

Clinical Communications

Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients

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Clinical Implication

- Etanercept and adalimumab are first line of treatment for inflammatory and autoimmune diseases, but local and systemic hypersensitivity reactions may preclude their use in sensitized patients. Desensitization through the subcutaneous route in patients with local and systemic hypersensitivity reactions provides an effective management option.

TO THE EDITOR:

Etanercept and adalimumab are first line therapies for the treatment of inflammatory and autoimmune diseases. However, local and systemic hypersensitivity reactions preclude their use in sensitized patients. Immune-mediated adverse reactions to etanercept and adalimumab reported in the literature include injection site reactions (ISRs) and immediate systemic hypersensitivity reactions such as pruritus, urticaria, angioedema, and anaphylaxis.¹⁻⁴ ISRs are thought to be T lymphocyte-mediated delayed type IV hypersensitivity reactions, which may preclude subsequent medication administration.^{5,6} Rapid drug desensitization protocols have been developed for the delivery of a variety of parenteral chemotherapeutic agents, including monoclonal antibodies, to sensitized patients.⁷ However, desensitization protocols have not been standardized for the treatment of ISRs and systemic reactions following subcutaneous medication injections. We have previously reported 2 patients who experienced an ISR to etanercept⁸ and adalimumab⁹ and were successfully desensitized to allow subsequent medication administration. On the basis of this experience, we standardized the protocols for subcutaneous administration in patients sensitized to etanercept and adalimumab. We report the successful desensitization of 7 patients who experienced adverse reactions to etanercept (6 ISRs and 1 systemic reaction), and of 5 patients with reactions to adalimumab (4 ISR and 1 urticaria).

PATIENTS WITH ISRS AND SYSTEMIC REACTIONS TO ETANERCEPT (TABLE I)

Patient 1: The patient presented with local pruritus, erythema, and edema (10 cm in diameter) followed by generalized urticaria and pruritus within 10 minutes of the 24th injection.

Patient 2: The patient developed local pruritus, erythema, and swelling (8 × 7 cm in diameter) 8 hours after the 4th injection.

Patient 3: The patient developed local pruritus, erythema, and swelling (10 × 5 cm in diameter) within 5 hours after the first dose and following 12 injections.

Patient 4: The patient developed local pruritus, erythema, and swelling (10 × 5 cm in diameter) within 24 hours after the 5th and 6th injections.

Patient 5: Five hours after the 5th injection the patient developed facial and lip swelling, diffuse urticaria, wheezing, dyspnea, nausea, vomiting, and a 30 mmHg fall in blood pressure, which required epinephrine (0.3 mg, IM), antihistamine (feniramine 45.5 mg, IV), and methylprednisolone (40 mg, IV). The symptoms relapsed 6 hours after discharge with generalized urticaria and/or angioedema.

Patient 6: The patient developed local erythema, pruritus, and edema (6 × 5 cm in diameter) within 24 hours of the 4th injection.

Patient 7: The patient developed local pruritus, erythema, and edema (5 × 5 cm in diameter) within 48 hours of the 4th injection, which progressed to 10 × 8 cm in diameter after the 6th and 7th injections.

PATIENTS WITH ISRS AND SYSTEMIC REACTIONS TO ADALIMUMAB (TABLE I)

Patient 1: The patient developed an ISR (4 × 4 cm in diameter) within 1 hour of the 11th injection with progressive swelling (10 × 8 cm in diameter) after the 11th and 12th injections.

Patient 2: The patient reported an ISR (4 × 4 cm in diameter) within 6 hours of the first injection, which recurred during the next 6 injections.

Patient 3: The patient reported an ISR (5 × 6 cm in diameter) within 2-3 hours of the first injection and recurred during next injections for a year.

Patient 4: The patient experienced an ISR (20 × 20 cm in diameter) within 2-3 hours of the 4th injection, which increased in size after each of the next 2 injections.

Patient 5: The patient experienced urticarial lesions on the right arm and face within 2-3 hours of the 3rd injection. This was a new course after a 9-month interruption of treatment. The patient had received a total of 42 lifetime injections.

SKIN TESTING AND DESENSITIZATION PROTOCOLS

The skin prick test with full strength of both drugs was read at 20 minutes. A wheal diameter of 3 mm or more, greater than the negative control, was considered positive. Concentrations of 1:1000 (0.05 mg/mL), 1:100 (0.5 mg/mL), and 1:10 (5 mg/mL) dilutions of etanercept and 1:1000 (0.04 mg/mL), 1:100 (0.4 mg/mL), and 1:10 (4 mg/mL) dilutions of adalimumab were used for intradermal testing (IDT). IDTs were read at 15 min, 24, 48, and 72 hours.

