Immediate Type I Hypersensitivity Response Implicated in Worsening Injection Site Reactions to Adalimumab

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Background: Tumor necrosis factor (TNF) inhibitors such as adalimumab, etanercept, and infliximab play an increasingly important role in the management of a variety of chronic inflammatory disorders. With their increasing use, a wide spectrum of dermatological adverse effects, including injection site reactions and the development of dermatitis, have been recognized. Previous studies have implicated the role of the delayed-type hypersensitivity reaction in mediation of injection site reactions to etanercept. To our knowledge, there have been no published studies on immunologic mechanism of injection site reactions to adalimumab to date.

Observations: We describe 2 patients with a history of worsening injection site reactions to adalimumab. Findings from skin testing in both patients were suggestive of an immediate type I hypersensitivity reaction to adalimumab. A histamine release assay performed on peripheral blood leukocytes from both patients demonstrated significant histamine release on exposure to adalimumab. Furthermore, passive transfer of serum from one of the allergic patients to basophils from a nonatopic, healthy donor sensitized those cells to release significant amounts of histamine with exposure to adalimumab.

Conclusion: This study demonstrates that an IgE-mediated immediate type I hypersensitivity reaction plays a role in the mediation of worsening injection site reactions in some patients receiving adalimumab.

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The advent of tumor necrosis factor (TNF) inhibitors has dramatically changed the therapeutic approach to an increasing number of immune-mediated inflammatory disorders including psoriasis and psoriatic arthritis,1 rheumatoid arthritis,2,4 juvenile idiopathic arthritis,3 ankylosing spondylitis,5,7 ulcerative colitis,8 and Crohn disease.9 Currently available anti-TNF agents include 1 soluble p75 TNF receptor (etanercept) and 2 monoclonal anti-TNF antibodies (infliximab and adalimumab). While generally well tolerated and safe, a variety of adverse effects including a wide spectrum of dermatological conditions are increasingly being recognized in the setting of TNF inhibitors.

In clinical trials, a variety of skin conditions have been reported, including cutaneous eruptions and injection site reactions (ISRs) during adalimumab therapy,5,10 urticarial reactions and stomatitis during infliximab therapy,11 and ISRs during etanercept therapy.3 Zeltser et al12 conducted a retrospective study of patients who experienced etanercept-induced ISRs by performing an immunohistological analysis of reaction sites in 3 patients with rheumatoid arthritis. The authors observed an inflammatory infiltrate composed largely of T cells bearing an activated cytotoxic phenotype (HLA-DR+/CD3+/CD4−/CD8+), CD14 monocytes, CD1Langerhan cells, eosinophils, and neutrophils. The authors speculated that their findings were most consistent with a T-cell–mediated delayed hypersensitivity reaction, mediated by CD8+ T cells.12 As with etanercept, patients receiving adalimumab therapy commonly experience ISRs. To our knowledge, however, no studies have been conducted to assess the immunologic mechanism of ISRs with adalimumab therapy to date. We describe 2 patients with prominent and worsening ISRs to adalimumab and present evidence demonstrating that immediate-type hypersensitivity reaction plays a role in the mediation of ISRs in both patients.
REPORT OF CASES

CASE 1

A 41-year-old Asian woman with a history of HLA-B27–positive spondyloarthropathy was treated with adalimumab, 40 mg subcutaneously injected every other week, for arthritis involving both knees and the left ankle. The patient’s arthritic symptoms improved considerably; however, after 5 injections she began to develop ISRs consisting of prominent edema, erythema, and pruritus at the injection sites on the abdomen and thighs. The initial reactions were localized to a small area within approximately 3 cm of injection site and appeared several hours after an injection, and subsequent ISRs developed more rapidly (within minutes) and involved an increasingly greater area. Edema and erythema around the injection site lasted 2 to 3 days after injection before gradual and complete resolution. After 2 months of therapy, the patient developed multiple pruritic erythematous scaly patches in a generalized distribution and discontinued the therapy. The dermatitis subsequently resolved with initiation of topical corticosteroids (clobetasol propionate, 0.05%, ointment applied to the body and hydrocortisone, 2.5%, cream applied to the face) and narrow-band UV-B therapy.

CASE 2

A 60-year-old white woman with a history of irritable bowel syndrome, psoriasis, and psoriatic arthritis, attended our dermatology clinic for treatment of persistent psoriasis and psoriatic arthritis. The patient was being treated with etanercept, 25 mg every week for 4 years, with incomplete clearance of psoriasis and persistent arthritic symptoms. The patient had been previously treated with methotrexate and phototherapy with limited success. Etanercept therapy was discontinued, and adalimumab therapy, 40 mg weekly for the first 4 weeks, was initiated. The patient initially experienced notable improvement of her arthritic symptoms and psoriasis but developed edema and erythema around the injection site within several hours after the second injection. Gradually, each subsequent injection of adalimumab resulted in a more prominent edema and erythema around the injection site and developed more rapidly. Each ISR lasted 2 to 3 days before gradual resolution. The patient subsequently experienced decreased efficacy of the drug in the treatment of psoriasis and psoriatic arthritis and discontinued the therapy.

