



Letter

Successful desensitization with anakinra in a case with immediate hypersensitivity reaction

Familial Mediterranean fever is an autosomal recessive inflammatory disease for which colchicine is the primary treatment.^{1–3} Nevertheless, in patients in whom colchicine treatment is not successful or leads to side effects, interleukin-1 antagonists are used as a novel treatment approach.³ Anakinra (Kineret; Sobi, Inc, Stockholm, Sweden) is a recombinant form of human interleukin-1 receptor antagonist. Although it is generally safe and tolerated well, the most important side effect is local skin reaction at the injection site.⁴ Systemic reactions to anakinra have been reported rarely.^{5,6} The present report describes the case of a 25-year-old woman who presented with urticaria and angioedema in reaction to anakinra treatment and underwent successful desensitization.

A 25-year-old woman was referred to our allergy clinic for anakinra-related urticaria and angioedema. She was diagnosed with familial Mediterranean fever in 2001 and had been on colchicine since then. Daily subcutaneous anakinra injections (100 mg/d) were commenced 6 months previously for nephropathy. After the 12th dose, an erythematous rash with edema occurred locally at the injection site 4 hours after injection, which was resolved by oral antihistamine. Therefore, an oral antihistaminic was given before each injection, which helped the patient tolerate the anakinra for further injections. However, because she was planning to become pregnant, anakinra was discontinued. Treatment with colchicine was continued. However, proteinuria increased, and anakinra was reintroduced and safely given for 19 subsequent doses. However, 4 hours after the 20th dose, urticaria and angioedema developed on the face and diffuse erythema developed over the entire body, which responded well to oral antihistamine. Then, the patient was referred to our clinic for evaluation of possible desensitization to anakinra.

Skin prick test results with undiluted drug were negative, whereas positivity was observed by intradermal tests at 1/10-fold dilution. The same concentration in the intradermal test yielded negative responses in 3 healthy controls. Therefore, the reaction of the patient was regarded as a type I hypersensitivity reaction to anakinra and desensitization was planned. A signed informed consent was obtained. Premedication with 10 mg of cetirizine orally 1 hour before desensitization was administered. Because no predetermined protocol for an immediate reaction to anakinra existed, a new desensitization protocol was established. For desensitization, 2 10-fold dilutions (1/10 and 1/100) were prepared. The initial concentration of anakinra selected for desensitization was 1/100 of the therapeutic dose (100 mg) because the patient's reaction history was mild (diffuse erythema, urticaria without dyspnea, and hypotension). Initially, the starting dose was given as a full volume of the 1/100 dilution (1 mg) and the doses were

planned to increase gradually every 60 minutes by subcutaneous route until a cumulative dose of 100 mg was reached. A reaction was noticed 15 minutes after administration of the third dose (5.5-mg injection, 10-mg cumulative dose). Diffuse erythema was noticed on the patient's face. Pheniramine maleate was administered and the symptoms successfully disappeared. Then, the protocol was revised; in this protocol, the 1/100 dilution was administered in 3 doses starting from 0.15 mg and the doses were gradually increased (0.45 and 0.9 mg; Table 1). This time, no reaction occurred and desensitization was completed successfully. On the second day, 50 mg of anakinra was administered at 1-hour intervals. On the third day, the total dose of 100 mg was administered. After desensitization, the intradermal test result was negative. During follow-up, the patient took a 15-day treatment holiday and then was re-desensitized with the same protocol. She successfully completed the protocol. The patient has continued self-administering anakinra every day, without any problems.

Currently, interleukin-1 antagonists are used as an alternative treatment for familial Mediterranean fever and rheumatoid arthritis.^{2,4,7} Although anakinra is usually well tolerated, some side effects, such as skin irritation at the injection site, have been reported in approximately 50% to 80% of patients.⁷ Reactions are usually mild in many patients.⁷ Delayed local reactions, such as erythema, itching, pain, and edema, occur rarely and are characterized by inflammatory lesions.⁴ Although a local injection site reaction was noticed in the present case for the initial doses of anakinra, for subsequent doses, a systemic reaction characterized by urticaria and angioedema beyond the injection area occurred. Therefore, one can presume that some local injection site reactions can precede systemic IgE-mediated reactions.

