

Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients

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Summary

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Background Anakinra, a recombinant human form of interleukin-1 receptor antagonist, is used to treat patients with active rheumatoid arthritis (RA).

Objectives To report five patients with cutaneous adverse drug reactions due to anakinra and to evaluate the histopathological and immunohistochemical findings with the aim of understanding the possible mechanisms involved.

Methods Five patients of a series of 10 patients with RA undergoing treatment with anakinra in a clinical trial presented inflammatory lesions at the anakinra injection sites. In each case, clinical features were recorded and skin biopsy specimens were obtained. In one patient sequential biopsy specimens were obtained from skin lesions at different stages of development. Tissue sections of the biopsy specimens were stained with haematoxylin and eosin and May–Grünwald–Giemsa, and were immunoreacted with antibodies to leucocyte common antigen, CD68, CD3, CD45RO, CD20 and CD45RA.

Results The onset of reaction was within the first month of treatment and appeared as well-defined erythema and oedema involving the injection sites. In two patients the treatment had to be discontinued because of the skin reaction, and in one patient it was associated with systemic involvement. All biopsy specimens exhibited marked dermal oedema and a lichenoid dermal infiltrate composed mainly of lymphomononuclear cells with prominent populations of eosinophils and large CD68+ dermal macrophages and an increase in the number of mast cells, which were spindle shaped in a significant proportion.

Conclusions Cutaneous toxicity is a frequent, usually well-tolerated complication of treatment with anakinra in patients with RA, although in some cases it can be associated with systemic involvement. The most relevant histopathological findings include dermal oedema and a lichenoid, perivascular and periadnexal predominantly lymphomononuclear infiltrate, with many eosinophils and the presence of enlarged CD68+ macrophages. These findings resemble those seen in skin reactions in patients receiving chemotherapy and colony-stimulating factors. We also found an increase in mast cell numbers that could be a specific effect of anakinra.

Rheumatoid arthritis (RA) is an inflammatory disorder characterized by symmetrical, erosive and disabling polyarthritis and a wide array of extra-articular complications. As the disease progresses, irreversible joint damage may lead to loss of function and to deformity.

Although the aetiology of RA is poorly understood, studies both in experimental animal models and in clinical settings suggest a pivotal role for interleukin (IL)-1 in its pathogenesis.^{1–3}

IL-1 promotes inflammation, as well as bone and cartilage resorption, and appears to play a major role in the promotion of rheumatic inflammation.⁴

IL-1 receptor antagonist (IL-1Ra) is an endogenous inhibitor of IL-1⁵ that acts by blocking the binding of IL-1 to type I receptors^{6,7} and thereby prevents IL-1 signalling.⁸ IL-1Ra expression is increased in patients with RA, although it appears insufficient to prevent IL-1 signalling.⁸

Anakinra, a recombinant human form of IL-1Ra that differs only by the addition of an N-terminal methionine, is used to treat patients with active RA. The objective of IL-1Ra-based therapy is to occupy enough receptors with IL-1Ra to block IL-1 cell signalling.⁹ Anakinra arrests joint destruction and improves health-related quality of life in these patients. Nuki *et al.* have recently demonstrated the long-term efficacy and safety of anakinra in RA.¹⁰ Anakinra is administered as a daily subcutaneous injection and in general it is safe and well tolerated. The most frequently encountered adverse effect of anakinra is cutaneous, dose-related and consists of a reaction at the injection site. In a recent study carried out by Cohen *et al.*, 64% and 63% of subjects treated with anakinra 1 mg kg⁻¹ and 2 mg kg⁻¹, respectively, experienced injection site reactions.⁹ We report five patients with cutaneous drug reactions due to anakinra, as well as the results of histopathological and immunohistochemical studies in skin biopsy specimens with the aims of providing a detailed description and of understanding the possible mechanisms involved.

Patients and methods

Between March and July 2002 five women with active RA were referred to the Department of Dermatology of the Hospital de la Santa Creu i Sant Pau for evaluation of cutaneous lesions. All had given their informed consent to be enrolled in a clinical study that included 10 participants, and were being treated with anakinra in association with other antirheumatic drugs. In each case, punch biopsy specimens of skin lesions were obtained. In one patient who could be closely followed and gave informed consent, three consecutive biopsy specimens were obtained from skin lesions that had been

developing for 12, 36 and 72 h. The specimens were fixed in 10% buffered formalin, embedded in paraffin and stained with haematoxylin and eosin and May–Grünwald–Giemsa. Immunohistochemical studies were performed using the avidin–biotin–peroxidase complex technique and monoclonal antibodies (mAbs) against leucocyte common antigen (Dako, Glostrup, Denmark; mouse mAb, 1 : 300), CD68 (Dako; mouse mAb, 1 : 20), CD3 (Dako; rabbit mAb, 1 : 20), CD45RO (Dako; mouse mAb, 1 : 700), CD20 (Dako; mouse mAb, 1 : 200) and CD45RA (Dako; mouse mAb, 1 : 200).

