

Case Report

Anakinra-responsive lichen planus in a woman with Erdheim-Chester disease: a therapeutic enigma

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Abstract

Background: Anakinra is a recombinant form of interleukin-1 receptor antagonist. It is the drug of choice for Schnitzler syndrome and cryopyrin-associated periodic syndromes. It has also recently been demonstrated to have activity in the treatment of the non-Langerhans cell histiocytosis known as Erdheim-Chester disease.

Purpose: To describe the activity of anakinra in a patient with co-existing lichen planus and Erdheim-Chester disease.

Methods: A 43-year-old woman with progressive Erdheim-Chester disease presented for management of her night sweats and chills, systemic skeletal bone pain, and neurologic (diabetes insipidus) manifestations. She also had widespread cutaneous lichen planus. Anakinra, 100 mg subcutaneously daily, was initiated for the treatment of her Erdheim-Chester disease.

Results: Within 2 days of starting anakinra, there was prompt resolution of her Erdheim-Chester disease-related symptoms. Subsequently, her bone pain resolved and her diabetes insipidus improved. Also, the lichen planus-associated pruritus rapidly ceased and most of the skin lesions improved.

Conclusions: Our experience confirms the efficacy of anakinra for the treatment of Erdheim-Chester disease. The concomitant improvement of her lichen planus on anakinra suggests that this agent warrants additional study in this disorder.

Key Words: anakinra, Chester, Erdheim, lichen, planus

Introduction

Anakinra is a recombinant form of interleukin-1 receptor antagonist (IL-1Ra), a naturally occurring IL-1 antagonist. Lichen planus is an idiopathic papulosquamous dermatosis that may be refractory to treatment. We describe a woman who has co-existing Erdheim-Chester disease (a form of non-Langerhans cell histiocytosis) and lichen planus, in whom successful management of her Erdheim-Chester disease with anakinra was also associated with progressive improvement of her lichen planus.

Case synopsis

A 43-year-old woman presented in May 2012 with progressive Erdheim-Chester disease. Four years earlier, in May 2008, she had developed diabetes insipidus as the initial manifestation of her disease. Work up with a brain MRI showed pituitary stalk thickening up to 9 mm. She has been maintained on DDAVP (Minirin spray), 1 to 2 intranasal sprays twice daily.

Her past medical history was significant for primary autoimmune hypothyroidism diagnosed in 2002; she had been managed with daily levothyroxine (Eltaroxin 100 mg). She also had menstrual irregularity; her cycles were successfully regulated with a progesterone supplement: progylutron 1 tablet daily. In August 2009, she was diagnosed with growth hormone deficiency and received daily subcutaneous replacement (norditropin, 3 clicks on the pen). She also had a history of vitamin D deficiency and is on oral vitamin D supplementation with calcium.

Also in May 2008, she developed lichen planus. Pruritic papules originally presented on her flexor arms. The lesions became more generalized and responded to topical treatment with a mid potency corticosteroid cream (mometasone furoate 0.1% cream). Approximately one year previously, the lesions recurred and again responded to the same topical therapy.

A PET scan in May 2010 was negative for distant involvement of Erdheim-Chester disease. However, in March 2012, she developed night sweats, chills, and lower extremity pain. Roentgenograms of her hips and femur showed mixed lytic and sclerotic lesions, consistent with Erdheim-Chester disease; there were no xanthelasmas.

PET/CT scans in May 2012 showed areas of FDG activity in the distal femur, proximal tibia, and distal tibia, bilaterally; she also had bilateral activity in the maxillary sinuses. A bone marrow biopsy from the right proximal tibia showed sclerotic bone with thickened intramedullary trabeculae and stromal fibrosis; immunohistochemical stains showed S100 negative, CD1a positive, and CD68 positive cells. Correlation of the radiographic presentation and the overall cytoarchitectural features, as well as the pathology review, confirmed the diagnosis of Erdheim-Chester disease.

In March 2012, she also developed a widespread flare of her lichen planus skin lesions. Although they were unresponsive to mometasone furoate 0.1% cream, they showed some flattening with temovate 0.05% cream. However, she discontinued the latter medication after developing a diffuse acneiform eruption at sites of application. Cutaneous examination in May 2012 not only showed an acneiform eruption on the upper back and shoulders, but also pruritic pink 1-2 mm flat-topped papules extending from her mid to lower back (Figures 1 and 2). These papules were also located on her ventral wrists, knees, and ankles.



