

## Case Report

# Treatment of idiopathic hypereosinophilic syndrome with azelastine hydrochloride and biscoclaurine alkaloids\*

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### ABSTRACT

This is the first report that suggests that azelastine hydrochloride (AZE) and biscoclaurine alkaloids (CEPH; Cepharanthin®; Kaken Shoyaku, Tokyo, Japan) are useful in the treatment of idiopathic hypereosinophilic syndrome (HES). A 9-year-old boy was referred to our hospital because of fever and a cutaneous eruption. Full blood examination showed a normal hemoglobin level and leukocytosis of 66 400 / $\mu$ L with 95% mature eosinophils. There was no history of allergy, no clinical or serological evidence of a parasitic infection and no evidence of a connective tissue disease, neoplastic disease, leukemia or immunodeficiency. The patient was treated with prednisolone, which induced a rapid but not sustained remission. Cepharanthin was then given to reduce the dose of the intermittent courses of prednisolone required. Azelastine HCl, prescribed by an otolaryngologist for perennial rhinitis when the patient was also receiving CEPH, unexpectedly reduced and maintained the eosinophil count at normal levels. Ultimately, AZE alone was tried and was ceased after 3.5 months; however, 5 weeks after discontinuation of AZE therapy, the eosinophil count had risen again to > 25 000 / $\mu$ L. After reinstatement of AZE with CEPH followed by AZE alone, the patient did well for 30 months, so the AZE was ceased. Eleven months later the eosinophil count again increased. Reinstatement of AZE with CEPH in doses proportional to the

weight increase that had occurred in the interim resulted in a complete resolution of symptoms. Azelastine HCl with or without CEPH may be effective in HES patients, enabling the adverse effects of long-lasting steroid therapy to be minimized.

**Key words:** azelastine hydrochloride, biscoclaurine alkaloids, idiopathic hypereosinophilic syndrome.

### INTRODUCTION

Idiopathic hypereosinophilic syndrome (HES) is a disorder characterized by a sustained eosinophilia of at least 6 months duration, multiple organ system infiltration and lack of evidence of known causes of eosinophilia.<sup>1,2</sup> Various modalities have been used to treat HES, including corticosteroids, hydroxyurea, leukopheresis, vincristine, 6-mercaptopurine, cyclosporine, recombinant interferon- $\alpha$ , allogeneic bone marrow transplantation and imatinib.<sup>1-3</sup> The present paper reports the first case of HES that responded well to treatment with the drug azelastine hydrochloride (AZE; Azeptin®; Eisai, Tokyo, Japan) and biscoclaurine alkaloids (CEPH; Cepharanthin®; Kaken Shoyaku, Tokyo, Japan).

### CASE REPORT

#### Clinical summary

A previously healthy 9-year-old Japanese boy was taken to his local physician because of a 4 day history of fever. The fever persisted and a cutaneous eruption associated with pruritus developed 5 days later. The child's initial white blood cell (WBC) count revealed a leukocytosis (18 800 / $\mu$ L) and marked eosinophilia (10 500 / $\mu$ L or 56%). He was referred to Teikyo University Hospital on 25 April 1996. His birth weight was 3250 g and his birth

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and medical history were unremarkable. The family had no pets and there was no history of travel before the onset of the rash. Both parents were healthy. Findings of a physical examination were unremarkable, except for small cervical lymph nodes.

Laboratory data showed the following: hemoglobin 12.0 g/dL; WBC count 66 400 / $\mu$ L with 1% banded neutrophils, 4% lymphocytes and 95% eosinophils (the actual eosinophil count was 63 080 / $\mu$ L); platelet count 270 000 / $\mu$ L; erythrocyte sedimentation rate 66 mm/h; normal leukocyte alkaline phosphatase levels; and no chromosomal abnormalities (Table 1). A bone marrow aspirate was normocellular with 70% mature eosinophils. No abnormal cells were present. Immunoglobulin G, IgA, IgM and IgE levels were all normal. Stool analyses for ova and parasites were negative. Titers for visceral larva migrans were also negative.

On 25 April 1996, oral prednisolone (2 mg/kg per day) was started (Fig. 1). The eosinophil count began to decrease on day 2 and had decreased to 124 / $\mu$ L on

day 6. The steroid was then tapered and discontinued 14 days after its commencement. The patient then did well without any therapy until October 1996, at which time the eosinophil count was found to have risen to > 20 000 / $\mu$ L. Prednisolone (1 mg/kg per day, p.o.) was restarted. The eosinophil count again decreased rapidly and the steroid was tapered and stopped within the next 10 days. This short-course steroid therapy was repeated again 2 months later.

In February 1997, 9.5 months after the treatment was started initially, a fourth episode of worsening of eosinophilia was defined. After parental consent had been obtained, CEPH<sup>4</sup> treatment was started with oral doses of 70 mg (1.5 mg/kg) per day in an attempt to decrease the dose of steroid administered, with the prednisolone being given at a dose of 0.05–0.5 mg/kg per day for 14 days. Because of an increasing eosinophil count and the development of an urticarial rash, this combination therapy was repeated on four occasions at intervals of 1–2 months.