An additional biopsy specimen from an abdominal lesion of one of our patients was submitted for direct immunofluorescence studies. In one case bacterial and mycobacterial cultures of skin biopsy specimens were performed.

Results

Clinical data

Clinical data are summarized in Table 1. Skin adverse reactions due to anakinra were seen in five of 10 patients (50%) included in the study. All patients were women, age range 38–73 years (mean 51.2). All had a history of active RA, which had been diagnosed 2–35 years before, were being monitored at the Department of Rheumatology of the Hospital de la Santa Creu i Sant Pau, and had been included in a clinical trial of anakinra. All patients were treated with anakinra in combination with a disease-modifying antirheumatic drug (methotrexate or salazopyrin), corticosteroids and/or nonsteroidal anti-inflammatory drugs, antacids or folic acid supplements, which had been prescribed previously and had not been modified in the 3 months prior to enrolment in the study. No

Table 1 Clinical findings

Patient no./age (years)	Appearance of lesions (days)	Medical history	Other medications	Sites of lesions	Response to treatment and follow-up
1/53	14	RA Hallux valgus surgery L-5 vertebral fracture	MTX, NSAIDs Ranitidine Folic acid	Abdomen	Good response Stopped AK due to skin reaction
2/73	16	RA Hypothyroidism Bone fracture right foot	MTX, PDN Calcium Folic acid	Arms Abdomen Thighs	No response Stopped AK due to lack of response
3/38	12	RA Sjögren's syndrome Hydatid cyst surgery Hallux valgus surgery	MTX, NSAIDs Folic acid Omeprazole	Abdomen Thighs	Good response Stopped AK due to skin reaction with eventual systemic involvement
4/51	13	RA Popliteal thrombosis Haemorrhoids and anaemia Foot lipoma surgery	MTX, NSAIDs Prednisolone Ranitidine Folic acid	Abdomen Thighs	Moderate response Continued with AK until the end of the study. Occasional skin lesions, well tolerated
5/41	8	RA Nephrolithiasis Right knee synovectomy Right femur, left knee and right shoulder prostheses	Salazopyrin PDN NSAIDs Omeprazole Estradiol	Arms Abdomen Thighs	Good response Continued AK until the end of the study. Frequent skin lesions, well tolerated

RA, rheumatoid arthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; MTX, methotrexate; PDN, prednisone; AK, anakinra.

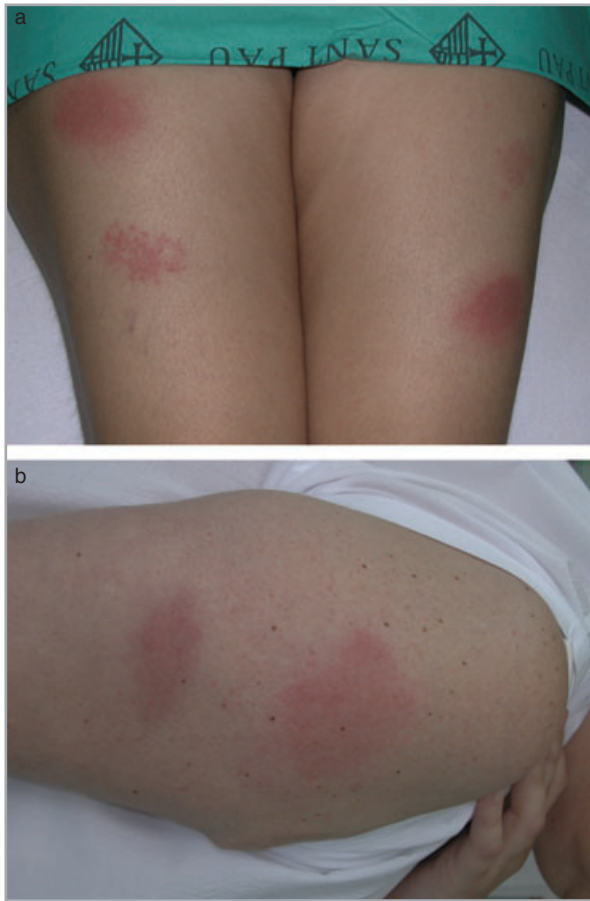


Fig 1. (a,b) Clinical appearance of cutaneous lesions.

other treatments were introduced in the course of the study. Anakinra 100 mg was self-administered daily by the subcutaneous route with rotation of the puncture sites and had been recently introduced in all subjects. The patients were referred to the Department of Dermatology when inflammatory lesions appeared at the anakinra injection sites. There was no history of atopy in any patient.

