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Anaphylactic Reaction to Anakinra in a Rheumatoid Arthritis Patient Intolerant to Multiple Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs

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Abstract

OBJECTIVE—To report a case of probable anaphylaxis due to anakinra in a patient with rheumatoid arthritis and multiple drug allergies.

CASE SUMMARY—A 46-year-old Indian female with rheumatoid arthritis demonstrated distinct adverse reactions to all commercially available anti-tumor necrosis factor therapies, sulfasalazine, and hydroxychloroquine. Over a 4-year period her disease remained active during therapy with methotrexate and prednisone. Biologics were added sequentially, with development of intolerable reactions, first to infliximab (urticarial rash, infusion reactions) after 3 doses, and then to etanercept (autoantibodies, worsening Raynaud's phenomenon, digital microinfarcts) after 1 year. Following 2 months of daily injections of anakinra, she experienced an immediate immunoglobulin E-mediated anaphylactic reaction within 20 minutes of an injection, as evidenced by positive testing to both anakinra and histamine with the skin prick method. The patient subsequently started adalimumab therapy, which was discontinued after the fourth dose due to the development of generalized hives.

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DISCUSSION—The Naranjo probability scale demonstrated a probable relationship between anaphylaxis and anakinra in this patient. Although cases of anakinra-related hypersensitivity have been reported in patients in which therapy was interrupted and then reintroduced, to our knowledge, this is the first report of anaphylaxis with continuous therapy.

CONCLUSIONS—This unusual case of a patient with multiple drug allergies presents a difficult clinical scenario, which was unsuccessfully managed with multiple biologic therapies on a trial-and-error basis. In the future, pharmacogenetics may help to better identify individuals at risk for multiple drug reactions and preclude unnecessary exposure to potentially harmful therapeutic options in similar patients.

Keywords

adverse drug reactions; anakinra; anaphylactic reaction; anti-rheumatic drugs; biological therapy; rheumatoid arthritis

Tumor necrosis factor- α (TNF- α) and interleukin 1 (IL-1) are 2 major proinflammatory cytokines that have pathologic roles in rheumatoid arthritis (RA). The management of RA has evolved from the use of nonspecific disease-modifying antirheumatic drugs (DMARDs) such as methotrexate to targeting specific cytokines with biologics such as TNF inhibitors (eg, etanercept, infliximab, adalimumab) and IL-1 receptor antagonists (eg, anakinra). A variety of adverse effects has been reported with each of these drugs, ranging from minor local injection site reactions to severe life-threatening anaphylaxis.¹ We describe a case of anaphylaxis following 2 months of uninterrupted anakinra therapy in a patient with RA who demonstrated allergic manifestations to all commercially available anti-TNF therapies, sulfasalazine, and hydroxychloroquine. Although cases of anakinra-related hypersensitivity have been reported in patients in whom therapy was interrupted and then reintroduced,^{2,3} to our knowledge, this is the first report of anaphylaxis with continuous therapy.

Case Report

A 46-year-old Indian woman with a 16-year history of RA had poorly controlled disease despite treatment with DMARDs including methotrexate, hydroxychloroquine, and sulfasalazine. She had a history of recurrent eczematous dermatitis and lichen simplex chronicus. She denied a personal or family history of asthma, hay fever, or antecubital and popliteal dermatitis. Human leukocyte antigen (HLA) typing was significant for HLA-A*24 and B*1502. Outpatient medications included methotrexate 25 mg/wk, folic acid 1 mg/day, prednisone 5 mg/day, clopidogrel 75 mg/day, aspirin 325 mg/day, alendronate 70 mg/wk, calcium carbonate 1250 mg twice daily, multiple vitamin daily, extended-release nifedipine 30 mg/day, naproxen 500 mg twice daily, and ferrous sulfate 325 mg/day. She denied the recent use of over-the-counter medications or dietary supplements. Her height and weight were 157 cm and 60 kg, respectively, and her serum creatinine level was stable at 0.9 mg/dL.