Systemic reactions to anakinra have been reported rarely.^{5,6} An anaphylactic reaction to anakinra was reported in a patient with rheumatoid arthritis.⁵ In a 7-year-old girl with juvenile idiopathic arthritis, an early severe systemic reaction characterized by urticaria and angioedema on the face and hands and a pruritic tongue were reported.⁶ In another patient with previous cutaneous reaction to anakinra, 3 hours after the administration of anakinra, itching and erythema on the face and abdominal region, shortness of breath, and abdominal pain developed. The skin prick test result with anakinra was positive in this case. The result are consistent with type I hypersensitivity reaction.⁷ The present patient had negative skin prick test reactions to anakinra, whereas a positive response was observed with an intradermal 1/10-fold dilution of anakinra, indicating IgE-mediated hypersensitivity to anakinra.

Desensitization is a safe way of reintroducing the culprit drug.^{8,9} Thus far, desensitization to anakinra has been reported only in a 34-year-old man who had a delayed local injection site reaction and was desensitized successfully.¹⁰ To our knowledge, the present case

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Table 1
Protocol for rapid subcutaneous desensitization to anakinra^a

Steps ^b	Dilution	Injected volume (mL)	Injected dose (mg)	Cumulative dose (mg)
1	1/100 ^c	0.1	0.15	0.15
		0.3	0.45	0.6
		0.6	0.9	1.5
2	1/10	0.3	3	4.5
3		0.55	5.5	10
4	1/1	0.125	12.5	22.5
5		0.25	25	47.5
6		0.525	52.5	100

^aPremedication with 10 mg of cetirizine 1 hour before desensitization was performed.

^bAt 1-hour intervals.

^cFor unsuccessful desensitization, this concentration was given at the full dose.

is the first report of an adult who was successfully desensitized after an IgE-mediated systemic reaction. Because no predetermined protocol for an immediate reaction to anakinra existed, a new desensitization protocol was established for this case and successful re-desensitization confirmed the safety of this protocol. This protocol was planned for a relatively mild reaction with only urticaria or angioedema and without dyspnea or hypotension. Therefore, treatment for more severe reactions should be started with lower concentrations than described in this protocol.

In summary, for the first time, a documented type I immediate reaction to anakinra was successfully desensitized with a new established protocol. This protocol can be recommended in patients with immediate reactions to anakinra.

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References

- [1] Meinzer U, Quartier P, Alexandra J, Hentgen V, Retornaz F, Kone-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. *Semin Arthritis Rheum*. 2011;41:265–271.
- [2] Grattagliano I, Bonfrate L, Ruggiero V, Scaccianoce G, Palasciano G, Portincasa P. Novel therapeutics for the treatment of familial Mediterranean fever: from colchicine to biologics. *Clin Pharmacol Ther*. 2014;95:89–97.
- [3] Alpay N, Şumnu A, Çalışkan Y, Yazıcı H, Türkmen A, Gül A. Efficacy of anakinra treatment in a patient with colchicine-resistant familial Mediterranean fever. *Rheumatol Int*. 2012;32:3277–3279.
- [4] Kaiser C, Knight A, Nordström D, et al. Injection-site reactions upon Kineret [anakinra] administration: experiences and explanations. *Rheumatol Int*. 2012;32:295–299.
- [5] Desai D, Goldbach-Mansky R, Milner JD, et al. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. *Ann Pharmacother*. 2009;43:967–972.
- [6] Anton J, Ros J, Ricart S, et al. Desensitization to anakinra in a systemic onset juvenile idiopathic arthritis patient [abstract P-079]. *Clin Exp Rheumatol*. 2005;23(suppl 37):24.
- [7] Vila AT, Puig L, Fernández-Figueras MT, Laiz AM, Vidal D, Alomar A. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol*. 2005;153:417–423.
- [8] Cernadas JR, Brockow K, Romano A, et al. European Network of Drug Allergy and the EAACI Interest Group on Drug Hypersensitivity. General considerations on rapid desensitization for drug hypersensitivity—a consensus statement. *Allergy*. 2010;65:1357–1366.
- [9] Scherer K, Brockow K, Aberer W, et al. ENDA, the European Network on Drug Allergy and the EAACI Drug Allergy Interest Group. Desensitization in delayed drug hypersensitivity reactions—an EAACI position paper of the Drug Allergy Interest Group. *Allergy*. 2013;68:844–852.
- [10] Verduga MZ, Tavera UMA, Pereira DA, et al. Desensitization to anakinra: case report [abstract P-947]. *J Allergy Clin Immunol*. 2014;133:AB274.