Physical examination revealed well-demarcated, erythematous, oedematous, painful and itching plaques on the arms, abdomen and thighs (Fig. 1). They appeared between the 8th and 16th day after the beginning of treatment. Clinically, they were considered to be a drug eruption secondary to anakinra administration and in each case therapy with antihistamines and topical corticosteroids was initiated. Anakinra was completely stopped in patient 1, and temporarily stopped in patients 3 and 5; in these two patients the drug was reintroduced 3 and 5 days after the skin lesions resolved, in 5 and 7 days, respectively. In patient 3, 2 weeks after the drug was reintroduced the patient developed a severe reaction consisting of abdominal pain, dyspnoea, facial and abdominal erythema with pruritus 3 h after injection of anakinra, that required treatment with intramuscular methylprednisolone and antihistamines. Treatment with anakinra was completely stopped after this adverse event. In patient 5, immediately after

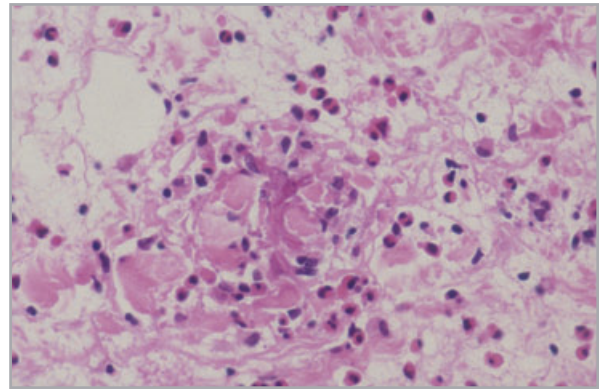


Fig 2. Prominent eosinophilic infiltrate and flame figures (patient 1).

anakinra was reintroduced new plaques appeared but they were well tolerated and resolved in 48 h with oral antihistamines and topical corticosteroids. The patient continued receiving the medication until the end of the study with continuing well-tolerated and minor skin reactions at the sites of injection and experienced an improvement in the activity of her RA. Patients 2 and 4 completed the period of study and did not require discontinuation of anakinra despite the occasional reappearance of the drug eruption, which was well tolerated and did not require any treatment.

Histopathological, immunohistochemical and direct immunofluorescence findings and microbiological culture data

Table 2 summarizes the histopathological findings in skin biopsy specimens. Dermal changes were the most evident abnormality (Figs 2–4). Although in patient 1 the subcutaneous tissue was severely involved, in biopsy specimens from two other patients the involvement was mild and the subcutaneous tissue was not involved. All biopsy specimens exhibited marked dermal oedema that was prominent in the papillary dermis in three patients. Epidermal changes varied slightly between patients. A lichenoid pattern was observed in all patients. The lichenoid changes consisted of a lymphomononuclear infiltrate at the dermoepidermal junction, basal vacuolization and rare necrotic keratinocytes. These were moderate in biopsy specimens from three patients and were less evident in two (only in the second biopsy specimen of patient 2 was lichenoid damage practically absent). All biopsy specimens presented some epidermal spongiosis, which was moderate in intensity only in patient 3. Eosinophilic spongiosis was observed in two biopsy specimens. All specimens showed hyperkeratosis in a basket-weave pattern and in three of them there was slight epidermal hyperplasia. Within the dermis, a moderately dense superficial and deep perivascular and periadnexal lymphoid infiltrate was present in all biopsy specimens. Lymphocytes were also present interstitially in small to moderate numbers. Exocytosis of lymphocytes was more evident within the adnexal epithelium than within the

