Desensitization to Adalimumab: An Example of Repeated Desensitization to a Biological Agent

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Abstract Biological agents seem to have been more effective than classic immunosuppressive drugs; however, the adverse events including the hypersensitivity reactions are the main drawbacks of these drugs. We report a 35-year-old man who was treated with adalimumab for ankylosing spondylitis, had a local reaction on the injection site, and generalized itching with rash at the 62nd dose and repeated desensitizations to him with adalimumab. One month after the reaction, skin prick test was performed with a commercial preparation of adalimumab. The skin prick test result was determined positive comparing to positive and negative controls. Because of insufficient responses to other drugs, adalimumab desensitization was performed and the whole process was completed without any reaction. Six months later the patient gave up therapy because of a new reaction which was caused by a possible viral infection. Desensitization was repeated successfully 3 months later. Because there are few cases in the literature about adalimumab desensitization process, there is no standard desensitization protocol for the adalimumab allergy yet. Therefore, we suggest that our case report may contribute to the formation of a standardized desensitization protocol in adalimumab hypersensitivity.

Key Points
Adalimumab is an important biological agent in rheumatic diseases and its use has been increasing on daily practice. Although, adalimumab is generally well tolerated by the patients, some hypersensitivity reactions may be seen. If a type-I hypersensitivity reaction occurs and later is demonstrated with a positive skin test result, desensitization can be performed successfully. This case report may contribute to the formation of the standardized desensitization protocol in adalimumab hypersensitivity reactions.

Introduction
For numerous disorders, biological agents such as cytokines, antibodies, fusion proteins and soluble receptor constructs that affect the immune system have emerged as a more effective therapeutic approach than classic immunosuppressive drugs. Because their use has been increasing in daily practice, adverse reactions including hypersensitivity due to these drugs have also been increasing concurrently.

Adalimumab (Humira; Abbott Laboratories, USA) is a recombinant human high-affinity immunoglobulin G1 (IgG1) monoclonal antibody that inhibits tumor necrosis factor-α (TNFα) [1]. Adalimumab is approved for the treatment of severe chronic psoriasis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease and ankylosing spondylitis. Adalimumab is generally well tolerated by patients, and hypersensitivity reactions seem to be approximately 1% [2]. Urticaria, angioedema and other skin reactions to
adalimumab have been reported rarely [2–7]. Hitherto, there are few published case reports regarding adalimumab hypersensitivity and a successful desensitization protocol [2, 8]. Here we describe a case of a systemic hypersensitivity reaction to adalimumab and successful desensitization.

Case Report

A 35-year-old man presented at our clinic with edema on the injection site, generalized itching, and rash after subcutaneous adalimumab injection. He had been monitored by the Department of Physical Medicine and Rehabilitation for ankylosing spondylitis since the age of 26 years. He had shown a poor response to several treatments including sulfasalazine and methotrexate.

The patient was administered adalimumab 40 mg every other week. At dose 62, after 2 h of adalimumab subcutaneous injection, the patient developed an edema with erythema over a zone of 20 cm in diameter at the injection site, then generalized itching and rash occurred within a few minutes. He also had abdominal pain, malaise, and dizziness concurrently. The reaction peaked at 2 h and lasted 5 h. He was treated with intramuscular injections of methylprednisolone 80 mg and feniramin maleat 45.5 mg. Adalimumab therapy was subsequently stopped.

One month after the reaction, a skin prick test was performed with a commercial preparation of adalimumab (Humira 50 mg/mL, adalimumab 40 mg in distilled water 0.8 mL). Histamine and saline were used as positive and negative controls, respectively. We used an undiluted form of the drug for the prick test. This concentration was proved to be non-irritating in ten healthy control subjects [9]. The skin prick test resulted positive with a wheal of 4 × 5 mm and a flare of 30 × 30 mm for adalimumab (Fig. 1).

In view of the efficacy of adalimumab therapy and insufficient responses to other drugs, desensitization with adalimumab was performed (Table 1). Written consent was obtained from the patient and then the desensitization regimen started with an initial subcutaneous dose of 0.5 mg (1/100) that was progressively increased until a cumulative dose of 44.25 mg was attained (Table 1).