Because of continued active disease, as well as a history of allergic reactions to hydroxychloroquine and sulfasalazine, additional therapy with a number of biologic agents was tried concurrently with methotrexate and prednisone. Beginning with intravenous infliximab 3 mg/kg monthly, she began to develop a progressively worsening pruritic, urticarial rash that would occur within 30 minutes of the infusion and last for approximately 1 day. Although intravenous diphenhydramine 50 mg initially controlled these symptoms, infliximab was discontinued after only 3 doses when she experienced an episode of orthostatic hypotension, tachycardia, chills, and low-grade fever. Therapy was switched to etanercept, which the patient tolerated for approximately 1 year. However, this medication was ineffective and was subsequently discontinued because of development of antinuclear antibodies (ANA) and high levels of double-stranded DNA (dsDNA) titer antibodies (>200 IU/mL), worsening

Raynaud's phenomenon, and digital microinfarcts (Figure 1). With cessation of etanercept, and initiation of warfarin, vasodilator therapy with nifedipine, and a tapering regimen of prednisone, these symptoms resolved.

After withdrawal of etanercept for approximately 5 weeks (>6 half-lives), the patient was started on daily anakinra 100 mg injections. Although she experienced moderate injection site reactions from the first dose, which gradually progressed into episodic pruritus and hives, she was able to tolerate the drug for 2 months and showed improvement in clinical symptoms. A component of the needle cover of prefilled anakinra syringes contains a latex derivative, but the patient had no known history of latex allergy. After 2 months, her allergic symptoms worsened so that, within 20 minutes of an anakinra injection, she abruptly developed perioral and facial swelling with flushing, shortness of breath, dizziness, and generalized urticaria without any other identifiable etiologies. Although her neutrophil count within 2 weeks prior to this event was normal, the eosinophil count was elevated, suggesting a possible allergic versus infectious etiology. Likewise, her symptoms responded to intravenous hydration and treatment with epinephrine, diphenhydramine, and methylprednisolone. There were no abnormal laboratory findings, including negative ANA and dsDNA titers.

Allergy testing with the skin prick method was performed, using anakinra, infliximab, etanercept, and adalimumab (anticipating potential future use) with histamine and glycerin as the positive and negative controls, respectively. The concentration of each drug used for the skin prick test was identical to the concentration used for drug administration, as this most closely reflected the actual dosing of the drug that elicited the systemic reaction, without the need for subcutaneous administration. Therefore, serial dilutions of the administered concentration were not performed. The patient reacted to anakinra with a 9-mm diameter wheal and flare, compared with 7 mm for histamine, and had no response to infliximab, etanercept, adalimumab, and control. These results are consistent with a type 1 hypersensitivity immunoglobulin (Ig) E-mediated reaction (Figure 2).

The patient was started on adalimumab 40 mg subcutaneously every other week, following a negative skin test. While the first dose did not elicit any adverse symptoms, the second, third, and fourth injections resulted in localized site reactions, progressing from pruritus to a wheal with subsequent development of generalized hives. She denied chest pain, fever, or shortness of breath. The reaction gradually subsided after discontinuation of adalimumab, treatment with diphenhydramine, and increased prednisone dosing.

Discussion

Our patient experienced an anaphylactic reaction to anakinra and demonstrated unique allergic reactions to all 3 commercially available anti-TNF agents, as well as sulfasalazine and hydroxychloroquine. As observed in our patient, the most common adverse effects associated with infliximab are infusion-related reactions, typically occurring within 1–2 hours of administration.⁴ However, a delayed reaction may occur from 1 to 14 days following an infusion of infliximab.⁵ Infusion reactions have been reported in up to 20% of patients, compared with a 10% incidence with placebo.^{4,5} Symptoms may include fever, chills, chest pain, hypotension, hypertension, dyspnea, pruritus, urticaria, and/or cardiopulmonary reactions, with less than 1% of patients experiencing anaphylaxis, seizures, or erythematous rash.¹ Although rapid onset of symptoms after starting infliximab infusions suggests an IgE-mediated type 1 hypersensitivity reaction,^{6,7} one study reported that infusion reactions are not IgE-mediated.⁵ To minimize infusion-related adverse events, infliximab should be administered over more than 2 hours. If infusion reactions occur, symptoms may improve after slowing or discontinuing the infusion. Subsequent reinstitution of therapy at a lower infusion rate and/or premedication with antihistamines, acetaminophen, and/or corticosteroids may be

considered. Since these interventions were unsuccessful in our patient, infliximab was discontinued and an alternative anti-TNF therapy was considered.