Table 2 Histopathological findings

Patient	Lichenoid pattern	Spongiotic pattern	Lymphomononuclear infiltrate	PMN, eosinophils, mast cells	CD68+ macrophages	Adnexal involvement	Immunohistochemistry	Oedema	Involvement of hypodermis
1	+	+	Diffuse + Perivascular ++	PMN 0 Eo +++ Mast cells +	+++ (atypical ++)	++/hair follicle, sweat glands	90% T (CD3++, UCHL-1++). 10% B (CD20+, CD45RA+/-)	DD ++/+ UD ++/+++	+++
2	++	++	Diffuse + Perivascular +/++	PMN 0 Eo ++ Mast cells ++	++	+	90% T	DD +/- UD +	+
3	++	+	Diffuse +/- Perivascular +/++	PMN 0 Eo ++ Mast cells ++	++	++/hair follicle	90% T	DD ++ UD ++	+
4	+	+	Diffuse + Perivascular +	PMN + Eo ++ Mast cells ++	++	++/hair follicle, sweat glands	90% T	DD ++ UD ++	0
5, 12 h	++	+	Diffuse + Perivascular ++	PMN 0 Eo ++/+++ Mast cells +	++ (atypical +/-)	++/hair follicle, sweat glands	90% T	DD +/- UD ++	NE
5, 36 h	+/++	Eosinophilic spongiosis	Diffuse ++ Perivascular +/++	PMN +/- Eo ++/+++ Mast cells +	++ (atypical +)	++/sweat glands	90% T	DD 0 UD ++	NE
5, 36 h	+	0	Diffuse + Perivascular +	Mast cells + PMN + Eo +/-	++ (atypical ++)	+/sweat glands	90% T	DD 0 UD ++	0
5, 72 h	0	+	Diffuse + Perivascular ++	Mast cells ++ PMN 0 Eo +/-	++ (atypical ++)	++/sweat glands	90% T	DD + UD ++	NE

Relative intensities graded from 0 to +++; NE, non-evaluable; PMN, polymorphonuclear leucocytes; Eo, eosinophils; UD, upper dermis; DD, deep dermis.

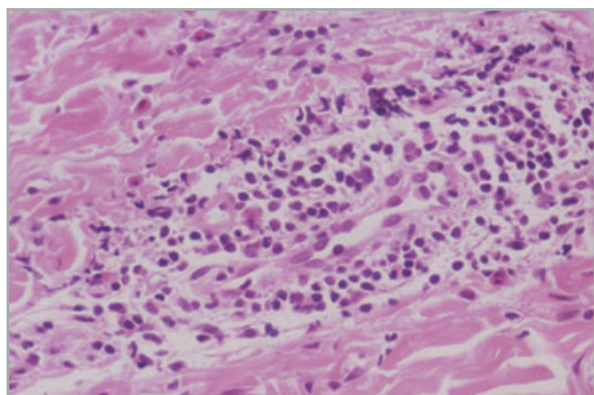


Fig 3. Capillary damage with image of lymphocytic vasculitis.

epidermis. The most striking feature in all biopsy specimens was a prominent eosinophilic infiltration, showing a tendency to concentrate around vessels and surrounding nerve fibres in some cases. In patient 1 'flame figures', which can be attributed to extracellular deposition of major basic protein from eosinophil granules, were seen (Fig. 2). There was a moderate to marked increase in the number of mast cells, many of which were spindle shaped. The population of mast cells was better seen after staining with May–Grünwald–Giemsa. Neutrophils and plasma cells were almost totally absent, except for some dermal capillary vessels that were filled with neutrophils in two patients. In four patients there was evidence of capillary damage, with lymphocytic vasculitis that was more evident in patients 3 and 4 (Fig. 3). All biopsy specimens contained a prominent population of CD68+ enlarged dermal macrophages, some of them grouped around blood vessels (Fig. 4).

Table 3 Consecutive biopsy specimens (patient 5)

	12 h	36 h	72 h	Evolution
Lichenoid pattern	+ / ++	+	–	↓↓
Spongiosis	+	+ / –	+	=
Lymphocytic infiltrate	+ / ++	+ / ++	+ / ++	=
			lymph vessels	
Eosinophils	+++	++ / +++	+ / ++	↓
Mast cells	+	+ / ++	++	↑
Lymphocytic vasculitis	+	+ / ++	–	↓
Macrophages	++	++	++	=
Atypical macrophages	+	++	+++	↑
Oedema	++	++	++	=

Quantitative differences could be seen in the three consecutive biopsy specimens obtained from lesions of known evolution (12, 36 and 72 h) in patient 5 (Table 3). The lichenoid pattern was less evident in the second biopsy specimen and had disappeared in the third. There was a slight decrease in the eosinophilic infiltrate and a parallel increase in the number of mast cells. The density and disposition of the lymphoid infiltrate were the same in the three specimens, and the oedema persisted also with the same intensity. As regards the macrophagic infiltrate, while the number of macrophages was almost constant, there was a marked increase in the proportion of atypical forms in the second biopsy specimen and especially in the third specimen.

