

Anaphylaxis to Etanercept in Two Children With Juvenile Idiopathic Arthritis

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Abstract: Anti-tumor necrosis factor α (TNF α) medications have revolutionized the care of children and adults with chronic arthritis. They are quick acting, highly effective, and remarkably safe, particularly in children with juvenile idiopathic arthritis (JIA). Anti-TNF α agents come in 2 basic varieties: monoclonal antibodies to TNF α (e.g., infliximab, adalimumab) and a fusion protein containing a TNF receptor (etanercept). Although hypersensitivity reactions are not uncommon with some of the TNF α antibodies (e.g., infliximab), there are only rare reports of anaphylaxis to subcutaneous injections of etanercept in adults with rheumatoid arthritis. Herein, we report 2 cases of anaphylaxis in children with JIA after etanercept injections. Although rare, pediatricians need to be aware of this potentially dangerous occurrence.

Key Words: juvenile arthritis, anaphylaxis, etanercept

(*J Clin Rheumatol* 2013;19: 129–131)

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and can lead to disability if inadequately treated.¹ Treatment options include corticosteroids, nonsteroidal anti-inflammatory drugs, and disease-modifying antirheumatic drugs, such as methotrexate (MTX) and anti-tumor necrosis factor α (anti-TNF α) agents.^{1–3} The introduction of anti-TNF α drugs to the treatment of chronic arthritis has revolutionized the care of adults with rheumatoid arthritis (RA) and children with JIA.⁴ Etanercept, a fusion protein containing the TNF receptor, is a safe and effective anti-TNF α therapy for JIA.^{5,6} A reasoned treatment approach to arthritis combining MTX and etanercept is also relatively safe and can lead to higher response rates in both JIA and adult RA.^{7,8} Of the adverse effects attributed to etanercept, injection site reactions are the most common and do not typically cause discontinuation.⁹ More serious adverse events are rare but include infections requiring hospitalization.⁵ Compared with infliximab, an anti-TNF α monoclonal antibody known to cause infusion reactions and anaphylaxis, systemic allergic reactions to etanercept are rare.¹⁰

Nevertheless, 1 case study describes an anaphylactic reaction in an adult on concomitant MTX and etanercept treatment for RA¹¹ (Table 1). The reaction occurred minutes after subcutaneous (SQ) injection of the 41st weekly MTX dose and 6 months after beginning etanercept.¹¹ It was hypothesized that the combination of etanercept and MTX can provoke an asthma-like anaphylactic reaction.¹¹ A second case reports an adult with RA who experienced multiple allergic reactions to several anti-TNF α medications when combined with MTX¹² (Table 1). Anaphylaxis to anakinra was also noted in this individual.¹² The patient tolerated

etanercept for a year before discontinuing for worsening Raynaud phenomena and microinfarcts.¹² To our knowledge, no reports of anaphylaxis to etanercept, either as monotherapy or concomitantly with MTX, in pediatric patients have been documented. Herein, we report 2 cases of anaphylaxis associated with etanercept injections in children with JIA.

A 10-year-old white boy with long-standing anti-nuclear antibody+ polyarticular JIA and linear scleroderma presented to the emergency department with an allergic reaction after administration of etanercept (Table 1). He had been receiving weekly MTX 17.5 mg SQ injections for 4 years before adding etanercept 25 mg SQ weekly (49 kg). These were his only medications, and he had no known drug allergies at the time of presentation. Immediately after the fifth weekly injection of etanercept, he noticed itching and mild periorbital swelling. He awoke the next morning with a rash, nausea, and difficulty breathing. Physical examination findings at presentation included generalized urticaria, diffuse facial edema, and mild angioedema. Respiratory distress and swelling resolved with 2 doses of epinephrine, a normal saline intravenous bolus, prednisolone, and ranitidine. His facial rash persisted throughout his hospitalization. He continued to receive prednisolone and scheduled diphenhydramine until discharge. Etanercept was stopped immediately, and the patient was started on adalimumab 40 mg SQ every other week. To date (2.5 years since anaphylaxis), this patient has reported no adverse events with combined MTX and adalimumab therapy.

