Rapid paper

Anakinra desensitisation in patients with cryopyrin-associated periodic syndromes

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ABSTRACT

Cryopyrin-associated periodic syndrome (CAPS) is rare and patients experience rashes, arthralgias and fevers despite supportive treatment. In these cases, anakinra subcutaneous therapy is indicated which provides symptom control. However, adverse reactions notably injection-site related, are common resulting in treatment cessation in these patients. Ongoing symptoms lead to morbidity and predispose patients to complications such as amyloidosis. We describe our experience with anakinra desensitisation in two cases with CAPS who had injection-site related reactions. We also propose a 34-day outpatient desensitisation protocol.

Anakinra (Kineret) is a recombinant human interleukin-1 (IL-1) receptor antagonist administered subcutaneously daily for a variety of auto-inflammatory conditions. Injection-site reactions to anakinra occur in 50–80% of patients, resulting in cessation of treatment in up to 5% of cases (1).

Cryopyrin-associated periodic syndromes (CAPS), such as familial cold auto-inflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) are rare. In an Australian survey, the estimated prevalence for CAPS was 1 per million persons (2). CAPS result from an *NLRP3* activating gene mutation, which causes dysregulated active interleukin-1beta (IL-1β) release (3, 4). IL-1β is responsible for symptoms such as fever, rash and arthralgias (5). Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine often fail to provide adequate symptomatic relief in these patients. Furthermore, complications such as amyloidosis has been reported in up to 25% of cases (6). Therefore, treatment should be pursued to not only ensure symptom control but also reduce morbidity, and prevention of such disease-related complications.

In addition to anakinra, there are three agents for the treatment of CAPS: canakinumab, a monoclonal antibody against IL-1β; rilonacept, a soluble decoy IL-1 receptor; and gevokizumab, a humanised monoclonal antibody against IL-1β (5). In Australia, whilst both canakinumab and anakinra are licensed for CAPS, only anakinra is approved by the Pharmaceutical Benefits Scheme (PBS).

Adverse reactions to anakinra are common and can be identified as either immediate or delayed hypersensitivity. Broadly, immediate reactions are IgE mediated, occurring usually within one hour of drug administration and include local site injections or systemic reactions typical of anaphylaxis, such as urticaria, angioedema and cardiorespiratory compromise (7). In contrast, delayed reactions occur days following drug exposure, presenting from maculopapular exanthema to rarer cases of severe cutaneous adverse reactions, which are due to a T-cell dependent mechanism (7).

As anakinra is the only approved medication, in those with adverse reactions (including localised injection-site reactions) and inadequate symptomatic relief from NSAIDs or colchicine, desensitisation remains the only option. Desensitisation induces a temporary state of immune tolerance through incremental dose administration until therapeutic dose is reached, however the mechanisms and molecular targets leading to such tolerance is not well established (8).

In our tertiary hospital, two patients with CAPS had adverse reactions to anakinra therapy. Our objective was to undertake a modified two-day inpatient desensitisation protocol to anakinra in

Table I. Summary of two cases with anakinra desensitisation: adverse reaction, in-*vivo* testing, desensitisation and clinical outcome.

Case	Age and gender	Diagnosis	Anakinra reaction	In-*vivo* testing	Anakinra desensitisation outcome	Clinical progress
1	34 F	FCAS	Severe large localised erythema on day 7	IDT positive: 1:10.	Tolerated*	Symptomatic improvement
2	34 F	MWS	Severe localised blistering reaction, general un-wellness on day 7	Not performed	Failure with initial localised reaction* Modified protocol with up titration of pre-medication and tolerated thereafter ~	Symptomatic improvement

*Two-day modified protocol: day one: 0.15mg, 0.45mg, 0.9mg, 1.5mg, 3mg, 9mg and day two: 15mg, 45mg, 100mg (60 minutely intervals) adapted from Soyyigit *et al*. 2014 (10).
~Thirty-four-day protocol: 0.15mg, 0.45mg, 0.90mg, 1.5mg, 3mg, 9mg, 15mg, 30mg, 60mg and 100mg (dose increase every three days) adapted and modified from Soyyigit *et al*. 2014 (10) and Verduga *et al*. 2014 (11).
FCAS: familial cold auto inflammatory syndromes; MWS: Muckle-Wells syndrome; IDT: intradermal test.

these patients. We also report an extended outpatient desensitisation protocol, which was successful following failure of a modified two-day protocol. There was no ethics approval sought for this desensitisation given clinical need for therapy. Patient verbal consent was obtained only, as case presentations have precluded any personal details.

Case 1

A 34-year-old female with FCAS as well as novel missense variant of unknown clinical significance in NLRP12 gene was started on anakinra. On day seven she started to develop painful large local injection site reactions, lasting for more than 48 hours. On one occasion, she also described generalised itch and urticaria on her arms and legs, managed with a short course of oral corticosteroid.

