Expedited Desensitization to Canakinumab

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Abstract

Introduction: Interleukin-1 (IL-1) antagonists have been successful in the management of monogenic auto-inflammatory diseases, notably classic hereditary fever syndromes, such as Familial Mediterranean Fever (FMF). Anakinra (Kineret®), a human recombinant IL-1 receptor antagonist (IL-1Ra), has been clinically effective in the management of persistent auto-inflammation, such as FMF. Few studies report anaphylaxis in response to anakinra, which were resolved with an anakinra desensitization or the anti-IL-1β monoclonal antibody canakinumab (ILARIS®). We describe the first reported desensitization protocol to canakinumab.

Case Report: A 51-year-old man with a prior history of FMF presented with history of failed colchicine, nonsteroidal anti-inflammatory drug, and anakinra trials. Anakinra desensitization and canakinumab intradermal testing (IDT) resulted in anaphylactic and allergic symptoms, respectively. Expedited desensitization to canakinumab was successfully performed with 15-minute intervals between 13 doses of incremental increase to 150 mg.

Discussion: Biological agents are immune modulators that may evoke unanticipated hypersensitivity reactions, including anaphylaxis. These anaphylactic reactions to biologics have been infrequently reported, but the expanding market may increase the risk of IgE-mediated hypersensitivities and subsequent need for desensitization protocols. The current, expedited desensitization evaluated several published protocols involving anakinra desensitization to determine appropriate dosing for canakinumab.

Conclusion: We report the gastrointestinal intolerance and continued FMF flares on colchicine, followed by anaphylactic responses to anakinra and allergic reaction to IDT of canakinumab, in the present case of FMF. Our novel, expedited canakinumab desensitization protocol serves as an effective and alternative therapy in cases when other appropriate biologic agents are not tolerated.

Keywords

canakinumab (ILARIS®), anakinra (Kineret®), interleukin-1 receptor antagonist, Familial Mediterranean Fever, anaphylaxis, intradermal testing

Introduction

Interleukin-1 (IL-1) is a pro-inflammatory cytokine overproduced in auto-inflammatory disorders.[1] IL-1 antagonists have been successful in the management of monogenic auto-inflammatory diseases, notably classic hereditary fever syndromes, such as Familial Mediterranean Fever (FMF), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency, and tumor necrosis factor (TNF) receptor associated periodic syndrome.[2–4]

Colchicine and canakinumab (ILARIS®), the human recombinant anti-IL-1β monoclonal antibody, are the only Food and Drug Administration (FDA)-approved medications for FMF.[2] Anakinra (Kineret®), a human recombinant IL-1 receptor antagonist (IL-1Ra), has been widely studied in the management of persistent auto-inflammatory diseases including FMF and is more cost effective and clinically yields immediate and sustained symptom control.[2–6] Anaphylactic and/or

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allergic events have rarely been associated with administration of anti-IL-1 agents when administered via intradermal testing (IDT).[6] Few studies report an allergic reaction in response to anakinra administration, which were resolved with an anakinra desensitization or switching to canakinumab.[1,3,7–9] We describe the first reported desensitization protocol to canakinumab.

Case Report

A 51-year-old man with a prior history of FMF presented with a persistent flare of recurrent fevers, arthralgias, abdominal pains, pleuritic chest pains, and joint swelling ongoing for several weeks. The patient was initially started at 0.3 mg three times daily of colchicine, increased to 0.6 mg twice daily, and titrated down to 0.6 mg, due to adverse effects of abdominal discomfort and diarrhea, as well as ineffective FMF symptom management. He was also unable to tolerate nonsteroidal anti-inflammatory drugs, as he developed acute kidney injury. The patient was then treated with anakinra with subsequent resolution of FMF symptoms. After 3 months of anakinra therapy (100 mg subcutaneous injection [SQ] daily), the patient acutely developed hives, diffuse pruritus, angioedema of the tongue and throat, and shortness of breath. The anakinra was discontinued, and the patient underwent subsequent trials of tociluzumab (ACTEMRA®) and entanercept (ENBREL®) within a 3-month time span without success. Desensitization to anakinra was conducted with a goal dose of 100 mg SQ every 4 weeks.

Postdesensitization, after approximately 3 months, the patient experienced breakthrough FMF flares prior to the next scheduled dose of anakinra. The patient reported unusual "golf ball-sized," raised, pruritic reactions at the injection site and unassociated sites, including the lower extremities. The anakinra was discontinued after 5 months, and the patient was trialed on adalimumab (HUMIRA®). The above medication trials and procedures were conducted at another hospital system. When the patient was admitted to our hospital system, the clinical decision to start a new IL-1 antagonist canakinumab was advised. Given the patient's prior anaphylaxis to anakinra, our allergy/immunology service proceeded with canakinumab IDT.

