

Anaphylaxis to anakinra in a pediatric patient with systemic juvenile idiopathic arthritis successfully treated with canakinumab: a case-based review

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Abstract We present the case of a 2-year-old boy with a history of necrotizing enterocolitis (NEC) with ileostomy diagnosed with systemic juvenile idiopathic arthritis (sJIA) at 10 months of age controlled on anti-interleukin-1 (anti-IL-1) therapy (anakinra). At 17 months of age, ileostomy reversal and bowel re-anastomosis was scheduled with anakinra discontinued 3 days prior to the surgery and steroids initiated in its place. Ten days postoperatively, anakinra was re-started for signs of sJIA flare. Three months later, he developed persistent peripheral eosinophilia and subsequent anaphylactic reaction 6 months postoperatively. The patient safely tolerated an alternative anti-IL-1 agent (canakinumab). Anaphylaxis to anakinra has not been previously reported in the pediatric literature. This case highlights an important issue in a pediatric patient with sJIA: safety of an alternate anti-IL-1 agent, following development of allergy to one initial agent.

Keywords Anaphylaxis · Anakinra · Anti-interleukin-1 · Canakinumab · Interleukin-1 receptor antagonist · Systemic juvenile idiopathic arthritis

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is an autoimmune disease characterized by fever and arthritis with rash,

lymphadenopathy, hepatosplenomegaly, or serositis [1]. Interleukin-1 (IL-1) is one of the predominant pro-inflammatory cytokines implicated in sJIA pathogenesis [2]. Anakinra, an IL-1 inhibitor, has proven effective in sJIA treatment with rapid effects on systemic features and laboratory measures of inflammation [3]. We report a pediatric patient with sJIA on anakinra in whom therapy was briefly interrupted and then re-introduced with subsequent development of an anaphylactic reaction to anakinra 6 months later. The patient was switched to an alternative anti-IL-1 agent (canakinumab) without subsequent reaction. Although rare cases of hypersensitivity related reactions to anakinra have been reported [4–8], to our knowledge, this is the first report of anaphylaxis in a pediatric patient with sJIA who was safely switched to alternative anti-IL-1 therapy.

Case report

A 10-month-old (ex-30 week twin) male with a past medical history of necrotizing enterocolitis (NEC) requiring ileostomy was diagnosed with sJIA based on documented daily fevers, evanescent rash, elevated inflammatory markers, and inflammatory arthritis of upper and lower extremities. This was confirmed by synovial fluid aspiration and magnetic resonance imaging (MRI). Due to persistent disease activity with an inadequate response to non-steroidal anti-inflammatory (NSAID) therapy (diclofenac 3 mg/kg), anakinra 50 mg daily (6.5 mg/kg) was started.

Initiation of anakinra resulted in a good clinical and laboratory response. Three days prior to surgical correction of the ileostomy, prednisone 1 mg/kg was begun, while anakinra was held. As there was no evidence in the literature to support the safety of continuing anakinra intra-operatively, the potential peri-operative risks of steroids for infection and poor

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wound healing were felt by the surgical team to be preferable to the unknown risks of anti-IL-1 therapy. Steroid risks were offset by the short pre-operative course (3 days) with anticipated brief postoperative use until bowel function regained and anakinra could be re-started. Signs of emerging arthritis were noted on postoperative day (POD) 6 followed by leukocytosis and transaminitis suggestive of sJIA disease activity. Anakinra was re-started on POD 10 with resolution of lab abnormalities and arthritis. The patient was discharged on POD 15.

Three months postoperatively, persistent peripheral eosinophilia developed (8–41.8 %; normal <8 %) on peripheral smear with elevated absolute eosinophils 0.86–5.24 (normal <0.8/nl) (Fig. 1). Extensive workup was unrevealing. Laboratory evidence of disease activity emerged, requiring increased prednisone dosing. Anakinra was increased from 50 to 100 mg daily with subsequent rash. Anakinra was then discontinued for suspected drug reaction. Two days later, despite methylprednisolone 8 mg daily, urticarial lesions, angioedema, tachypnea, and wheezing developed. He was treated for anaphylaxis with epinephrine, diphenhydramine, steroids, and intravenous hydration and started on methylprednisolone 2 mg/kg. As anaphylaxis is not well described for anti-IL-1 therapy, an anakinra challenge with a 25-mg test dose was administered. Forty-five minutes later, diffuse urticarial rash and mild hypotension developed without respiratory distress or mucosal involvement. Canakinumab (40 mg monthly) was substituted for anti-IL-1 effect with resolution of allergic symptoms and peripheral eosinophilia. The patient did not have active clinical systemic features prior to discontinuation of anakinra. Canakinumab was initiated when anaphylaxis to anakinra occurred. Subsequently, dosing escalation of