Intradermal test (IDT) to anakinra was positive at 1:10 dilution on immediate reading. Desensitisation was undertaken with cetirizine 10mg twice daily (BD) for 24 hours as pre-medication (Table I). On day two, 60 minutes after the 45mg injection dose, she felt hot and pruritic. Examination revealed urticaria of the upper and lower limbs. She was treated with additional cetirizine 10mg and the next dose of anakinra given an hour later, with no recurrence of symptoms.

She continues to tolerate anakinra therapy two years following desensitisation, currently on alternating day therapy with improvements in symptom and inflammatory markers (normal CRP and mild elevation in ESR 25mm/hr).

Case 2

A 34-year-old female with MWS was started on anakinra. She developed a large localised injection site reaction on day five treatment. Despite alternating the site of injection, use of topical corticosteroids and oral antihistamines, these reactions continued to occur (Fig. 1). The most recent injection site reaction prompted a seven-day course of oral prednisolone due to painful blistering site reactions and malaise. There was no in-*vivo* testing performed.

Desensitisation protocol as per case 1 with pre-medication was commenced due to significant interference with quality of life. Six hours after the 9mg injection (cumulative dose 15mg) on day one, increased erythema, swelling and pain was present at the injection site. A skin biopsy showed features consistent with urticaria (Fig. 1) and desensitisation was discontinued. Complements and incident tryptase were normal.

Due to MWS symptoms, a modified outpatient anakinra desensitisation protocol was undertaken with a dose increase every three days over 34 days (Table I). The patient experienced localised erythema at 1.5mg, 3mg and

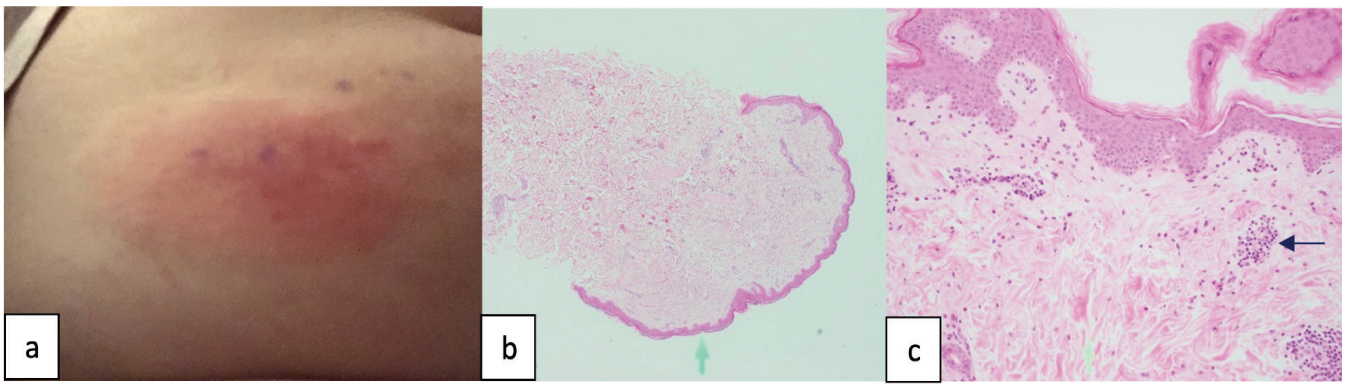

Fig. 1. Localised injection site reaction and histology.
a) Localised anakinra injection-site reaction at abdomen during day-one desensitisation; **b**) Histology of injection-site reaction showing oedema and dermal infiltrate; **c**) Higher magnification showing pronounced dermal infiltrate and presence of eosinophils (blue arrow).

Table II. Summary of anakinra desensitisation protocols in the literature.

Anakinra Desensitisation Protocols	Disease entity	Description of hypersensitivities	In-*vivo* testing	Desensitisation outcome
Soyyigit et al. 2014 ***Two-day protocol**** Day 1: 0.15mg, 0.45mg, 0.90mg, 3mg, 5.5mg, 12.5mg. 52.5mg. Day 2: 50mg, 50mg	FMF (n=1)	Type 1 Hypersensitivity	IDT 1:10 positive.	0mg cumulative dose on day one with diffuse erythema. Protocol modified with further 1/100th dilution with success.
Yilmaz, Turk and Bahcecioglu 2018 ***One-day protocol**** 0.015mg, 0.045mg. 0.09mg, 0.15mg, 0.45mg, 0.9mg, 3mg, 6mg, 10mg, 25mg, 55mg	FMF (n=1)	Type 1 Hypersensitivity	Negative SPT and IDT.	One week following desensitisation, localised erythema and swelling. Dose split, and subsequent tolerated.
Verduga *et al*. 2014 ***Eighteen-day protocol*** 10mg with incremental rise to 100mg as final dose, every three days.	FMF (n=1)	Delayed Hypersensitivity: localised symptoms only.	IDT 1:1 and 1:10 positive at 48-hours.	Successful as per protocol. IDT negative after desensitisation.
Leyroy *et al*. 2016 ***Three-day protocol^*** Day 1: 1mg, 2mg, 4mg, 8mg, 16mg, 20mg Day 2: 1mg, 2mg, 4mg, 8mg, 16mg, 20mg Day 3: 1mg, 2mg, 4mg, 8mg, 16mg, 33mg, 37mg	Adult Onset Still Disease (n=1)	Delayed Hypersensitivity: erythematous skin plaques back and lower limbs	NA	Successful as per protocol.
Emmi *et al*. 2016 ***Four-day protocol#*** Day 1: 0.1mg, 0.3mg, 0.6mg, 1mg, 2.5mg Day 2: 2.5mg, 5mg, 10mg, 15mg Day 3: 10mg, 15mg, 25mg Day 4: 50mg, 50mg	FMF (n=1) and Idiopathic non-infectious uveitis (n=1)	Delayed Hypersensitivity: erythematous skin plaques trunk and lower limbs	NA	Successful as per protocol.