An IDT of canakinumab was scheduled before proceeding to the therapeutic use of this medication (1.5 mg/mL SQ daily). The positive canakinumab IDT (3 mm+, negative saline, and positive histamine controls) resulted in an allergic reaction of throat pruritis and chest tightness within 15 minutes after intradermal placement of canakinumab. After administration of intravenous (IV) methylprednisolone (SOLU-MEDROL®, 40 mg IV) and diphenhydramine (Benadryl®, 50 mg IV), the patient clinically improved to his baseline health status. The patient was monitored, and epinephrine was not administered, given the patient's clinical improvement.

Serum histamine and tryptase tests were drawn within 40 minutes of the allergic reaction to the canakinumab IDT. Tryptase (5 mcg/L), plasma histamine (0.20 μg/mL), and 24-hour urine histamine (32 μg/24 hrs) were within normal limits but were determined as an unreliable marker of anaphylaxis, with precedence of clinically relevant symptoms. Desensitization to canakinumab was advised, in consideration of the patient's history of anaphylaxis to anakinra and response to his allergic reaction from the canakinumab IDT.

Expedited desensitization to canakinumab was performed as a revision of our anakinra desensitization protocol (Table 1). Desensitization was conducted with 15-minute intervals between 13 doses of incremental increase in canakinumab concentration without any adverse reactions to canakinumab. The patient was monitored for several hours postdesensitization and has been maintained on a biweekly regimen of 150 mg of canakinumab.

Discussion

Canakinumab has demonstrated efficacy in controlling FMF flare recurrence in patients resistant to colchicine but has primarily been studied for management of other autoinflammatory conditions.[10–14] Studies reporting management of urticarial vasculitis, systemic juvenile idiopathic arthritis, for which is it also FDA-approved, and idiopathic recurrent pericarditis with canakinumab have indicated successful outcomes.[4,11–14] To our knowledge, a canakinumab desensitization protocol does not exist in the literature; however, several protocols for a mechanistically similar biologic, anakinra, do exist.

Verduga et al. described a 34-year-old FMF patient with injection-site reactions to anakinra.[8] After an 18-day anakinra desensitization, progressing from 10 mg/0.6 mL for 3 days to 100 mg/0.6 mL as the final dose, IDTs were negative.[8] Soyyigit et al. introduced a novel anakinra desensitization protocol with 1-hour intervals ranging from 1/100 to 1/1 dilutions in a 25-year-old woman diagnosed with FMF and presenting with anakinra-associated urticaria and angioedema.[3]

Yilmaz et al. discussed a 38-year-old FMF patient who developed immediate hypersensitivity to anakinra and tolerated subcutaneous desensitization.[9] Premedication with 5 mg of desloratadine and 40 mg of methylprednisolone was provided 30 minutes prior to the protocol desensitization procedure, which was administered at 30-minute intervals and spanned 1/1000 to 1/1 dilutions.[9] The current, expedited desensitization evaluated several of the above protocols involving anakinra to determine appropriate dosing for canakinumab (Table 1).[3,8,9]

Table 1. Subcutaneous Desensitization of Canakinumab (ILARIS®).

Steps[a]	Dilution[b]	Volume (mL)	Injected Dose (mg)	Cumulative Dose (mg)
1	1/10000	0.10	0.0015	0
2	1/1000	0.10	0.015	0
3	1/1000	0.30	0.045	0
4	1/1000	0.60	0.09	0
5	1/100	0.10	0.15	0
6	1/100	0.30	0.45	1
7	1/100	0.60	0.9	2
8	1/10	0.20	3	5
9	1/10	0.40	6	11
10	1/1	0.10	15	26
11	1/1	0.16	24	50
12	1/1	0.33	49.5	99
13	1/1	0.34	51	150
Dilution		Instructions		
1/10 000		Draw 0.05 mL from 150 mg/1 mL vial; mix w/ 500 mL sterile water		
1/1000		Draw 0.05 mL from 150 mg/1 mL vial; mix w/ 50 mL sterile water		
1/100		Draw 0.05 mL from 150 mg/1 mL vial; mix w/ 5 mL sterile water		
1/10		Draw 0.1 mL from 150 mg/1 mL vial; mix w/ 1 mL sterile water		
1/1		Stock vial solution of 150 mg/1 mL		

[a]Each step is 15 minutes.
[b]Dilution instructions.

Biologics target the IL-1 receptor or neutralize the IL-1 cytokine, and, thus, have been successful in managing IL-1-mediated inflammation.[1] FMF is among the monogenic auto-inflammatory disorders that benefit from IL-1 antagonists, including anakinra and canakinumab.[5] We report intolerance and lack of clinical efficacy with colchicine, followed by an anaphylactic responses to anakinra and, subsequently, to IDT of canakinumab, in the present case of FMF. Our novel, expedited canakinumab desensitization protocol serves as an effective and alternative therapy in cases when other appropriate biologic agents are not tolerated.

Ethical Approval

This study was approved by our institutional review board.

Declaration of Conflicting Interests

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Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

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