Figure 1. Distant view of the back of a 43-year-old woman with Erdheim-Chester disease. The upper central back and right scapula region shows an acneiform erythematous pustular eruption. Lichen planus, presenting as diffusely distributed itchy red papules, extends across the mid back to the lower back.



Figure 2 (a and b). Close (a) and closer (b) views of the hundreds of widespread pruritic, erythematous, flat-topped individual and confluent papules of biopsy-confirmed lichen planus on the mid back to the lower back of a woman with Erdheim-Chester disease. There are only focal sparse areas of normal skin between the papules. The ink circle shows the lesion that was biopsied.

Lesional skin biopsies from the right distal flexor arm and the upper mid back both revealed vacuolar alteration of basal keratinocytes, increased intraepidermal dyskeratotic keratinocytes, and colloid bodies along the dermal-epidermal junction and within the superficial dermis. There was a band-like, predominantly lymphocytic inflammatory infiltrate in the upper dermis with admixed melanophages and a few scattered histiocytes. The overlying epidermis was acanthotic and showed hypergranulosis with hyperkeratosis and spongiosis. Correlation of the clinical presentation and pathology confirmed the diagnosis of lichen planus; hepatitis A, B, and C serologies were all negative.

Treatment for her Erdheim-Chester disease was initiated with subcutaneously administered anakinra, 100 mg per day. Oral prednisone was considered for managing her lichen planus. However, in order to be able to evaluate the response of her Erdheim-Chester disease to anakinra alone, the patient was not started on oral corticosteroids. Because of her topical corticosteroid-associated acneiform eruption, the patient declined using topical corticosteroids on her lichen planus skin lesions.

Within two days after starting anakinra, both her Erdheim-Chester disease-associated symptoms (of night sweats, chills, and leg pain) and lichen planus-related pruritus resolved. Also, without any topical corticosteroids, many of the lichen planus lesions on her back began to flatten and eventually resolved. However, shortly after starting treatment with anakinra, she developed local skin reactions at the injection sites: pruritic and erythematous dermal plaques. The injection site reaction resolved and did not recur once she began 5 mg of levocetirizine, an oral antihistamine, each day.

Follow up examination after three months of daily anakinra showed that she was feeling much better. Her bone pain had resolved and her need for DDVAP (to treat her diabetes insipidus) had decreased. In addition, many of the lichen planus lesions on her back had either resolved or flattened (Figure 3). Levocetirizine administration eliminated the injection site reactions. She has returned to her home in the Middle East and shall be maintained on subcutaneous anakinra treatment.



Figure 3 (a and b). Close (a) and closer (b) views of the back after the woman with Erdheim-Chester disease received 100 mg daily of subcutaneous administered anakinra for 3 months. There is a dramatic decrease in the number of lichen planus papules and the normal-appearing skin between the residual papules is increased. Erythematous macules are now observed in several of the areas where prior lichen planus papules have completely resolved. The papules that remain are much flatter.

Discussion

Lichen planus is a papulosquamous, chronic and remitting, inflammatory condition of unknown etiology. Lesions are classically pruritic, purple, polygonal plaques. However, the clinical presentation is variable and the disease may involve the skin or the mucosa or both. The condition has been associated with medications (such as anti-inflammatory drugs, antimalarials, beta blockers, and gold) and several other diseases (such as alopecia areata, dermatomyositis, discoid lupus erythematosus, hepatitis C virus infection, lichen sclerosis et atrophicus, morphea, myasthenia gravis, primary biliary cirrhosis, ulcerative colitis, and vitiligo) [1-4].

The pathogenesis of lichen planus may be multifactorial; the hypothesized mechanisms of immunopathogenesis include antigen-specific cell-mediated immune response, non-specific mechanisms, autoimmune response, and humoral immunity. Both activated

CD4+ helper T-lymphocytes and CD8+ cytotoxic T-lymphocytes are recruited to the dermal-epidermal junction and are present in the lichenoid infiltrate of lichen planus lesions. However, the latter cell type predominates in the dermal inflammation of mature lesions. The activated T-lymphocytes induce basal keratinocyte apoptosis as a result of up regulation of the T-helper-I (Th-I) arm of cell-mediated immunity. Several mediators may be involved in this process, including apoptosis-related molecules (such as Bcl-2 and Fas/Apo-I), CXCL10 (a cytokine induced by interferon gamma), interferon-gamma, nuclear factor-kappa B-dependent cytokines (such as interleukin-I alpha, interleukin-6, and interleukin-8), and tumor necrosis factor-alpha [4-7].