A desensitization protocol for 50 mg of weekly etanercept was generated as shown in Table II for cases 2 to 7. A modified 7-step rapid desensitization protocol for adalimumab was used for cases 2 to 5 (Table II). The desensitization protocols used for case 1 for etanercept and adalimumab, respectively, have been previously published.^{8,9} Aspirin 325 mg, montelukast 10 mg, benadryl 25 mg, and famotidine 40 mg were given 1 hour before desensitization.

Prick test results with etanercept (25 mg/1 mL for case 1 and 50 mg/1 mL for all others) were negative. Twelve healthy controls were prick and intradermal skin test negative to all dilutions with the exception of 2 controls who were positive at a

TABLE I. Demographic and clinical features of patients with hypersensitivity reactions to etanercept and adalimumab

Etanercept					Adalimumab				
Patients	Reaction type (size)	Injection at which the reaction occurred	Intradermal test (drug concentration, mg/mL)	Follow-up (mo)	Patients	Type of reaction (size)	Injection at which the reaction occurred	Prick/intradermal test (drug concentration, mg/mL)	Follow-up (mo)
1-28 y, M, AS	ISR (>10 cm), and urticaria	24th	+ (0.025)	27	1-26 y, F, RA	ISR (8 × 10 cm)	11th	-/+ (0.04)	33
2-33 y, M, RA	ISR (8 × 7 cm)	4th	+ (0.05)	23	2-55 y, F, RA	ISR (4 × 4 cm)	1st	+ (40)/+ (0.04)	22
3-58 y, F, PA	ISR (10 × 5 cm)	1st	+ (0.05)	21	3-36 y, F, AS	ISR (5 × 6 cm)	1st	+ (40)/+ (0.04)	9
4-48 y, F, RA	ISR (10 × 5 cm)	5th	+ (0.5)	18	4-48 y, F, AS	ISR (20 × 30 cm)	4th	+ (40)/+ (0.04)	5
5-35 y, M, AS	Late anaphylaxis (U/AO, wheezing vomiting, and hypotension)	5th	+ (0.5)	7	5-29 y, M, AS	Urticaria	1st of the 3rd course	+ (40)/+ (0.04)	6
6-32 y, F, AS	ISR (6 × 5 cm)	4th	+ (0.05)	15					
7-31 y, F, AS	ISR (8 × 10 cm)	4th	+ (0.5)	13					

ISR, injection site reaction; F, female; M, male; RA, rheumatoid arthritis; AS, ankylosing spondylitis; PA, psoriatic arthritis; O, edema; E, erythema; U/AO, urticarial/angioedema.

TABLE II. Subcutaneous desensitization protocols with etanercept and adalimumab

Etanercept					Adalimumab			
Day 1, 2	Dose (mg)	Dilution	Volume administered (mL)	Time (min)	Dose (mg)	Concentration (50 mg/mL)	Volume (mL)	Cumulative dose (mg)
0	0.50	1:100 (0.5 mg/mL)	1	0	0.5	0.5	1	0.5
30	1.0	1:10 (5 mg/mL)	0.2	30	0.75	5	0.15	1.25
60	2	1:10 (5 mg/mL)	0.4	60	1.25	5	0.25	2.50
90	4	1:10 (5 mg/mL)	0.8	90	2.50	5	0.50	5.0
120	8	1:1 (50 mg/mL)	0.16	120	5.0	50	0.10	10
150	9	1:1 (50 mg/mL)	0.18	150	10	50	0.20	20
Total dose	24.5			180	20	50	0.40	40 mg/mL
Day 3								
0	0.50	1:100 (0.5 mg/mL)	1.0					
30	1.00	1:10 (5 mg/mL)	0.2					
60	2.00	1:10 (5 mg/mL)	0.4					
90	4.00	1:10 (5 mg/mL)	0.8					
120	8.00	1:1 (50 mg/mL)	0.16					
150	16.00	1:1 (50 mg/mL)	0.32					
180	18.5	1:1 (50 mg/mL)	0.37					
Total dose	50							

1:10 dilution at 15 minutes. All readings at 24, 48, and 72 hours in patients and controls were negative. Patients 1, 4, 5, and 7 developed mild local erythema during desensitization. Once the desensitization was completed, all patients were maintained on weekly etanercept injections with cetirizine premedication. All patients have been able to continue with etanercept, with minor local erythema resolving within 1-2 hours (Figure 1, A, B).

The prick test result with 40 mg/mL of adalimumab was positive in 4 cases while positive by intradermal testing at a concentration of 1:1000 in all patients. Readings at 24, 48, and

72 hours were all negative in patients and 7 controls. To exclude hypersensitivity to polysorbate 80, an excipient in adalimumab, the patients were also tested with polysorbate 80. Full strength skin prick test and 1/10 dilution (4 mg/mL) IDT results were all negative. During subcutaneous desensitization with adalimumab, local erythema that was smaller than the initial reaction occurred in all patients at the injection site. All patients were successfully desensitized and maintained on weekly adalimumab for 3 months with premedication (Figure 2, A, B). Adalimumab injections were then spaced to every other week without further problems.