When we substituted etanercept for infliximab in our patient, her ANA and anti-dsDNA titers increased and she developed worsening Raynaud's phenomenon and digital microinfarcts. The appearance of new-onset ANA and ds-DNA antibodies occur in approximately 11% and 15% of etanercept-treated patients compared with 5% and 4% of individuals receiving placebo, respectively.^{8–10} As observed with our patient, titers usually normalize following discontinuation of etanercept. Although seroconversion is rarely associated with drug-induced lupus, patients sometimes develop lupus-like symptoms that typically resolve following drug withdrawal.^{11–14} It is postulated that TNF blockade may promote the development of autoantibodies¹⁵ and may impair TNF-mediated leukocyte expression of CD44 involved in apoptotic neutrophil clearance.¹⁶ Further, anti-TNF therapy may induce apoptosis of cells that express TNF, resulting in the release of nuclear-derived antigens.¹⁷

Several case reports of cutaneous vasculitis associated with etanercept, similar to that seen in our patient, have been published.^{14,18–23} One potential mechanism for anti-TNF therapy–induced vasculitis is the deposition of immune complexes of either antibodies to etanercept or autoantibodies in small capillaries, activating complement, and subsequently triggering a type 3 hypersensitivity reaction.^{18,19} This mechanism does not explain the development of ANA or antibodies to dsDNA. However, it has been suggested that TNF blockade may lead to a switch from the predominant Th1 profile of T lymphocyte response in RA to a Th2 response, common to other Th2 lymphocyte-mediated vasculitic diseases, such as lupus and Wegener's granulomatosis.¹⁹ This same pathway associated with a change in the Th profile has been proposed for several case reports of TNF blockade–associated atopic dermatitis.^{24,25} Conversely, T cell lymphocytic vasculitis with a Th1-predominant profile has been reported in a patient with Crohn's disease.²³ This particular case was associated with increased systemic chemokines, defensins, cytokines, and angiogenesis factors; local activation of innate and adaptive immune responses; and highly active peripheral B cells. The authors postulated that aggressive TNF suppression may have promoted loss of immune tolerance to self.

Although anecdotal reports suggest that substitution with an alternative TNF blocker may not be associated with recurrence of vasculitis,²⁶ cases of vasculitis resulting from the administration of both etanercept and infliximab have been described, thereby suggesting the potential for a class effect^{19,21–23} and cross-sensitivity. Corticosteroids remain the standard treatment for systemic vasculitis in patients with RA²⁷ and have been useful in cases of etanercept-induced vasculitis.^{19–21} Our patient responded to cessation of etanercept and a temporary increase in the dose of corticosteroids.

Since our patient continued to have active disease, we opted to initiate therapy with anakinra. Surprisingly, after tolerating therapy for 2 months, she suddenly developed an anaphylactic reaction, which was confirmed by the skin prick test. The patient subsequently responded to hydration, epinephrine, antihistamines, and corticosteroids, which is considered standard of care.²⁸ Use of the Naranjo probability scale found anakinra to be the probable cause of the patient's anaphylaxis.²⁹ Since anakinra is produced by recombinant DNA technology using an *Escherichia coli* bacterial expression system,³⁰ it is possible that our patient may have had a hypersensitivity reaction to *E. coli*–derived proteins. However, she had no prior history of allergy to proteins synthesized by *E. coli*.

Rare reports of hypersensitivity to anakinra have occurred.^{2,3,30} One case involved a systemic reaction consisting of abdominal pain, dyspnea, and facial and abdominal erythema with pruritus 3 hours after reintroduction of anakinra in a patient with a prior cutaneous reaction.³ In a second case report in which anakinra therapy was interrupted, a severe immediate allergic

reaction with urticarial lesions, edema of the patient's feet and hands, and a pruritic tongue occurred in a 7-year-old girl with juvenile idiopathic arthritis once therapy was restarted.² She responded to drug withdrawal and corticosteroids. Anakinra therapy was reintroduced using a desensitization protocol.