Lichen planus may resolve spontaneously. However, in some patients it is chronic. Initial treatments include topical, intralesional, or systemic corticosteroids. Several other alternative, of varying efficacy, have been used in patients with refractory or recurrent disease: biologics (alefacept, basiliximab, efalizumab), cyclosporine, griseofulvin, low molecular weight heparin (enoxaparin sodium), metronidazole, phototherapy (narrow and non-narrow band ultraviolet B, psoralen and ultraviolet A), retinoids (acitretin), sulfasalazine, tetracycline, and thalidomide [1-4].

Erdheim-Chester disease is an idiopathic, progressive, non-Langerhans cell histiocytosis with a highly variable clinical course, ranging from asymptomatic bony disease to life-threatening multisystemic involvement. The most common systemic manifestations include cardiovascular (affecting the aorta and pericardium), neurological (diabetes insipidus and gait ataxia), ophthalmologic (proptosis), pulmonary (cough and dyspnea), retroperitoneal (histiocytic infiltration of adipose tissue with secondary organ involvement such as renal failure and ureteric obstruction), and skeletal (knee and leg pain) involvement [8-12]. In addition, cutaneous manifestations of Erdheim-Chester disease may include upper and lower eyelid plaques (xanthelasma) that are often located near the medial canthi [9,13-15]. Less commonly, papulonodular lesions or vulva and clitoris infiltration have been observed [14,16,17]. Lichen planus is not known to be associated with Erdheim-Chester disease.

Radiologic and pathologic observations confirm the diagnosis of Erdheim-Chester disease. Roentgenograms of the long bones of the upper and lower extremities show diffuse sclerosis (with trabecular coarsening and cortical thickening) throughout the long bones. Biopsy of affected tissue, including skin, shows an infiltrate of CD68-positive lipid-laden histiocytes with foamy or eosinophilic cytoplasm that expresses neither S-100 protein nor CD1a—except in those patients who have possible overlap or simultaneous appearance of Erdheim-Chester disease and Langerhans cell histiocytosis; in addition, electron microscopic evaluation does not show Birbeck granules in the cytoplasm [8-10].

The pathogenesis of Erdheim-Chester disease is unknown. Recent investigation has demonstrated that an underlying systemic immune Th-1-oriented perturbation is associated with Erdheim-Chester disease, as evidenced by the activation of several cytokines in these patients, including interferon alpha, interleukin-1/interleukin-1-receptor antagonist, interleukin 6, interleukin 12, and MCP-1 [9,18]. Therefore, whether Erdheim-Chester disease is a neoplastic disorder or a reactive condition that behaves in a malignant manner remains to be determined [10,19].

Several therapeutic interventions have been described for patients with Erdheim-Chester disease. Interferon alpha is one of the best-studied medications [9,12,13]. However, other treatments, of variable efficacy, include anthracyclines, 2-chlorodeoxyadenosine (cladribine), corticosteroids, infliximab, imatinib, and vinca alkaloids [10,20,21]. More recently, targeted therapy with vemurafenib has been initiated for patients whose disease demonstrated a *BRAF V600E* mutation [14,22]. Anakinra has been advocated in patients with recurrence, intolerance, incomplete response to interferon alpha [15,23], or multiple recurrences following systemic corticosteroids and tretinoin [24].

Anakinra competitively inhibits the inflammatory effects of interleukin-I (IL-I) [25,26]. It is the first-line therapy for Schnitzler syndrome: a chronic, eventually pruritic, often neutrophilic, urticarial dermatosis associated with recurrent fever, relapsing arthralgias, bone pain and myalgias, lymphadenopathy, organomegaly, and a monoclonal immunoglobulin M (IgM) gammopathy which may progress to a hematologic malignancy [27,28]. Indeed, it is also a drug of choice for the treatment of cryopyrin-associated periodic syndromes (CAPS) with dermatologic involvement owing to mutation in the NALP3 gene, chronic infantile neurological cutaneous and articular (CINCA) syndrome (also known as neonatal-onset multisystem inflammatory disease), familial cold autoinflammatory syndrome, familial cold urticarial, and Muckle-Wells syndrome [29,30]. In addition, anakinra is useful for the management of patients with adult-onset Still disease, familial Mediterranean fever, rheumatoid arthritis, and systemic juvenile arthritis [25,26,31-33]. More recently, anakinra has also been successfully used to treat patients with neutrophilic dermatoses such as neutrophilic panniculitis, pustular psoriasis, pyoderma gangrenosum, and Sweet syndrome [33,34].