*Each injection at 60-minute intervals; ^ each injection at 0, 30, 60, 90- and 120-minute intervals per day; # each injection at 15-minute intervals.
FMF: Familial Mediterranean fever; SPT: skin prick test; IDT: intradermal test.

9mg dosages and pre-medication modified to cetirizine to 20mg BD, followed by famotidine 20mg BD and montelukast 10mg once daily.

She successfully completed the desensitisation protocol, with an overall reduction in localised injection-site reactions. Over the subsequent eight weeks, medications were weaned to fexofenadine 180mg BD with no recurrence of injection site symptoms. She continues on therapy seven months following desensitisation with normal inflammatory markers (ESR and CRP) and serum amyloid level.

Discussion

Herein we describe two CAPS patients with anakinra-related severe injection-site reactions (Table I). Localised cutaneous reactions to anakinra are common, and in a case series of CAPS patients, accounted for 19% of adverse reactions, occurring within the first month of treatment (1, 9, 10). Due to its short half-life, daily injections are required (1, 9). As only a few cases of anakinra desensitisation are reported, there are no standardised protocols available (Table II) (11-15). A two-day modified desensitisation protocol was adapted from Soyyigit *et al*. (2014) given both our cases having had reactions within one week of starting anakinra (11)

Injection-site related reactions have been attributed to both IgE and non-IgE mediated mechanisms. In a mouse model, both constituents and high protein concentration of anakinra have been shown to induce localised direct mast cell degranulation, which resolves after corticosteroid administration (16). As seen in case 2, the tapering dosing of histamine (H1 and H2) blockers, as well as leukotriene antagonist therapy highlights that acquisition of tolerance may take longer in some patients.

In-*vivo* testing to anakinra has been described in desensitisation protocols in immediate and delayed reactions (11, 12, 15). Case 1 underwent in-*vivo* testing with IDT with positive immediate reading despite history consistent with a delayed reaction. In contrast, Verduga *et al*. (2014) describe one patient with delayed injection site reaction to anakinra in whom IDT was positive at 48 hours and had a successful 18-day desensitisation (12). In reviewing the literature for those undertaking anakinra desensitisation, of two cases with a typical history of IgE hypersensitivity, only one had a positive IDT (Table II), highlighting that IDT may not be adequately sensitive (11, 15).

In case 1, although initial day one desensitisation produced symptoms, the protocol was continued, and she con-

tinued anakinra treatment without further adverse reactions. In case 2 with MWS, following failure of the two-day inpatient desensitisation protocol, an outpatient slow up-titration desensitisation protocol was undertaken, modified from an eighteen-day protocol by Verduga *et al*. (2014) (12). A longer protocol was pursued due to the significant localised reaction experienced by patient on day one desensitisation after a very small dose, which lasted for more than 72 hours.

To our knowledge, we describe the first case of desensitisation to anakinra in MWS. The 34-day protocol in case 2 started with a 0.15mg injection, followed by 60-minute observation period, in our allergy unit. The remainder of doses were self-administered by the patient at home (Table I). This home regime provided her the freedom to return to work during the desensitisation process, and furthermore reduced hospital-related health care costs. Although the patient experienced local reactions during the desensitisation process, additional antihistamine and leukotriene agents-controlled symptoms. Since completing the desensitisation protocol, she has been able to wean premedications and has reported a significant improvement in symptoms and quality of life. This has also correlated with reduction in inflammatory markers.

Conclusion

We describe our experience with anakinra desensitisation in two patients with CAPS. We also propose a safe and effective slow-outpatient desensitisation protocol in a patient with delayed significant localised reactions to anakinra. Until alternative agents such as canakinumab are available in Australia, desensitisation remains the only option for those patients with CAPS who experience significant adverse reactions to anakinra.

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