The intervals within the doses were 60 min. No reaction occurred until the total dose was reached. The entire desensitization took 6 h. After the desensitization process the patient continued to receive subcutaneous adalimumab every other week without any reaction for 6 months. But later, he had generalized itching and rash 2 h after an adalimumab injection. Because he had already had such an experience due to adalimumab, he stopped administering the injections without consulting the doctor and started antihistamine therapy on his own. Three months later his lumbar pain had gradually deteriorated and he applied to our clinic without any skin lesions.

When we questioned the previous reaction that caused him to stop the adalimumab therapy, it was learnt that the patient had had symptoms of common cold such as fatigue, mild fever, sore throat, and runny nose a few days prior to the last injection. Because of 3 months interruption, a new desensitization was planned with adalimumab.

| Order | Concentration | Volume (mL) | Current dose (mg) | Cumulative dose (mg) |
|-------|---------------|-------------|-------------------|---------------------|
| 1     | 1/100         | 1           | 0.5               | 0.5                 |
| 2     | 1/10          | 0.25        | 1.25              | 1.75                |
| 3     | 1/10          | 0.5         | 2.5               | 4.25                |
| 4     | 1/1           | 0.1         | 5                 | 9.25                |
| 5     | 1/1           | 0.2         | 10                | 19.25               |
| 6     | 1/1           | 0.5         | 25                | 44.25               |

Time intervals between the sequential doses were 60 min

* Each dose was made up to a final volume of 1 mL with sterile water

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Fig. 1 The positive skin prick test result of Adalimumab

Table 1 Subcutaneous desensitization protocol with adalimumab [2]
Desensitization process was performed successfully again; however, this time the initial dose of adalimumab was divided into two equal parts (2 x 0.25 mg).

Discussion and Conclusion

Adalimumab is designed to be as similar to human proteins as possible by the phage-display technique, hence it is thought to be less immunogenic than any other monoclonal antibody [10]. The immunologic reason for our patient’s complaints seems to originate from specific IgE. The types of symptoms, their occurrence within 2 h of administration, and the positive skin prick test at immediate reading confirm the presence of specific IgE regarding adalimumab. Desensitization may be a proper alternative method for the patient who presents with IgE-mediated hypersensitivity to biological agents.

After the desensitization process, the patient continued to receive adalimumab injections until a reaction showed up. Actually this reaction was thought to be related to a previous non-specific T-cell activation-like viral infection, not adalimumab use. T lymphocytes were increased and activated after the viral infection, and then caused a non-specific reaction to adalimumab. That means it is possible that the patient would have had the same reaction if he had used a different drug to adalimumab.

The reason for re-desensitization was not the reaction, but the patient’s 3 months interruption to treatment. Because of this reason, it was not necessary to perform skin tests again. However, the second desensitization process was started with a lower initial dose because of the intervening reaction.

This case is worth consideration because, to the best of our knowledge, this case is one of the rare cases of a type-1 hypersensitivity reaction to adalimumab with positive skin test followed by successful desensitization. Bavbek et al. [3] reported a successful desensitization in a patient in whom a large local reaction occurred due to the injection of adalimumab. However, in our case, desensitization was applied as a result of systemic reaction due to the adalimumab injection. Because of the small number of cases in the literature, there is no standard desensitization procedure for adalimumab allergy as yet. Therefore, we suggest that our case report may contribute to the formation of a standardized desensitization protocol in adalimumab allergy.

The use of anti-TNF therapies seems to be increasing, therefore clinicians need to be aware of potentially serious reactions to these treatments.

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Author contributions All authors contributed to the conception and design of the study, data generation, analysis and interpretation of the data and preparation or critical revision of the manuscript.

Conflict of interest Fevzi Demirel, Ozgur Kartal, Mustafa Gulec, Sait Yesillik, Abdullah Baysan, Kutay Tezel, Ugur Musabak and Osman Sener declare that they have no conflict of interest.

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