Because abatacept and rituximab were either not available or not used in RA when our case occurred, adalimumab was our next therapeutic consideration. Because it is a fully human monoclonal antibody with only rare reports (<1%) of anaphylactoid or fixed drug reactions,^{31,32} there was the potential that our patient might tolerate adalimumab. However, beginning with the second dose, she experienced symptoms of hypersensitivity ranging from injection site reactions to generalized hives. Urticarial reactions similar to those seen in our patient have been reported with adalimumab.^{33–35} Therapy was again discontinued, necessitating the management of RA with methotrexate monotherapy.

In addition to these multiple biologic agents, our patient reacted to hydroxychloroquine and sulfasalazine. Because of her intolerance to multiple medications and an allergy to a sulfonamide, it was initially questioned whether she might have a condition known as “multiple drug allergy syndrome,” characterized by a propensity to react to different, chemically unrelated therapeutic agents.³⁶ This clinical scenario is observed predominantly in females and in individuals with a history of intolerance to at least one medication. Although acute urticaria and/or angioedema are the usual presenting symptoms, Stevens-Johnson syndrome, anaphylaxis, serum sickness, and immune-mediated cytopenias may also occur. The syndrome appears to have a genetic predisposition that may include an increased tendency to haptenize newly introduced antibiotics and small molecules to self-proteins, leading to increased risk for sensitization.³⁷ Furthermore, although our patient was allergic to sulfonamides, the absence of hypersensitivity to other antibiotics makes her presentation unique. Interestingly, 8 patients intolerant to multiple drugs were also shown to have strong wheal and flare reactions upon injection of autologous sera.³⁸ Additionally, drug recognition in IgE-mediated reactions of some patients with multiple drug allergies may be related to the presence of tertiary and quaternary amino groups present on many pharmacologically active agents.³⁹

Future management for our patient includes avoidance of the biologics previously administered and possibly other drugs associated with *E. coli*-derived proteins, such as anakinra, as well as careful therapeutic decisions with close monitoring. The 3 anti-TNF agents that our patient received all share an IgG₁ structure. However, she also reacted to anakinra, a recombinant IL-1 receptor antagonist with no structural similarities to the IgG molecule. It is plausible that, because anakinra is a recombinant protein expressed in bacteria, some contaminant may serve as a neo-antigen. In addition, unlike endogenous IL-1 RA or a recombinant protein expressed in eukaryotic cells, it is not glycosylated. Thus, portions of its surface structure, with an additional methionine on the *N*-terminus, are exposed, otherwise hidden in the natural protein.

Currently, clinical or genetic predictors of toxicity to biologics are not known. Specific human major histocompatibility gene complex (HLA) phenotypes, such as HLA-A*24 and HLA-B*1502 in our patient, may be associated with susceptibility to certain drug allergies, such as dipyrone-induced agranulocytosis and carbamazepine hypersensitivity, respectively.⁴⁰ The use of skin testing as a predictive measure for future reactions must be validated for each drug individually. Given the low rate of type 1 hypersensitivity reactions to anakinra, such validation cannot be performed unless and until type 1 reactions to biologics become far more common. Moreover, positive and negative tests in patients who have or have not had a reaction to anakinra simply cannot be interpreted and used as guidelines for therapy. However, pharmacogenetics has the potential to identify genetic variations associated with both improved therapeutic outcomes and safety. Although the influence of several candidate genes on response to TNF inhibition have been studied,^{41–44} genetic data assessing polymorphisms associated with

either toxicity or discontinuation of any biologic agent used in RA are limited. A recent report on IgE-mediated hypersensitivity to cetuximab identified galactose- α -1,3-galactose as the antigen recognized by serum IgE antibodies that were present prior to the reactions.⁴⁵ This oligosaccharide is found in biologics produced by mouse cell lines and other sources.

Our case is a unique example of a patient with RA and multiple drug allergies who manifested distinct adverse reactions to several DMARDs and biologics, including an anaphylactic reaction to anakinra. This presented a difficult clinical management scenario that required introduction of each agent on a trial-and-error basis over a 4-year period. Hopefully, in the future, pharmacogenetics may help to better identify individuals at risk for multiple drug reactions and preclude unnecessary exposure to potentially harmful therapeutic options in similar patients.

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Figure 1.
Digital microinfarct secondary to etanercept.

Figure 2. Skin prick test demonstrating wheal and flare reaction to anakinra (9 mm wheal and flare) with negative (glycerin) and positive (histamine; 7 mm wheal and flare) controls.