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CASE REPORT

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Management and Successful Desensitization in a Patient with Abatacept-Induced Anaphylaxis

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ABSTRACT

Abatacept is a fusion protein that blocks T cell activation. It is used in a variety of conditions including organ transplantation, immune deficiency, and autoimmune diseases. Even though abatacept-induced adverse events are observed, hypersensitivity reactions are rare. Desensitization protocols that can be implemented in the case of hypersensitivity reactions are present in the literature for many biological agents. However, a desensitization protocol for abatacept has not yet been established.

Our patient, who was started on one of the biological agents, abatacept, for rheumatoid arthritis due to insufficient response to disease-modifying antirheumatic drugs, developed immediate hypersensitivity reaction with the first dose. Since it was planned to continue the treatment, abatacept desensitization was performed. The rapid desensitization protocol performed with prior premedication was successful and the patient was able to receive subsequent doses of abatacept using the same protocol.

Keywords: Abatacept, anaphylaxis, desensitization

INTRODUCTION

Abatacept is a chimeric protein composed of the Fc region of immunoglobulin G1 (IgG1) fused to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It suppresses T cell activation and immune response by blocking T cell co-stimulation (1-4). It is used in the treatment of a variety of conditions including organ transplantation, immune deficiency, and autoimmune diseases (5,6). Abatacept may be preferred in patients with rheumatoid arthritis (RA) who fail to respond to disease-modifying antirheumatic drugs (DMARDs) and other biological agents (2-4). It has subcutaneous (SC) and intravenous (IV) forms.

Even though local injection site reactions with subcutaneous administration and infusion reactions with intravenous administration of biological agents are commonly encountered, hypersensitivity reactions (HSRs) are rare (7). Biological agent-induced HSRs are increasing along with the increased used of these medications. There are many HSRs due to various biological agents reported in the literature. Abatacept-induced neutrophilic dermatosis (Sweet's syndrome), atopic dermatitis exacerbations, lichenoid and psoriasiform reactions, and asthma attacks have been reported (8-13). However, abatacept-induced HSRs and other immune reactions are rarely observed (1,14).

Desensitization is a clinical procedure in which the mast cell response is attenuated by administering incremental doses of a drug causing an allergic reaction with certain time intervals. It induces a state of tolerance for the drug that triggers HSR. Desensitization is indicated when the drug causing a reaction has no alternative available or it is more effective than the alternatives.

There are many desensitization protocols used in immediate and delayed HSRs induced with various biological agents. However, a desensitization protocol for abatacept has not yet been established. Our case is the first to undergo abatacept desensitization.

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CASE REPORT

A 42-year-old female patient had been treated for rheumatoid arthritis and Sjögren's disease for 9 years. She had insufficient response to DMARDs including hydroxychloroquine, methotrexate, leflunomide and sulfasalazine as well as methylprednisolone. Therefore, she had been started on biological agents one year ago. Etanercept had to be discontinued for a large local reaction following the first dose and immediate HSR with the second dose. Three months after these reactions, she had been started on the interleukin-6 receptor inhibitor tocilizumab. This agent had to be discontinued because the patient experienced severe itching with the first dose, and itching, dyspnea, and hypotension 30 minutes after the second dose. Six months after these reactions, she had been started on the CTLA-4 inhibitor abatacept. Fifteen minutes after subcutaneous abatacept administration, she developed itching, flushing, coughing, dyspnea, dizziness, and hypotension. Considering these as anaphylaxis, intramuscular adrenalin, IV antihistamine agents and steroids, and salbutamol nebule were given. The signs and symptoms of the patient regressed within half an hour with this treatment.

Because the reaction developed right after SC abatacept administration and there was no other drug use on the same day, anaphylaxis was considered to be abatacept-induced. The patient had a prior history of immediate HSRs with other biological agents. Serum tryptase level ordered for investigating mast cell disorders was found to be within normal range (4.89 μg/L).

Because the rheumatology department planned to continue abatacept treatment, we planned to perform abatacept desensitization. Her symptoms did not resemble cytokine release syndrome, which usually presents with fever, chills, back pain, flushing, nausea, and vomiting. Skin tests were performed 6 weeks after the reaction for IgE-mediated immediate HSRs. Prick (1/1), intradermal (1/1000, 1/100, and 1/10) skin tests with abatacept were negative. The histamine reaction was positive, although not sufficiently as concomitant steroid use could not be ceased for the desired time. Rapid desensitization was planned because the patient experienced immediate hypersensitivity. There was no abatacept desensitization protocol in the literature. Therefore, we reviewed previous protocols with other biological agents and decided on a suitable one (15). The SC desensitization protocol modified for abatacept is given in Table I.