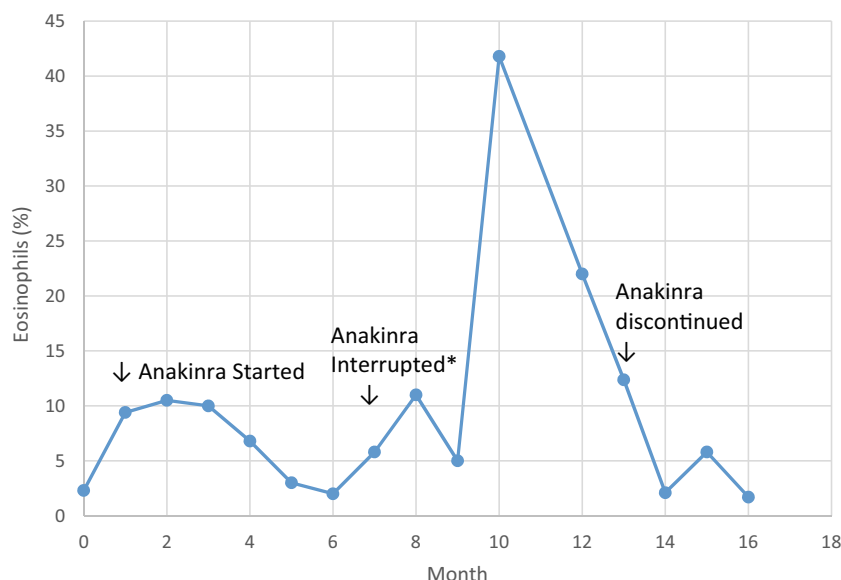
canakinumab to 180 mg (16 mg/kg) monthly was required and tolerated. This has been safely used for 17 months.

Discussion

Anakinra is a human recombinant interleukin-1 receptor antagonist (IL-1Ra) that blocks the biologic activity of IL-1 α and β by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI). One year after starting anakinra (6 months after interrupting use), the patient developed anaphylaxis in the context of persistent peripheral eosinophilia. Sensitization during the peri-operative period when anakinra therapy was interrupted is plausible. A delayed onset drug reaction is likely since anaphylaxis occurred 2 days after anakinra was discontinued. The type 1 IgE-mediated drug reaction is supported by the immediate allergic reaction to anakinra challenge with urticarial lesions and tachypnea as well as by the resolution of peripheral eosinophilia with discontinuation of anakinra. Anakinra is a recombinant protein and differs from native human IL-1RA by a single methionine residue on its amino terminus. Allergic reactions may be directed to this or an exogenous component of the medicine. Other anaphylactic reactions to biologic therapies have been described including to those of the anti-tumor necrosis factor α (anti-TNF α) class of medications [4]. As a recombinant human protein, anaphylactic reaction to anakinra was unexpected.

PubMed was queried for “anakinra” or “anti-interleukin-1” or “interleukin-1 receptor antagonist” and “anaphylaxis,” “hypersensitivity,” or “allergic.” Relevant articles and their references were checked, and results are described in Table 1.

Fig. 1 Eosinophilia trend (%) in relation to clinical events



*Anakinra was held peri-operatively, re-started after 13 days

Table 1 Cases of allergic reactions to anakinra

Case	Age (year)/sex	Diagnosis	Duration of anakinra use prior to reaction	Allergic manifestations	Prior medication allergies	Reaction after interrupted use
Current report	2/M	sJIA	12 months	Anaphylaxis	None	Yes
Vila et al. [5]	38–73/F ^a	RA	Within 1 month	Cutaneous drug reactions	NA	No
Regula et al. [6]	52/F	RA	21 months	Erythematous plaques (IGDR)	NA	No
Vordenbäumen et al. [7]	57/M	AoSD	3 months	Pruritic rash	NA	Yes
Desai et al. [8]	46/F	RA	2 months ^b	Anaphylaxis	HCQ, SSA, IFX	No
Anton et al. [9]	7/F	sJIA	1 week	Hypersensitivity/severe allergic reaction	NA	Yes

RA rheumatoid arthritis, sJIA systemic juvenile idiopathic arthritis, AoSD adult-onset Still's disease, IGDR interstitial granulomatous drug reaction, HCQ hydroxychloroquine, SSA sulfasalazine, IFX infliximab

^a Age range of five patients in study

^b Moderate skin reactions after first dose

Among adult patients with rheumatoid arthritis (RA) or adult-onset Still's disease, adverse cutaneous reactions have been described [5–7]. A suspected delayed anaphylactic reaction to anti-IL-1 confirmed by an immediate hypersensitivity to drug challenge to our knowledge has not been previously reported.

One study of ten RA patients receiving treatment with steroids or NSAIDs and other disease-modifying anti-rheumatic drugs (methotrexate or salazopyrin) in addition to anakinra describes five adverse cutaneous injection site reactions [5]. Biopsy specimens showed a prominent eosinophilic infiltration and were successfully treated with antihistamines and topical corticosteroids. Minor skin reactions occurred with resuming medication in three patients. In one, a more severe reaction was seen, but without features of anaphylaxis and with good response to antihistamines and methylprednisolone. An interstitial granulomatous drug reaction, after 21 months of uninterrupted anakinra use, has been reported in one RA patient [6]. This cleared with discontinuation of anakinra and recurred with re-introduction. Continuation of anakinra despite development of a pruritic rash has also been reported in a patient with adult-onset Still's disease [7].

