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# Successful rapid subcutaneous desensitization to anakinra in a case with a severe immediate-type hypersensitivity reaction

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## KEY WORDS

*drug allergy; immediate hypersensitivity; interleukin-1 receptor antagonist; anakinra; immunologic desensitization*

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## Summary

*Anakinra, one of the novel biological agents, is a recombinant human IL-1 receptor antagonist. It is preferred as an alternative drug for familial Mediterranean fever cases where colchicine is not sufficient or cannot be used due to its side effects. Like all other biologics, hypersensitivity reactions to anakinra are quite rare. This is the first case which was successfully desensitized with anakinra after a severe immediate-type hypersensitivity reaction.*

## Introduction

Anti-interleukin (IL)-1 agents are one of the biological agents that have increased use in recent years. The anti-IL-1 agent anakinra is a recombinant human IL-1 receptor antagonist that is used as a treatment option in various disorders (1). Despite a good safety profile, local reactions at the injection site are common (2-4). Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disease in which colchicine is used as the primary treatment (5-7). Anakinra is an alternative drug for FMF cases where colchicine is not sufficient, or colchicine cannot be used due to its side effects (7). Systemic reactions are quite rare with anti-IL-1 agents and they are generally well tolerated (8,9). We present a 38-year-old female who developed an immediate-type hypersensitivity reaction after the use of anakinra and then underwent successful desensitization.

## Case presentation

The patient was referred to our clinic by the Department of Rheumatology due to a history of anaphylaxis after the use of anakinra. Her prior medical history revealed that after the diagnosis of FMF a year before, she was prescribed with colchicine at first. However, she had developed nausea, vomiting, cough, dyspnea, wheezing, dysphagia, and fatigue within 30 minutes after ingestion of the first colchicine dose. She had rapid recovery within one hour of treatment, but at the emergency room she was not able to remember the names of the drugs taken. She retried colchicine on her own a week later, and presented to emergency room again with the same reactions. Anakinra treatment was started by the rheumatology department, due to the history of immediate-type hypersensitivity reaction with colchicine and newly diagnosed renal amyloidosis. She again developed vomiting and nausea, dyspnea,

**Table I** - Protocol for subcutaneous desensitization with anakinra<sup>1</sup>.

Steps <sup>2</sup>	Dilution	Volume (mL)	Injected dose (mg)	Cumulative dose (mg)
1	1/1000	0.1	0.015	0.015
2		0.3	0.045	0.06
3		0.6	0.09	0.15
4	1/100	0.1	0.15	0.3
5		0.3	0.45	0.75
6		0.6	0.9	1.65
7	1/10	0.3	3	4.65
8		0.6	6	10.65
9	1/1	0.1	10	20.65
10		0.25	25	45.65
11		0.55	55	100.65

<sup>1</sup>Premedication with 5 mg of desloratadine and methyl-prednisolone 40 mg was administered 30 minutes before the desensitization procedure.

<sup>2</sup>Administered at 30-minute intervals.

cough, wheezing, and dysphagia 5 minutes after the first dose of subcutaneous injection of anakinra (Kineret® 0.67 mL [100 mg]; Sobi Inc., Stockholm, Sweden). She was treated with methylprednisolone, pheniramine maleate and oxygen therapy. Her symptoms relieved within one hour.

The patient was referred to our clinic for drug allergy evaluation and desensitization. The results of skin prick and intradermal tests with the undiluted form of Kineret® were all negative. Desensitization with anakinra was planned due to nonexistence of an alternative drug. Although there was no doubt about the typical hypersensitivity reaction, a single blind placebo challenge was performed with physiological saline prior desensitization procedure, to rule out the possibility of a psychosomatic basis. No reaction was observed with the placebo challenge (3 different physiological saline doses of 0.1 cc, 0.5 cc, and 1 cc administered SC with 30 minute intervals). Premedication with desloratadine oral tablet and methylprednisolone 40 mg IV was administered one hour before the desensitization procedure. The initial concentration for the desensitization was 0.1 ml of a 1/1000 dilution of the therapeutic dose (100 mg = 0.67 ml). Cumulative dosing was achieved by SC administrations of increasing doses at 30-minute intervals (**table I**). The desensitization protocol was completed without any reaction. One week later, total injection dose was divided into two and administered SC into separate arms, as local erythema and edema (about 10 cm) developed at the injection site. The patient was able to use anakinra without premedication and without any problems after the desensitization procedure.

## Discussion

Interleukin-1 antagonists have been recently used, beyond rheumatoid arthritis, in different disorders, such as FMF (4,6). Anakinra is a safe drug that is generally well tolerated. Local reactions at the injection site are frequently reported, but systemic reactions are quite rare (4,8-10). As far as we know, this is the second case that developed a severe immediate-type hypersensitivity reaction and successfully desensitized with anakinra.

The role of an IgE-mediated mechanism in anaphylaxis is a controversial issue in the instance that a patient has never been exposed to a drug before. On the other hand, some studies show that previous contact with the causative drug is not an obligatory prerequisite for immune-mediated drug hypersensitivity, and cross-reactivity between the involved drug and unrecognized prior exposure to similar chemical structures cannot be ruled out (11). Our patient did not have a prior history of anakinra usage and her skin tests were negative. The timing and type of reaction strongly suggest a non-IgE-mediated immediate-type hypersensitivity mechanism to anakinra.

Desensitization is a safe method of re-administering a drug that causes immediate-type hypersensitivity reactions (12). Desensitization with anakinra has previously been reported in four separate case reports in the literature (10,13-15). Three of these cases were desensitized for a late-onset hypersensitivity reaction, and one case was desensitized for an immediate hypersensitivity reaction with anakinra (13-15). In the first reported case with an immediate-type hypersensitivity reaction (urticaria + angioedema) sensitization to anakinra was shown with skin tests, and the patient was successfully

desensitized (10). However, the reaction was thought to be a mild systemic reaction due to the presence of skin and mucosa findings only. Desensitization was started with 0.1 ml of a 1/100 dilution of anakinra, since starting with higher doses was recommended for cases with mild systemic reactions. Since the reaction intensity of our case was more severe, desensitization was started with more diluted doses and the protocol was completed without any reactions. In conclusion, this is the first case which was successfully desensitized with anakinra after a severe immediate-type hypersensitivity reaction to anakinra. Desensitization can be performed using this protocol in cases with a severe systemic reaction. Total daily dose may be divided into two and administered SC into separate arms, if local reactions develop during follow-up.

### Patient consent

Obtained.

### Conflict of interest

The authors declare that they have no conflict of interest.

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