In patient 2, direct immunofluorescence study of lesional skin revealed faint deposits of IgM and C3 on some reticular dermal vessels, with perivascular and diffuse deposition of fibrinogen in the reticular dermis.

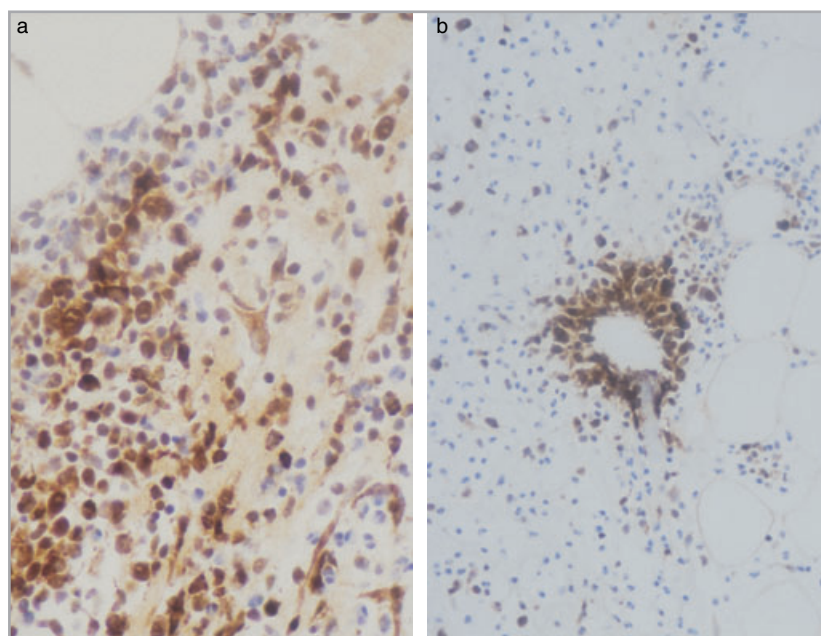


Fig 4. (a,b) Prominent population of enlarged CD68+ dermal macrophages, some of them grouped around blood vessels.

In patient 1, microbiological cultures of cutaneous biopsy specimens yielded negative results for bacteria and mycobacteria.

Discussion

Anakinra, a recently introduced biological therapy for RA, is a recombinant form of human IL-1Ra that is administered at a dose of 100 mg daily as a subcutaneous injection, with a half-life of 6 h. Anakinra, alone or in combination with methotrexate, has been more effective than placebo in randomized, controlled trials involving approximately 900 patients with RA.¹¹ A long-term extension study documented that responses seen in the first 24-week phase of the study were durable: after 48 weeks, 18% of patients treated with anakinra had a 50% improvement in disease activity according to American College of Rheumatology criteria, and 3% had a 70% improvement.¹⁰ Although results of comparative studies between anakinra and infliximab, adalimumab and etanercept are not available, to our knowledge, antitumour necrosis factor (TNF) drugs seem to be more effective than anakinra in RA. Anakinra is considered useful in patients who have no response to or are unable to tolerate methotrexate, leflunomide or TNF antagonists.¹¹ In our experience, RA activity did not improve in every patient, but in some the response to treatment was excellent, so anakinra should be considered as a second-line drug in the therapeutic arsenal for RA in some patients.¹²

Despite being generally well tolerated, the most frequent adverse effect of anakinra is dose-dependent skin irritation at the injection site, which has been reported to occur in 50–80% of patients, requiring withdrawal of the drug in approximately 5% of cases,¹³ but this appears to be less frequent in clinical use than observed in clinical trials.¹⁴ Most reactions appear to be mild. A small number of patients reported more severe allergic-type reactions involving itching, swelling and pain.¹¹ The lesions first appeared during the first month of treatment;^{13,15} according to Fleischmann *et al.*, if no such reaction is seen by this time then it is unlikely to occur.¹⁵ Injection site reactions represent the main reason for treatment withdrawal.¹⁶

In our series, three patients developed mild to moderate and well-tolerated reactions; cutaneous lesions presented as erythematous, oedematous, warm and pruritic plaques of 3–5 cm in diameter, located at the injection sites (arms, thighs and abdomen). They appeared between the 8th and 16th day of treatment. Initial flares were more severe and were treated with application of cool packs, oral antihistamines and topical corticosteroids, with symptomatic improvement.