There is one prior report of anaphylaxis to anakinra, after 2 months of uninterrupted use, in an adult RA patient [8]. This patient had a history of multiple prior allergic reactions including to biologic therapies. Concurrent with methotrexate and prednisone, anakinra was started. The patient had a moderate injection site reaction with the first dose, with eventual progression to anaphylaxis. Allergy testing with skin prick method was consistent with a type 1 hypersensitivity IgE-mediated reaction to anakinra. The pediatric literature reveals one reported sJIA patient with a severe allergic reaction (although not anaphylactic) to anakinra following interruption for infection [9]. This patient underwent successful desensitization to anakinra.

Canakinumab is an effective anti-IL-1 beta monoclonal antibody approved for use in sJIA [10]. It is a human monoclonal anti-human IL-1 β antibody of the IgG1/ κ isotype. It

binds to human IL-1 β and neutralizes its activity by blocking its interaction with IL-1 receptors, but does not bind IL-1 α or IL-1 receptor antagonist (IL-1Ra) as anakinra does. Since the anakinra challenge confirmed allergy to anakinra, canakinumab was considered for our patient. The rationale was that canakinumab would have a similar anti-IL-1 effect, but not the same allergic response as different receptors are bound. A newer alternative anti-IL-1 therapy is rilonacept, but safety and efficacy had not yet been established in sJIA. This has since been reported [11]. An alternative agent approved for treatment of sJIA is tocilizumab, an anti-interleukin-6 agent, which carries risk of bowel perforation [12, 13]. This medication was avoided, given our patient's history of NEC with recent surgical re-anastomosis.

There is an emerging body of literature looking at the role of the gut microbiome in the development of various autoimmune diseases [14]. The gut provides a major source for antigenic stimulation and variation in a genetically predisposed individual. Recently, commensal bacteria (*Prevotella copri*) were found to correlate with disease in new onset RA patients [15]. It is plausible that bowel surgery may have contributed to a dysregulation in the previously established commensal homeostasis in our patient and possibly a change in the gut milieu leading to lack of tolerance to a medication that was previously well tolerated. This represents the first report of anaphylaxis to an anti-IL-1 agent (anakinra) in a pediatric patient with sJIA safely switched to alternative anti-IL-1 treatment (canakinumab). Rheumatologists should be aware that interruption of anakinra therapy may carry a risk for subsequent anaphylaxis. Patients should be monitored for clinical signs of hypersensitivity and persistent peripheral eosinophilia.

Conflict of interest We (Cassianne Aguiar, Nancy Pan, Alexa Adams, Laura Barinstein, and Thomas Lehman) are aware of the contents of this manuscript and have no conflicts of interest to report.

References

- Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J et al (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 31:390–392
- Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y et al (2013) 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. *Arthritis Rheum* 65:2499–2512
- Nigrovic PA, Mannion M, Prince FH, Zeff A, Rabinovich CE, van Rossum MA et al (2011) Anakinra as first-line disease modifying therapy in systemic juvenile idiopathic arthritis. *Arthritis Rheum* 63:545–555
- Crayne CB, Gerhold K, Cron RQ (2013) Anaphylaxis to etanercept in two children with juvenile idiopathic arthritis. *J Clin Rheumatol* 19:129–131
- Vila AT, Puig L, Fernandez-Figueras MT, Laiz AM, Vidal D, Alomar A (2005) Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 153:417–423
- Regula CG, Hennessy J, Clarke LE, Adams DR, Ioffreda MD, Graber EM et al (2008) Interstitial granulomatous drug reaction to anakinra. *J Am Acad Dermatol* 59:S25–S27
- Vordenbäumen S, Ostendorf B, Sander O, Richter J, Schneider M (2009) Continuation of anakinra despite the development of a pruritic rash in an otherwise refractory case of adult-onset Still's disease. *Ann Rheum Dis* 68:450–451
- Desai D, Goldbach-Mansky R, Milner JD, Rabin RL, Hull K, Pucino F et al (2009) Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. *Ann Pharmacother* 43:967–972
- Anton J, Ros J, Ricard S, Giner MT, Plaza AM, Villaronga M et al (2005) Desensitization to anakinra in a systemic onset juvenile idiopathic arthritis patient [abstract]. *Clin Exp Rheumatol* 23:S24
- Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G et al (2012) Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 367:2396–2406
- Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ et al (2013) Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis Rheum* 65:2486–2496
- De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I et al (2012) Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 367:2385–2395
- van Vollenhoven RF, Keystone EC, Furie R, Blesch A, Wang C, Curtis JR (2009) Gastrointestinal safety in patients with rheumatoid arthritis treated with tocilizumab: data from Roche clinical trials [abstract]. *Arthritis Rheum* 60(Suppl 10):1613
- Yeoh N, Burton JP, Suppiah P, Reid G, Stebbings S (2013) The role of the microbiome in rheumatic diseases. *Curr Rheumatol Rep* 15: 314
- Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C et al (2013) Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *Elife* 2:e01202