Including our patient, subcutaneous treatment with anakinra has been described in five patients with Erdheim-Chester disease: 4 women (10 to 46 years old, median = 38 years) and a 55-year-old man. The patients received 100 mg per day (and the daily dose ranged from from 1.06 mg/kg/d to 2.0 mg/kg/d, median = 1.5 mg/kg/d). Within a few days of starting treatment, the patient's

constitutional symptoms, including fever and bone pain, improved and progressively resolved. Also, the erythrocyte sedimentation rate and C reactive protein levels returned to normal range [15,23,24].

Two of the anakinra-treated patients also had complete or partial regression of their retroperitoneal fibrosis [15]. A 46-year-old woman had complete resolution of her eyelid xanthelasma and regression of her periureteral infiltration and hydronephrosis after 3 months; yet, her leg bone roentgenograms remained unaltered. Similarly, there was improvement in the urologic involvement in the 55-year-old man and he was eventually able to remove a left ureteral stent. However, his bone films and periaortic disease-associated infiltrate remained unchanged after 8 and 11 months, respectively.

In contrast, a 10-year-old girl [23] and a 32-year-old woman [24] had no significant change in their retroperitoneal infiltration after 7 and 12 months of therapy, respectively. Although the girl gained 8 kg and grew 6 cm during the first 10 months of treatment, her bone lesions remained unchanged [23]. However, the woman showed a very good response of her skeletal involvement of her right tibia and femoral diaphysis after one year of treatment, with lower and smaller areas of hypermetabolism images on PET-CT [24].

Side effects from the anakinra were minimal. The 46-year-old woman had intermittent diffuse pruritus, but no skin lesions or rashes [15]. The other four patients, including our patient, had local skin reactions at the injection sites; these included redness and tenderness [15,23,24,35]. Our patient's pruritic and erythematous skin reaction to anakinra resolved and did not recur once she began daily therapy with 5 mg of levocetirizine.

After the initiation of anakinra therapy, our patient also had symptomatic improvement. After 3 months of treatment, objective improvement, reflected by a decreased need of DDVAP, was observed. She was continued on anakinra therapy.

Our patient is unique. The onset of her lichen planus coincided with the initial presentation of her Erdheim-Chester disease. In addition, after initiating anakinra for the management of her Erdheim-Chester disease, there was also improvement of our patient's lichen planus. The clinical response of lichen planus to therapy with anakinra is especially intriguing because the mechanism of action of this agent and the pathogenesis of lichen planus appear to be discordant. However, earlier studies have demonstrated increased IL-1 in the saliva of patients with oral lichen planus and more recent investigations show increased nuclear factor-kappa B-dependent cytokines, including IL-1 alpha, which is inhibited by anakinra [36,37]. Thus anakinra may have its therapeutic impact at a more distal point on the pathogenesis pathway of lichen planus, by preventing apoptosis of basal keratinocytes.

Conclusion

Erdheim-Chester disease is a non-Langerhans cell histiocytosis that may be associated with multiple systemic manifestations. Recently, several efficacious interventions, including anakinra, have been identified for this condition. We had the opportunity to treat a woman with Erdheim-Chester disease who coincidentally also had widespread, biopsy-confirmed, cutaneous lichen planus. Within a few days after initiating treatment with anakinra (100 mg daily), there was prompt resolution of both her Erdheim-Chester disease-associated and lichen planus-related symptoms. In addition, her bone pain was attenuated and her need for DDVAP decreased. Finally, most of her lichen planus skin lesions gradually resolved. Anakinra merits further exploration in both lichen planus and Erdheim-Chester disease.

