Low-Dose Interferon Alfa-2b for the Treatment of Churg-Strauss Syndrome With Prominent Skin Involvement

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REPORT OF A CASE

A 68-year-old man presented with a medical history of recurrent bronchial asthma and sinusitis maxillaris. He had a severe bronchial infection that was treated with a combination product of sulfamethoxazole and trimethoprim and subsequently with cefadroxil in combination with low-dose (20 mg/d of prednisolone) therapy for treatment of the asthma. Three weeks after discontinuation of antibiotic therapy but continuation of use of prednisolone, 20 mg/d, he developed severe bronchial asthma, sinusitis, systemic hypereosinophilia, and characteristic granulomatous skin lesions on the upper half of the back, in the axilla and inguinal region, rapidly expanding within days (Figure 1A). Skin lesions consisted of sharply marginated, erythematous plaques of dull red with a central clearing and a centrifugal spread (Figure 1A). The patient reported occasional mild pruritus. The presumptive diagnosis of Churg-Strauss syndrome (CSS) was confirmed by histological examination of lesional skin, showing a massive inflammatory infiltrate composed of numerous eosinophils and lymphocytes reaching from the midcorium to the lower margin of the biopsy specimen (Figure 2A). Pulmonary examination revealed an obstructive and restrictive respiratory disease, as shown by chest x-ray examination, body plethysmography with a forced expiratory volume in 1 second of only 50% (1.18 L), and bronchial lavage, containing 81% eosinophils. Leukocyte and eosinophil counts and serum levels of interleukin 5 (IL-5) and eosinophilic cationic protein (ECP) were elevated (Figure 3A-B).

THERAPEUTIC CHALLENGE

The therapeutic efficacy of interferon alfa for hypereosinophilic syndromes prompted us to evaluate the potential benefit of low-dose interferon alfa-2b treatment of this patient with CSS with prominent skin involvement.

SOLUTION

At day 12, after informed consent, systemic treatment with interferon alfa-2b was started by subcutaneous injection of 3 x 10^6 IU of interferon alfa-2a (Roferon-A) 3 times per week (Roche Pharmaceuticals, Basel, Switzerland). During the interferon alfa therapy, the oral low-dose corticosteroid therapy was continued with 20 mg/d of prednisolone. During the first injections, the patient reported flulike effects, which disappeared after the first week of treatment. Within 2 months of therapy, the skin lesions resolved completely (Figure 1B), and the leukocyte and eosinophil counts, as well as ECP and IL-5 serum levels, returned to normal levels (Figures 3A-B). Histological examination 14 days after onset of therapy showed a markedly reduced eosinophilic...
infiltration and the invasion of activated tissue macrophages (Figure 2B-C). Moreover, the pulmonary function improved to a forced expiratory volume in 1 second of 83% (2.75 L), and the results of the chest x-ray examination were normal (data not shown). Eighty days after onset and continuation of the interferon alfa therapy at 9 × 10^6 IU per week in combination with 20 mg/d of prednisolone, the patient has remained disease free.

Churg-Strauss syndrome is a rare allergic granulomatous disease that often develops in association with late-onset asthma. It was first described in 1951 as a necrotizing, hypereosinophilic vasculitis.1 In 1990, the American College of Rheumatology proposed 6 criteria for the diagnosis of this disease, with 4 being necessary for CSS to be diagnosed, including asthma, eosinophilia greater than 10%, paranasal sinusitis, pulmonary infiltration, histological proof of vasculitis, and mononeuritis multiplex.2 Often, CSS involves eosinophilic infiltration at extrapulmonary sites, in our case affecting the skin with characteristic dull red granulomatous plaques. Therapeutic options for CSS include high-dose corticosteroids in combination with other immunosuppressive agents such as cyclophosphamide or cyclosporine.3,4 Nevertheless, a clinical trial of 25 patients with CSS treated with corticosteroids and oral or pulse cyclophosphamide showed that these immunosuppressive therapies have a high risk of toxic effects.4

Churg-Strauss syndrome is considered to be a TH2-mediated disease, which in turn activates eosinophils, which then mediate the tissue damage. Accordingly, decreases in eosinophil counts are accompanied by clinical improvement. Recent publications show that TH2-mediated hypereosinophilic disorders, such as the idiopathic hypereosinophilic syndrome,3 Wells syndrome,5 or eosinophilic pustular folliculitis (Ofuji disease),6 improve after treat-
ment with interferon alfa. Very similar clinical observations have been made for interferon gamma in the treatment of eosinophilic pustular folliculitis (Ofuji disease), presumably by down-regulating IL-5 in peripheral mononuclear cells. Nevertheless, there is in vitro evidence that interferon gamma enhances eosinophil survival and IL-3 production. Furthermore, interferon gamma in contrast to interferon alfa has also been shown to induce rapid liberation of the chemokine RANTES in eosinophils. Moreover, the expression of the interferon alfa receptor has been demonstrated both on eosinophils and T cells, and ligation of the receptor inhibits the expression of eosinophil-activating cytokines on T cells and the release of cytotoxic mediators in eosinophils, such as ECP or neurotoxin. In addition, a clinical study by Tatsis et al showed successful high-dose interferon alfa therapy (up to $3 \times 10^6$ IU per week) for the treatment of 4 patients with severe systemic CSS, who were resistant to glucocorticoids and cyclophosphamide. We therefore decided to use interferon alfa instead of interferon gamma for the treatment of our patient.

Herein, we demonstrate low-dose interferon alfa-2b ($3 \times 10^6$ IU subcutaneously 3 times per week) to be effective in the treatment of skin-associated CSS. This is in part in contrast to the data shown for 2 of the patients described by Tatsis et al, who did not improve after low-dose interferon alfa treatment ($9 \times 10^6$ IU per week). We can only speculate that there is a correlation between the severity of the case, especially which organs are affected or the general condition of the patient, and the interferon alfa dose needed.

In our case, interferon alfa-2b induced a clinical improvement of the disease, correlated with a normalization of both leukocyte and eosinophil counts and IL-5 and ECP serum levels. Churg-Strauss syndrome is thought to result from a proliferation of CD4+ T cells, triggered by inhaled allergens, vaccination, desensitization, drugs, or, as in our case, pulmonary infection. Interleukin 5, which is produced by T helper type 2 lymphocytes, stimulates a massive expansion of eosinophils, which in turn secrete ECP as their cytotoxic effector substance. At present, we can only speculate on the precise mechanism by which interferon alfa-2b improved the disease in our case. However, the close correlation of disease activity and IL-5 levels suggests that interferon alfa down-regulates the activity of IL-5–producing T helper type 2 cells. Indeed, interferon alfa has been demonstrated to counteract T helper type 2–driven immune responses and to favor the preferential activation of T helper type 1 cells. Moreover, Nakajima et al showed interferon alfa to directly inhibit the production of IL-5 by CD4+ T cells, thereby suppressing eosinophil tissue recruitment in a murine model of antigen-specific airway late-phase reaction. The quick resolution of skin lesions by interferon alfa treatment has also been linked to the recruitment of tissue macrophages, as shown by Yoshida et al, and as demonstrated in biopsy specimens from lesional skin taken before and after 14 days of interferon alfa-2b therapy (Figure 2C).

We conclude that low-dose ($3 \times 10^6$ IU 3 times weekly) interferon alfa-2b in our case was an efficient and well-tolerated treatment modality for CSS with prominent skin lesions.