatment. Although the latter is easily explained as the result of a booster effect on immunogenic response of intermittent insulin administration (12,13), the possible influence of initial therapy with oral agents in predisposing type II diabetic subjects to insulin allergy still has to be clarified. The increasing frequency of insulin treatment in response to secondary failure of oral agents in type II diabetic subjects (14) should be considered in light of these data.

Our study confirms the theoretical advantage of semisynthetic human insulin in the long-term treatment of immunologic reactions to heterologous insulin, even in highly purified preparations. The disappearance or reduction of systemic and local allergic reactions (and lipoatrophy) is accompanied by a significant reduction in high initial levels of serum insulin-specific IgE antibodies as previously reported (15,16). Given the small number of subjects, the failure of IgG levels to show corresponding changes over time in three of eight patients studied is not surprising. In fact, elevated IgG, particularly IgG4, and reduced IgE/IgG ratios are common during desensitization procedures (17), and treatment with less immunogenic human insulin might be comparable to a slow and spontaneous process of this type.

Note that positive clinical results in our patients were obtained despite positive intradermal skin tests to human insulin that persisted (except for 1 subject) or even increased after long-term treatment with human semisynthetic preparations. This is in keeping with our knowledge about the immunogenicity of homologous insulin (5) and the hypersensitivity manifested during epicutaneous testing for allergy (18,19).

TABLE 4
Serum insulin-specific IgE (U/ml) before and after human insulin treatment in 8 patients

		Months after treatment					
Patient	Basal	6	12	18	24	30	36
1	2.5	1.8	0.4	<0.2	0.3	0.2	0.3
2	2.5	1.4	1.2	1.2	1.8	1.2	1.2
3	2.0	1.2	1.2	1.2	2.5	2.5	1.1
4	19.0	11.0	6.8	6.4	6.8	3.7	3.2
5	6.0	2.6	2.4	1.0	2.6		
6	4.4	3.6	1.9	1.4	0.9	0.4	0.7
7	18.0	18.0	11.0	1.3	6.8	4.8	3.4
8	4.7	4.0	0.3	0.2	0.3	0.5	<0.2
Mean ± SE	7.38 ± 2.47	5.45 ± 2.11	3.15 ± 1.3	1.61 ± 0.70	2.75 ± 0.9	1.9 ± 0.6	1.57 ± 0.53
P		.005	.005	.005	.01	.01	.025

TABLE 5
Serum insulin-specific IgG (mU/ml) before and after human insulin treatment in 8 patients

		Months after treatment					
Patient	Basal	6	12	18	24	30	36
1	21.5	20.4	8.9	7.9	5.1	4.4	3.3
2	8.3	5.6	5.1	4.7	3.1	2.5	2.9
3	3.6	3.9	3.5	6.9	7.8	7.9	7.8
4	11.2	9.8	5.8	5.9	7.7	5.2	4.0
5	6.8	5.2	4.7	5.4	10.1		
6	6.1	6.2	3.8	3.9	4.4	2.7	1.6
7	3.0	1.7	1.7	6.2	0.7	0.5	0.8
8	2.6	2.6	2.6	2.7	2.4	3.0	2.6
Mean ± SE	7.88 ± 2.2	6.92 ± 2.11	4.51 ± 0.78*	5.45 ± 0.5	5.16 ± 1.1	3.74 ± 0.89	3.28 ± 0.85

*Significant change ($P < .01$) vs. previous measurement.

ACKNOWLEDGMENTS

We are grateful to Dr. Karen Falholt, Dr. Kirsten Vilhelmsen, and co-workers of the Novo Research Institute, Bagsvaerd, Denmark, for support and assistance.

REFERENCES

1. Vialettes B: L'allergie à l'insuline. *Diabete Metab* 12:169–72, 1986
2. Schernthaner G, Borkenstein M, Fink M, Mayr WR, Menzel J, Schober E: Immunogenicity of human insulin (Novo) or pork monocomponent insulin in HLA-DR-typed insulin-dependent diabetic individuals. *Diabetes Care* 6 (Suppl. 1):43–48, 1983
3. Fineberg SE, Galloway JA, Fineberg NS, Rathbun MJ, Hufferd S: Immunogenicity of recombinant DNA human insulin. *Diabetologia* 25:465–69, 1983
4. Falholt K, Hoskam JAM, Karamanos BG, Süsstrunk H, Viswanathan M, Heding LG: Insulin-specific IgE in serum of 67 diabetic patients against human insulin (Novo), porcine insulin, and bovine insulin: four case reports. *Diabetes Care* 6 (Suppl. 1):61–65, 1983
5. Altman JJ, Pehuet M, Slama G, Tchobrousky G: Three cases of allergic reaction to human insulin (Abstract). *Lancet* 2:524, 1983
6. Grammer LC, Roberts M, Patterson R: IgE and IgG antibodies against human (recombinant DNA) insulin in patients with systemic insulin allergy. *J Lab Clin Med* 105: 108–13, 1985
7. Silverstone P: Generalized allergic reaction to human insulin. *Br Med J* 292:933–34, 1986
8. Korenblat PEK, Wedner HJ: *Allergy. Theory and Practice.* Orlando, FL, Grune & Stratton, 1984, p. 112–13
9. Falholt K: Determination of insulin specific IgE in serum of diabetic patients by solid-phase radioimmunoassay. *Diabetologia* 22:254–57, 1982
10. Christiansen AH: Radioimmunoelectrophoresis in the determination of insulin binding to IgG: methodological studies. *Horm Metab Res* 5:147–54, 1973
11. Siegel S: *Nonparametric Statistics for Behavioral Sciences.* New York, McGraw-Hill, 1956, p. 75–83
12. Staupendahl D: Die Insulin-allergie als therapeutische Komplikation des Diabetes mellitus. *Allergologie* 6:68–73, 1983
13. Kahn CR, Rosenthal AS: Immunologic reactions to insulin: insulin allergy, insulin resistance, and the autoimmune insulin syndrome. *Diabetes Care* 2:283–95, 1979
14. Turner RC, McCarthy ST, Holman RR, Harris E: Beta-cell function improved by supplementing basal insulin secretion in mild diabetes. *Br Med J* 272:1252–54, 1976
15. Kumar D: Insulin allergy: differences in the binding of porcine, bovine, and human insulins with anti-insulin IgE. *Diabetes Care* 4:104–107, 1981
16. Reeves WG: Insulin antibody determination: theoretical and practical considerations. *Diabetologia* 24:339–403, 1983
17. Shakib F, Stanworth DR: Human IgG subclasses in health and disease. *Ric Clin Lab* 10:463–79, 1980
18. De Weck L: Nouvelles perspectives immunologiques de la désensibilisation spécifique. *Schweiz Med Wochenschr* 48:107–13, 1977
19. Small P, Lesman S: Human insulin allergy. *Ann Allergy* 53:39–40, 1984