

Injection-site reaction to etanercept: role of skin test in the diagnosis of such reaction and successful desensitization

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Anti-tumor necrosis factor (TNF) treatment, etanercept, infliximab, and adalimumab, is recommended for ankylosing spondylitis (AS) with persistent disease activity despite conventional treatments (1–3). Injection-site reactions are the most common adverse reaction to etanercept; however, the mechanism underlying these reactions remains unclear (4).

A 28-year-old man with AS was treated with Humira (40 mg/0.8 ml, Adalimumab) subcutaneous injections and developed local swelling, diffuse itching, and shortness of breath after 26th injections, prompting drug discontinuation. He received salicylazosulfapyridine 1500 mg/day and indomethacin 50 mg/day for 3 months without benefit and switched to Enbrel (25 mg etanercept) 25 mg subcutaneously twice weekly. He tolerated injections for 3 months and within 10–15 min of the 22nd injection

developed local pruritus, redness and swelling 10 cm in diameter at the site of injection, followed by whole body urticaria and pruritus. Etanercept was discontinued. Prick testing with etanercept (25 mg/1 ml), which was performed after 13 days of the reaction, was negative but intradermal testing with 1/100 dilution resulted in a 7 × 7 mm wheal along with 17 × 21 mm flare and no late reactions (histamine control was 6 × 6 mm along with 16 × 19 mm flare). Two healthy controls were negative on intradermal testing to this dilution. Because several reports indicate that patients with injection-site reaction can be controlled with antihistamines and do not need to stop the medication, we

then decided to challenge the patient and diluted the drug in sterile water (1 : 10) before injection. We injected subcutaneously 2.5 mg etanercept in the upper thigh and the patient reacted within 15 min with urticaria over the whole trunk without an injection site reaction. The reaction was controlled with antihistamine within 1 h. However, the lesions spread over the trunk and legs, persisted for a month and required cetirizine 10 mg daily. The patient denied having chronic urticaria in the past. The patient was re-evaluated 1 month later and presented positive skin testing and challenge. A desensitization protocol was generated as shown in Table 1. Oral aspirin 325 mg, mont-

Table 1 Subcutaneous desensitization protocol with etanercept

	Dose (mg)	Dilution	Volume administered (ml)
Day 1 (Tuesday)			
0 min	0.25	1 : 100	1
30 min	0.5	1 : 10	0.2
60 min	1	1 : 10	0.4
60 min	2	1 : 10	0.8
90 min	4	1 : 1	0.16
120 min	4.5	1 : 1	0.18
Total administered	12.25		
Day 2 (Wednesday)			
0 min	0.25	1 : 100	1
30 min	0.5	1 : 10	0.2
60 min	1	1 : 10	0.4
60 min	2	1 : 10	0.8
90 min	4	1 : 1	0.16
120 min	4.5	1 : 1	0.18
Total administered	12.25		
Day 3 (Thursday)			
0 min	0.5	1 : 10	0.2
45 min	1	1 : 10	0.4
45 min	2	1 : 10	0.8
60 min	4	1 : 1	0.16
90 min	8	1 : 1	0.32
150 min	8.75	1 : 1	0.35
Total administered	24.75		
Day 4 (Monday)			
	25	1 : 1	1

elukast 10 mg, benadryl 25 mg, and famotidine 40 mg were given 1 h prior to desensitization while he was on daily Zyrtec during desensitization. Once the desensitization was completed, the patient was maintained on twice weekly, Monday, Thursday, etanercept injection with Benadryl 25 mg 1 h prior to each injection and daily Zyrtec. He reports now mild redness limited to the legs and small local reactions, which are <3 cm in diameter at the injection site.

Most injection-site reactions are thought to be T-lymphocyte-mediated delayed-type hypersensitivity reactions (4); however, the underlying mechanism may be T_H2 -mediated, and continued treatment may not always be advisable (5). Skin tests have been found positive in some patients with injection-site reactions to etanercept (6). In our patient, intradermal testing with etanercept was positive at the immediate reading and the patient reacted to the challenge, supporting an immediate and possible IgE-mediated immune reaction. Therefore, the desensitization was aimed at protecting the patient while providing a dis-

ease-modifying medication to improve his quality of life. This is the first reported case of subcutaneous desensitization with etanercept.

Conflict of interest

The authors do not have any conflict of interest on this paper.

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