METHODS

PIN-PRICK TESTING

Pin-prick testing was used to assess the presence of immediate-type hypersensitivity reaction to adalimumab in both patients using isotonic sodium chloride solution (normal saline), adalimumab vehicle (4.93 mg of sodium chloride, 0.69 mg of monobasic sodium phosphate dihydrate, 1.04 mg of citric acid monohydrate, 0.24 mg of sodium citrate, 1.22 mg of dibasic sodium phosphate dihydrate, 0.05% of sodium hydroxide, 0.8 mg of polysorbate 80, and water), and histamine (10 mg/mL in sterile normal saline) as controls. A drop of each solution was placed on patients’ forearm, and skin was lightly pricked with a 27-gauge needle. A reading was performed 15 minutes after the pin prick. In addition, 0.1 mL (40 mg/0.8 mL) of adalimumab, 0.1 mL of vehicle, and 0.1 mL of normal saline were injected intradermally in the attempt to reproduce ISRs in both patients. Similar testing was performed on 1 patient (patient 3), who had no history of ISR to adalimumab after 9 months of therapy.

BASOPHIL ISOLATION AND HISTAMINE RELEASE

Venous blood samples for basophil studies were collected into syringes containing 5mM EDTA from 2 patients with a history of ISRs to adalimumab, 1 patient (patient 3) with no history of ISRs to adalimumab, and 1 healthy, nonatopic control patient with no history of exposure to adalimumab. Mixed blood leukocytes were isolated by dextran sedimentation and then stimulated for histamine release with adalimumab (0.5-50 000 ng/mL) (Humira; Abbott Laboratories, Abbott Park, Illinois), human γ-globulin (50-50 000 µg/mL) (Sigma-Aldrich, St Louis, Missouri), polyclonal goat antihuman IgE (0.1 µg/mL), and N-formyl-methionine-leucine-phenylalanine (1µM) at 37°C for 45 minutes. Assays were performed in duplicate in standard buffers containing calcium as previously described.13 Histamine was quantified from supernatants using an automated fluorometric assay. Results are presented as the percentage of total histamine content minus the subject’s spontaneous histamine release.

BASOPHIL SENSITIZATION

In a separate experiment, basophils from the same nonatopic, healthy control patient were isolated by dextran sedimentation. Basophil surface IgE was stripped by incubating the cells with lactic acid (pH 3.9) in normal saline for 3.5 minutes at room temperature.14 Following lactic acid stripping, serum from patient 1 was incubated with cells from the nonatopic donor at 37°C for 60 minutes in buffers containing heparin and EDTA. Then the cells were stimulated for histamine release to adalimumab (500-50 000 ng/mL) as described in the previous subsection. As a control to confirm removal of surface-bound IgE, cells were stimulated for histamine release by polyclonal goat antihuman IgE (0.1 µg/mL) and showed a 59% decrease in response after stripping (14%) vs before stripping (34%), with subsequent recovery of response (42%) following incubation with serum from patient 1.

STATISTICAL ANALYSES

Quantitative data were analyzed for statistically significant differences between control and treatment groups using the GraphPad Instat Software Program (GraphPad Software, San Diego, California). Because multiple comparisons were examined, a 1-way analysis of variance was applied to the quantitative data. P < .05 was considered statistically significant.

RESULTS

Pin-prick testing resulted in the development of wheal and flare within 15 minutes at the adalimumab site in both patients with a history of ISRs to adalimumab (Figure 1 and Figure 2). A similar reaction was seen with histamine (positive control), and no reactions were seen with adalimumab vehicle or normal saline. No reaction was observed with adalimumab in patient 3 with no history of ISRs to the drug. Intradermal injection of adalimumab in patients 1 and 2 reproduced signs and
symptoms of ISRs in both patients, resulting in erythema and edema at the injection site (Figure 1 and Figure 2B). No notable reaction was seen at the injection sites of normal saline or vehicle control solutions. A skin biopsy at the adalimumab injection site 24 hours after injection in patient 1 revealed dermal edema with perivascular lymphocytic and eosinophilic infiltrates (Figure 3), which was consistent with an urticarial tissue reaction.