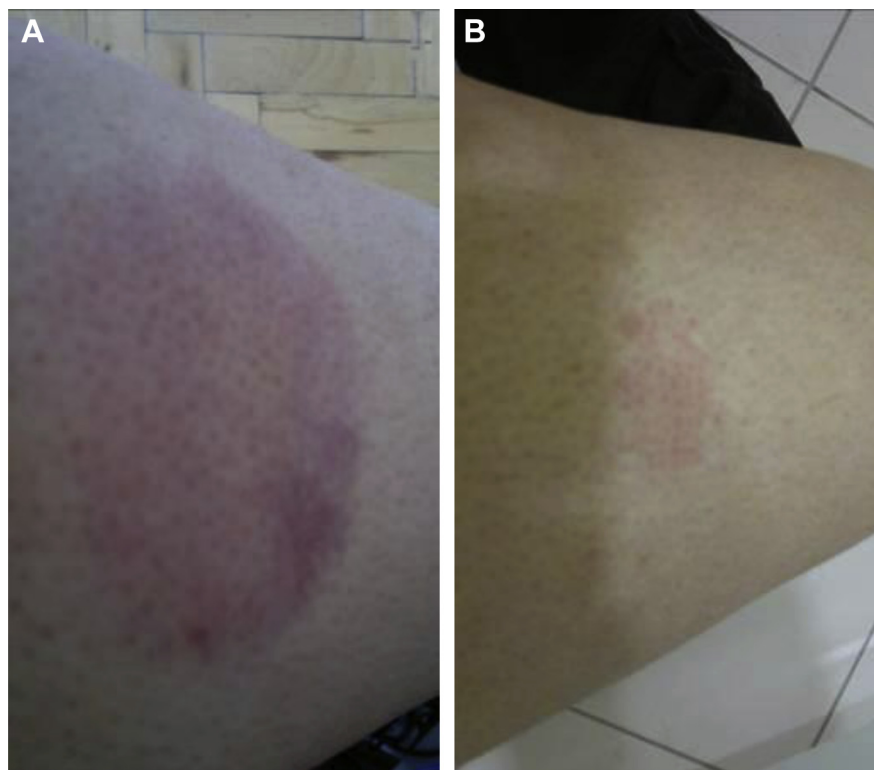


FIGURE 1. A, Typical etanercept ISR; B, Etanercept desensitization.

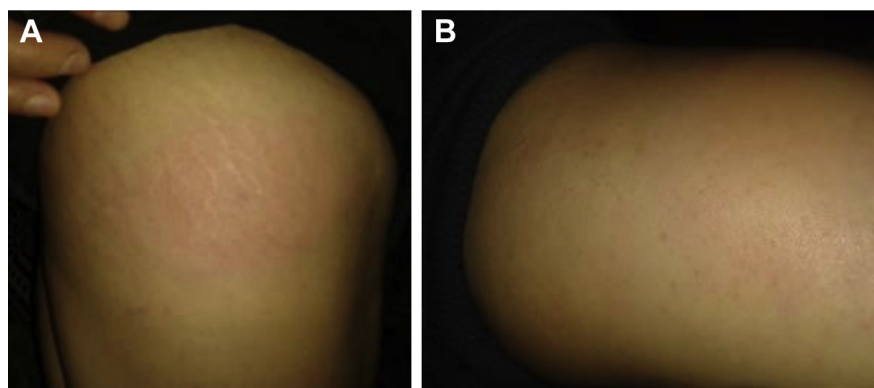


FIGURE 2. Typical adalimumab ISR (patient 4) pre- (A) and postdesensitization (B).

Rapid desensitization is a temporary phenomenon that appears to inhibit mast cell activation and mast cell-derived mediator release. Desensitization with an offending agent is a treatment option when there is no suitable alternative available.⁷ We chose to desensitize these patients because they had been treated with multiple anti-TNF agents and responded only to the one to which they presented a local and, in some cases, generalized hypersensitivity reaction.

Skin testing is a useful tool to provide evidence of an IgE mechanism and validate the need for a desensitization procedure for continued drug administration. Our patients demonstrated positive immediate skin test reactivity to their

offending drug, which suggests mast cell involvement and lends further support to using a desensitization approach to any further drug administration. Some authors have suggested that reactions to TNF inhibitors may also have a T-cell inflammatory component.^{5,6} Biopsies were not done for this study but are needed to further assess the mechanism of these reactions.

In conclusion, we present a group of patients with local and/or systemic hypersensitivity reactions to etanercept and adalimumab. They were skin test positive to these drugs and were successfully desensitized to allow continued administration with rapid subcutaneous protocols described.

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