One hour before the desensitization procedure, premedication was performed with intravenous diphenhydramine 1 mg/kg, ranitidine 4 mg/kg, and prednisone 1 mg/kg. Then, the 8-step procedure was executed with 30-minute intervals. Abatacept 125 mg administration was completed in 4 hours, the target dose was achieved, and desensitization was successfully accomplished. No reaction was observed during or after the desensitization procedure.

The next dose of 125 mg weekly sc abatacept was administered using the same protocol. Considering the half-life of abatacept, the third dose was planned to be given with premedication, omitting the desensitization protocol. However, immediate HSR recurred. Therefore, weekly doses were administered using the same desensitization protocol later. The patient has been continued on abatacept treatment with desensitization for 6 months and is able to tolerate the treatment.

Table I: Subcutaneous desensitization protocol for abatacept (125 mg/ml, weekly injection).

Time (min)	Dilution (Concentration)	Volume (ml)	Dose (mg)	Cumulative dose (mg)
0	1:100 (1.25 mg/ml)	1.00	1.25	1.25
30	1:10 (12.5 mg/ml)	0.15	1.875	3.125
60	1:10 (12.5 mg/ml)	0.25	3.125	6.250
90	1:10 (12.5 mg/ml)	0.50	6.250	12.50
120	1:1 (125 mg/ml)	0.10	12.5	25
150	1:1 (125 mg/ml)	0.20	25	50
180	1:1 (125 mg/ml)	0.20	25	75
210	1:1 (125 mg/ml)	0.40	50	125

DISCUSSION

CTLA-4-immunoglobulin G1 (Abatacept) is a synthetic and humanized fusion protein produced in Chinese hamster ovarian cells using recombinant DNA technology (1). It blocks the interaction of CD28 on T-cells with antigen presenting cells by binding to the CD80 (B7-1) and CD86 (B7-2) on antigen presenting cells. Therefore, T-cell activation and consecutive steps of immune response are inhibited (1-4).

Fusion proteins produced with genetic engineering methods can cause HSRs (14-17). These reactions may be immunological (Type 1, 2, 3 or 4) or nonimmunological with multicomplex mechanisms. The mechanisms of type 1 (IgE/non-IgE mediated) and type 4 (T-cell mediated) that arise during treatment with fusion proteins are well defined. Types 2, 3 and certain type 4 immune reactions are of an autoimmune nature (1,18,19).

The molecular sizes and chemical characteristics of biological agents may play a role in adverse reactions. Infusion reactions and cytokine release syndromes are frequently encountered, yet immediate or delayed HSRs are less common. HSRs may develop with the first dose or later doses. They are usually mild but may rarely present as anaphylactic reactions (7).

The immunogenicity of abatacept therapy is minor (14-17). A study that performed risk analysis of the biological agents used in RA in terms of HSRs revealed that rituximab and infliximab therapies were highly associated with HSRs while this association was low with abatacept (14).

Desensitization is not performed in drug-induced autoimmune reactions (type 2), immune complex deposits (type 3) and severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (type 4). Reusing the agent causing the reaction is strongly prohibited in these clinical scenarios

There are guidelines for the general approach and desensitization protocols for drug-induced HSRs (20). Diagnostic skin tests and desensitization protocols are performed for type 1 and certain type 4 immune responses based on these guidelines (1,15,18-23). However, a desensitization protocol for abatacept has not yet been established.

Because our patient was not able to discontinue antirheumatic drugs and steroids for a long time, the histamine response was inadequately positive. Skin tests performed to identify IgE-mediated reactions were negative. Whether the reaction is early or delayed is the most important factor determining the desensitization protocol (20). In our patient, rapid desensitization was planned because she experienced immediate HSR (anaphylactic/anaphylactoid). This protocol enabled the patient to tolerate weekly doses of abatacept. Currently, the drug has been continued for 6 months with this protocol. Our protocol is considered to be safe and effective for abatacept desensitization.

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