When peripheral blood leukocytes from both patients with history of ISRs and positive results of pin-prick testing with adalimumab were stimulated by adalimumab, significant in vitro histamine release was observed when compared with patient 3 (P < .001 for the 5000- and 50 000-ng/mL doses of adalimumab). No significant histamine release was observed when blood leukocytes from a healthy nonatopic adult volunteer with no history of exposure to adalimumab were stimulated by identical concentrations of adalimumab (Figure 4A). For a negative control, peripheral blood leukocytes from 3 patients and the control were stimulated with human γ-globulin at similar concentrations as used for adalimumab (data not shown), and none showed significant histamine release. As positive controls, peripheral blood leukocytes from each donor were also incubated with polyclonal goat antihuman IgE and N-formyl-methionine-leucine-phenylalanine and demonstrated in vitro histamine release to each stimulus (data not shown).

In the passive transfer experiment, basophils from the nonatopic, healthy donor were stripped with lactic acid to remove donor surface-bound IgE and sensitized with serum from patient 1. On stimulation with adalimumab, sensitized basophils released considerable amounts of histamine (Figure 4B), supporting the presence of adalimumab-specific IgE in the serum of patient 1. The same nonatopic donor was used as a control for both the basophil histamine release and basophil sensitization experiments.

**COMMENT**

The advent of anti-TNF agents in recent years has provided an important armamentarium in the treatment of...
various dermatologic, rheumatologic, and gastrointestinal conditions. Although generally well tolerated, increasing use of these medications in clinical practice has led to the recognition of a variety of dermatologic adverse effects. Considering the increasing use of anti-TNF agents in dermatologic and other inflammatory conditions, it is important to augment the body of knowledge about adverse reaction and to elucidate their dermatopathologic and immunologic features.

Injection site reactions are common with subcutaneously administered anti-TNF agents and occur at a frequency of approximately 37% with etanercept16 and 20% with adalimumab.17 Zeltser et al12 analyzed ISRs to etanercept and determined that the majority of the dermal infiltrate in these ISRs is composed of CD8+ T cells, indicating a cell-mediated Th1 reaction suggestive of a lymphocyte-mediated delayed-type hypersensitivity reaction. We present the first report, to our knowledge, demonstrating the role of immediate-type I hypersensitivity reaction in the development of ISRs in 2 patients receiving adalimumab.

Type I hypersensitivity reaction is a manifestation of acute allergic reaction resulting from the release of preformed chemokines, granule-associated mediators, membrane-derived lipids, and cytokines and when an allergen interacts with IgE that is bound to mast cells or basophils by the α-chain of the high-affinity IgE receptor (FcεRI-α). The complex of allergen, IgE, and FcεRI on the surface of the mast cell triggers a noncytotoxic, energy-dependent release of histamine and tryptase and the membrane-derived lipid mediators leukotrienes, prostaglandins, and platelet-activating factor.18 These mast-cell mediators have a critical role in urticarial-type reactions that has been observed in 2 of our patients with ISRs to adalimumab.

Patient 1 also developed multiple pruritic erythematous patches in a generalized distribution within 2 months of starting adalimumab therapy. Similar eruptions have been reported in other patients receiving anti-TNF therapy19-21; however, the pathophysiologic mechanisms of these eruptions remains to be elucidated.22 Patient 2 experienced decreased efficacy of adalimumab with continued use, and it is unclear if the adalimumab-specific IgE antibodies play a role in neutralizing the therapeutic effect of the drug.

In clinical trials with adalimumab, approximately 1% of patients experienced allergic reactions such as allergic cutaneous eruptions, anaphylactoid reaction, fixed drug reaction, nonspecified drug reaction, and urticaria.23 In addition, anaphylaxis and angioneurotic edema have been reported rarely in postmarketing experience with adalimumab.24 Our data suggest that some worsening ISRs to adalimumab are also allergic in nature and that further studies with a larger series of patients are warranted to determine whether type I hypersensitivity response is seen universally in patients with worsening ISRs to adalimumab.

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Author Contributions: Drs Paltiel and Gaspari had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Gaspari. Acquisition of data: Paltiel, Gober, Deng, Alexeeva, Saini, and Gaspari. Analysis and interpretation of data: Paltiel, Gober, Deng, Mikdashi, Alexeeva, Saini, and Gaspari. Drafting of the manuscript: Paltiel, Gober, Deng, Mikdashi, Alexeeva, Saini, and Gaspari. Critical revision of the manuscript for important intellectual content: Paltiel, Gober, Saini, and Gaspari. Statistical analysis: Gaspari. Administrative, technical, and material support: Paltiel, Gober, Deng, Mikdashi, Alexeeva, and Saini. Study supervision: Gaspari.

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REFERENCES