A 15-year-old white girl was diagnosed with anti-nuclear antibody+, human leukocyte antigen-B27+ enthesitis-related JIA. She presented with coxitis of both hips with morning stiffness, arthritis of her left ankle, severe lumbosacral back pain, and arthralgias of both knees and temporomandibular joints. Arthritis of the hips and the ankle were confirmed by ultrasound and magnetic resonance imaging (MRI), and MRI of the temporomandibular joints showed degenerative changes on the left. She was started on etanercept 20 mg SQ twice weekly (49 kg).

Within minutes after the third injection of etanercept, she developed a generalized urticarial rash and dyspnea. This was considered a likely allergic reaction because antihistamines and prednisone led to prompt and sufficient improvement of symptoms. Etanercept was discontinued, and she was started on adalimumab 20 mg SQ every other week. Methotrexate was later added because of persistent arthralgias. She has done well without any adverse events on this combination therapy for at least 1.5 years, when she transitioned to adult care.

These 2 cases of anaphylaxis in children with JIA after SQ injections of etanercept highlight the importance of discussing this potential drug reaction with patients and their families. Interestingly, both children had their allergic reactions within the first 3 to 5 doses of etanercept, suggesting that, if allergic reactions are to occur to etanercept, they may occur after only a few doses. In addition, both children responded well to standard therapy for severe hypersensitivity reactions. Whether all children treated with etanercept should be provided with self-administered epinephrine (Epi-pens) is a point to consider, particularly for those who may have had severe allergic reactions to other medications. However, neither of these 2 patients had a history, or a family

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The authors declare no conflict of interest.

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ISSN: 1076-1608/13/1903-0129

DOI: 10.1097/RHU.0b013e318285f1e9

TABLE 1. Reported Anaphylactic Reactions in Patients Treated With Etanercept

Age, y	Sex	Diagnosis	Therapies	Dose Provoking Anaphylaxis	Current Therapy	Other Adverse Events	Reference
46	F	RF+ erosive RA	Etanercept 25 mg twice weekly, MTX 25 mg SQ weekly	41st injection of MTX, 6 mo after starting etanercept	Unknown	No anaphylaxis reported; urticarial hypersensitivity reaction with additional MTX injection; no reactions with etanercept	11
46	F	RA	Infliximab 180 mg infusion	None reported	Unknown	Discontinued infliximab after 3 doses because of worsening pruritic urticarial rash	12
			Etanercept (dosage not reported)	None reported		Discontinued etanercept after 1 year because of Raynaud and microinfarcts	
			Anakinra 100 mg SQ daily Adalimumab 40 mg SQ every other week	2 mo of anakinra daily None reported		Urticarial hypersensitivity reaction beginning with 2nd injection; discontinued after 4th dose	
49	F	RA	Etanercept, 50 mg weekly	4 mo of dosing	Unknown	None reported	13
27	F	Still disease	Etanercept 25 mg twice weekly	2 mo of dosing	Unknown	None reported	13
10	M	Polyarticular JIA, linear scleroderma	Etanercept 25 mg SQ weekly, MTX 17.5 mg SQ weekly	5th injection of etanercept	Adalimumab 40 mg SQ every other week and MTX 17.5 mg SQ weekly	None	This report
15	F	HLA-B27+ enthesitis-related JIA	Etanercept 20 mg SQ twice weekly	3rd injection of etanercept	Adalimumab 20 mg SQ every other week and MTX	None	This report

RF, rheumatoid factor.

history, of atopy. In addition, both children responded well to, and have tolerated a switch to, an alternative anti-TNF α therapy, in both cases the anti-TNF α monoclonal antibody, adalimumab. Although anaphylactic reactions to etanercept are likely rare, it is important for treating pediatricians to be aware of this potentially life-threatening allergic reaction.

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