References

1. Le Cleach L, Chosidow O: Clinical practice. Lichen planus. *N Engl J Med* 2012;366:723-732. [PMID: 22356325]
2. Sharma A, Bialynicki-Birula R, Schwartz RA, Janniger CK: Lichen planus: an update and review. *Cutis* 2012;90:17-23. [PMID: 22908728]
3. Asch S, Goldernberg G: Systemic treatment of cutaneous lichen planus: an update. *Cutis* 2011;87:129-134. [PMID: 21488570]
4. Lehman JS, Tollefson MM, Gibson LE: Lichen planus. *Int J Dermatol* 2009;48:682-694. [PMID: 19570072]
5. Parashar P: Oral lichen planus. *Otolaryngol Clin N Am* 2011;44:89-107. [PMID: 21093625]
6. Roopashree MR, Goodhalekar RV, Shashikanth MC, George J, Thippesway SH, Shukla A: Pathogenesis of oral lichen planus—a review. *J Oral Pathol Med* 2010;39:729-734. [PMID: 20923445]
7. Srinivas K, Aravinda K, Ratnakar P, Nigam N, Gupta S: Oral lichen planus—review on etiopathogenesis. *Natl J Maxillofac Surg* 2011;2:15-16. [PMID: 22442603]
8. Andrysek K: Erdheim-Chester disease. A case study and literature review. *Dimens Crit Care Nurs* 2011;30:184-189. [PMID: 21654219]
9. Haroche J, Arnaud L, Amoura Z: Erdheim-Chester disease. *Curr Opin Rheumatol* 2012;24:53-59. [PMID: 22089098]

10. Wilejto M, Ablá O: Langerhans cell histiocytosis and Erdheim-Chester disease. *Curr Opin Rheumatol* 2012;24:90-96. [PMID: 22157416]
11. Sedrak P, Ketonen L, Hou P, Guha-Thakurta N, Williams MD, Kurzrock R, Debnam JM: Erdheim-Chester disease of the central nervous system: new manifestations of a rare disease. *AJNR Am J Neuroradiol* 2011;32:2126-2131. [PMID: 21960492]
12. Esmaeli B, Ahmadi A, Tang R, Schiffman J, Kurzrock R: Interferon therapy for orbital infiltration secondary to Erdheim-Chester disease. *Am J Ophthalmol* 2001;132:945-947. [PMID: 11730673]
13. Braiteh F, Boxrud C, Esmaeli B, Kurzrock R: Successful treatment of Erdheim-Chester disease, a non-Langerhans-cell histiocytosis, with interferon-alpha. *Blood* 2005;106:2992-2994. [PMID: 16020507]
14. Haroche J, Cohen-Aubart F, Emile J-F, Arnaud L, Maksud P, Charlotte F, Cluzel P, Drier A, Hervier B, Benameur N, Besnard S, Donadieu J, Amoura Z: Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood* 2013;121:1495-1500. [PMID: 23258922]
15. Aouba A, Georgin-Lavialle S, Pagnoux C, Martin Silva N, Renand A, Galateau-Salle F, Le Toquin S, Bensadoun H, Larousserie F, Silvera S, Provost N, Candon S, Seror R, de Menthon M, Hermine O, Guillevin L, Bienvu B: Rationale and efficacy of interleukin-1 targeting in Erdheim-Chester disease. *Blood* 2010;116:4070-4076. [PMID: 20724540]
16. Opie KM, Kaye J, Vinciullo C: Erdheim-Chester disease. *Australas J Dermatol* 2003;44:194-198. [PMID: 12869045]
17. Chester W: Uber lipoidgranulomatose. *Virchows Arch Pathol Anat* 1930;279:561-602. [PMID: Not Indexed]
18. Arnaud L, Gorochov G, Charlotte F, Lvovschi V, Parizot C, Larsen M, Ghillani-Dalbin P, Hervier B, Kahn J-E, Deback C, Musset L, Amoura Z, Haroche J: Systemic perturbation of cytokine and chemokine networks in Erdheim-Chester disease: a single-center series of 37 patients. *Blood* 2011;117:2783-2790. [PMID: 21205927]
19. Mazor RD, Kesler A, Shoenfeld Y: Erdheim-Chester disease: an orphan condition seeking treatment. *Israeli Med Assoc J* 2012;14:388-389. [PMID: 22891403]
20. Dagna L, Corti A, Langheim S, Guglielmi B, De Cobelli F, Doglioni C, Fragasso G, Sabbadini MG, Ferrarini M: Tumor necrosis factor alpha as a master regulator of inflammation in Erdheim-Chester disease: rationale for the treatment of patients with infliximab. *J Clin Oncol* 2012;30:e286-e290. [PMID: 22869874]
21. Janku F, Amin HM, Yang D, Garrido-Laguna I, Trent JC, Kurzrock R: Response of histiocytoses to imatinib mesylate: fire to ashes. *J Clin Oncol* 2010;28:e633-e636. [PMID: 20733125]