The reaction was intense in two patients: a woman who developed abdominal plaques 20 cm in diameter, and another who also presented abdominal pain, dyspnoea, facial and abdominal erythema and pruritus. In both patients the adverse reaction led to complete withdrawal of anakinra treatment.

Other biological drugs which are administered subcutaneously for treatment of RA, e.g. etanercept or adalimumab, also

produce injection site reactions. Minor redness and itching at the injection site, lasting a few days, are common among patients who receive these TNF antagonists.¹¹ Etanercept is a soluble TNF-receptor fusion protein that binds to both TNF- α and TNF- β , preventing each from interacting with its respective receptors. In a study group of 234 patients treated twice weekly with subcutaneous injections of etanercept 10 or 25 mg or placebo for 6 months, 49% of patients receiving etanercept 25 mg developed injection site reactions. Most patients who experienced injection site reactions had reactions to five or fewer of the approximately 52 injections given during the study, and the median duration was 3 days. The rate was highest in the first month of treatment. Only one patient discontinued therapy because of cutaneous lesions.¹⁷ Although anakinra and etanercept act differently, the most common adverse event associated with the administration of both is a similar injection site skin reaction. Results of comparative studies between anakinra and etanercept have not been published, if done at all. According to several studies cutaneous reactions due to etanercept are less frequent, seem to be slight, and the number of withdrawals due to skin lesions is smaller. That could be explained because both drugs have a different mechanism of action, and although the route of administration is the same, etanercept is administered twice weekly and anakinra daily.

As far as we know, this is the first time that a histopathological study of anakinra adverse cutaneous reactions has been reported. The main features are a lichenoid pattern, epidermal spongiosis and basket-weave hyperkeratosis. Within the dermis, the most striking feature is a prominent eosinophilic infiltrate, showing a tendency to concentrate around vessels and surrounding nerve fibres. Other histopathological features seen in all patients were marked dermal oedema, a moderately dense superficial and deep perivascular and periadnexal lymphoid infiltrate, exocytosis of lymphocytes within the adnexal epithelium, lymphocytic vasculitis, an increase in the number of mast cells, many of them being spindle shaped, and a prominent population of CD68+ enlarged dermal macrophages, some of them grouped around blood vessels.

We have not found any report in the literature on the histopathological findings of cutaneous reactions related to anakinra, but they bear some resemblance to the skin findings in patients receiving recombinant granulocyte and granulocyte-macrophage colony-stimulating factors. The dermal infiltrate in those reactions, which were first described by Horn *et al.*,¹⁸ is characterized by an increase in the number and size of dermal macrophages, with a predominantly perivascular distribution, and variable numbers of eosinophils. This pattern has been confirmed by other authors^{19–21} and has also been observed in patients receiving chemotherapy in the absence of colony-stimulating factors.²² A mild vacuolar interface dermatitis has also been observed in some reports.^{21,22} On the other hand, a prominent eosinophilic infiltrate has been observed in generalized rashes secondary to subcutaneous administration of recombinant granulocyte-macrophage colony-stimulating factor.²³ The clinical morphology in anakinra-associated

eruptions is mainly circumscribed to the injection sites, even though the reaction can become widespread and associated with systemic involvement in severe cases. The presence of large numbers of eosinophils and deposits of their granule proteins (flame figures) in the dermis suggest a role for eosinophils in the pathogenesis of the reactions. Several chemokines important for eosinophil recruitment have been demonstrated to be expressed at sites of allergic inflammation.²⁴ For instance, eotaxin and RANTES are two important chemotactic factors for eosinophils and largely contribute to the movement of eosinophils from the blood to the sites of inflammation.²⁵ Anakinra injection could be related to the expression of chemotactic factors, specific chemokines and their receptors, leading to the migration and degranulation of eosinophils at the injection sites and consequently in the inflammatory lesions, but we lack hard data to discuss this issue in further detail.

The observed increase in mast cell numbers could be related to a specific effect of anakinra on mast cells, different from mast cell degranulation that has been reported to occur in experimental models,²⁶ and which deserves further investigation. Modulatory effects of IL-1Ra on IL-1 production have been observed in mice under experimental conditions following intraperitoneal injection of anakinra,²⁷ but information is scarce on the effect of IL-1Ra on other cytokines in humans. Pharmacological modulation of local production or activity of IL-1 or other suitable cytokines at the high concentrations that can be achieved around the injection site might provide a plausible hypothesis to explain the cutaneous adverse effect we have seen in 50% of our patients.

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