22. Blombery P, Wong SQ, Lade S, Prince HM: Erdheim-Chester disease harboring the BRAF V600E mutation. *J Clin Oncol* 2012;30:e331-e332. [PMID: 23008323]
23. Tran TA, Pariente D, Lecron JC, Delwail A, Taoufik Y, Meinzer U: Treatment of pediatric Erdheim-Chester disease with interleukin-1-targeting drugs. *Arthritis Rheum* 2011;63:4031-4032. [PMID: 21898344]
24. Aubert O, Aouba A, Deshaves S, Georgin-Lavialle S, Rieu P, Hermine O: Favorable radiological outcome of skeletal Erdheim-Chester disease involvement with anakinra. *Joint Bone Spine* 2013;80:206-207. [PMID: 22999905]
25. Coetkovic RS, Keating G: Anakinra. *Biodrugs* 2002;16:303-311. [PMID: 12196041]
26. Waugh J, Perry CM: Anakinra. A review of its use in the management of rheumatoid arthritis. *Biodrugs* 2005;19:189-202. [PMID: 15984903]
27. Schuster C, Kranke B, Aberer E, Arbab E, Sturm G, Aberer W: Schnitzler syndrome: response to anakinra in two cases and a review of the literature. *Int J Dermatol* 2009;48:1190-1194. [PMID: 20064173]
28. Szturcz P, Adam Z, Hajek R, Mayer J: Successful anakinra therapy in 2 patients with Schnitzler syndrome. *Onkologie* 2011;34:265-268. [PMID: 21577034]
29. Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Bijlsma JW, Dougados M, Emery P, Keystone EC, Klareskog L, Mease PJ: Update consensus statement on biological agents, specifically tumour necrosis factor alpha (TNF alpha) blocking agents and interleukin-1 receptor antagonist (IL-1ra), for the treatment of rheumatic disease, 2005. *Ann Rheum Dis* 2005;64(Suppl 4):iv2-iv14. [PMID: 16239380]
30. Furst DE, Keystone EC, Braun J, Breedveld FC, Burmester GR, De Benedetti F, Dorner T, Emery P, Fleischmann R, Gibofsky A, Kalden JR, Kavanaugh A, Kirkham B, Mease P, Sieper J, Singer NG, Smolen JS, Van Riel PLCM, Weisman MH, Winthrop K: Update consensus statement on biological agents for the treatment of rheumatic diseases, 2011. *Ann Rheum Dis* 2012;71(Suppl 2):i2-i45. [PMID: 22460137]
31. Kotter I, Wacker A, Koch S, Henes J, Richter C, Engel A, Gunaydin I, Kanz L: Anakinra in patients with transient-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. *Semin Arthritis Rheum* 2007;37:189-197. [PMID: 17583775]
32. Meinzer U, Quartier P, Alexandra J-F, Hentgen V, Retornaz F, Kone-Paut I: Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. *Semin Arthritis Rheum* 2011;41:265-271. [PMID: 21277619]
33. Lipsker D, Lenormand C: Indications and modes of use for interleukin (IL)-1 antagonists in inflammatory dermatoses: a new therapeutic approach to immune-mediated inflammatory diseases. *Ann Dermatol Venereol* 2012;139:459-467. [PMID: 22721478]
34. Lipsker D, Perrigouard C, Foubert A, Cribier B: Anakinra for difficult-to-treat neutrophilic panniculitis: IL-1 blockade as a promising treatment option for neutrophil-mediated inflammatory skin disease. *Dermatology* 2010;220:264-267. [PMID: 20197651]

35. Kaiser C, Knight A, Nordstrom D, Pettersson T, Fransson J, Florin-Robertsson E, Pilstrom B: Injection-site reactions upon Kineret (anakinra) administration: experiences and explanations. *Rheumatol Int* 2012;32:295-299. [PMID: 21881988]
36. Rhodus NL, Cheng B, Myers S, Bowles W, Ho V, Ondrey F: A comparison of the pro-inflammatory, NF-kB-dependent cytokines: TNF-alpha, IL-1-alpha, IL-6, and IL-8 in different oral fluids from oral lichen planus patients. *Clin Immunol* 2005;114:278-283. [PMID: 15721838]
37. Ge Y, Xu Y, Sun W, Man Z, Zhu L, Xia X, Zhao L, Zhao Y, Wang X: The molecular mechanisms of the effect of dexamethasone and cyclosporine A on TLRA/NF-kB signaling pathway activation in oral lichen planus. *Gene* 2012;508:157-164. [PMID: 22903029]