In October 1997, 17.5 months after the patient was first seen, AZE at dose of 1 mg twice daily, p.o., was given by an otolaryngologist because of perennial rhinitis. At this time, the CEPH was still being administered. Azelastine HCl (4-(*p*-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepine-4-yl)-1-(2H)-phthalazine hydrochloride) is an anti-allergic drug that inhibits the release of various chemical mediators from mast cells and it has been used widely in Japan.<sup>5</sup> Surprisingly, 2 weeks after starting AZE, the eosinophil count had decreased from 3038 to 710 / $\mu$ L. Because the patient did well for the next 5 weeks on AZE and CEPH, the CEPH was discontinued. On AZE alone, the eosinophil count remained controlled for the next 2.5 months, so AZE was discontinued in January 1998. Five weeks later, the eosinophil count had risen to > 25 000 / $\mu$ L.

Azelastine HCl with low-dose prednisolone was restarted, with the steroid being tapered and ceased after 14 days. Cepharanthin was restarted in April, because of a slight increase in the eosinophil count while the patient was on AZE as single therapy. The disease was then well controlled for 10 months before the CEPH was again discontinued in January 1999. On AZE alone, the patient did well for next 21 months, so the AZE was ceased. Eleven months later, the eosinophil count had again risen, this time to a level of > 7965 / $\mu$ L. Azelastine HCl with low-dose prednisolone was again restarted, with the steroid tapered and stopped after 14 days. Cepharanthin was also added, because of an increase in the eosinophil

**Table 1** Laboratory data at first visit

White blood cells	66 400 / $\mu$ L
Banded neutrophils	1%
Lymphocytes	4%
Mature eosinophils	95% (63 080 / $\mu$ L)
Hemoglobin	12 g/dL
Platelets	270 000 / $\mu$ L
IgE, IgG, IgA, IgM	Normal
Erythrocyte sedimentation rate	66 mm/h
Serum IL-1 $\beta$	< 15.6 pg/mL
Serum IL-2	< 15.6 pg/mL
Serum IL-4	3.43 pg/mL
Serum IL-5	20.6 pg/mL
Serum IL-10	< 0.50 pg/mL
Bone marrow	
Nucleated cell counts	154 000 / $\mu$ L
Mature eosinophils	70%
No malignant cells	
Leukocyte alkaline phosphatase	Normal
Megakaryocytes	150 / $\mu$ L
Lymphocyte subsets	
CD4	14.5%
CD8	20.5%
OKDR	46.4%
CD24	34.6%
CD38	84.1%
CD11b	1.3%
CD34	3.5%
Chromosome analysis	46XY
Ova and parasites	Negative
Visceral larva migrans	Negative

IL, interleukin.

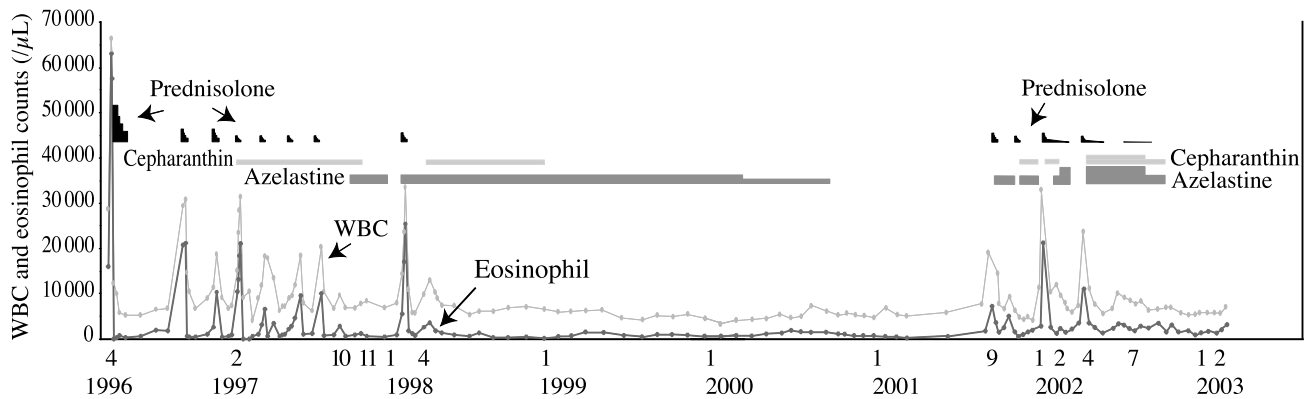


Fig. 1 Clinical course of a 9-year-old boy with idiopathic hypereosinophilic syndrome. WBC, white blood cells.

count. This combination therapy was repeated 2 months later.

In April 2002, after considering the possibility that the lack of response to these drugs may have been due to underdosing because the patient's weight had doubled during the intervening 6 years, the doses were doubled; the AZE dose was increased to 2 mg twice daily and the dose of CEPH to 140 mg/day. After increasing the doses of AZE and CEPH, the disease was well controlled. Azelastine HCl and CEPH were ultimately ceased again in August 2002.

Since then, the patient has been doing well with complete resolution of symptoms.

## DISCUSSION

The criteria for the diagnosis of HES as outlined by Chusid *et al.*<sup>1</sup> are as follows: (i) a persistent eosinophilia of 1500 / $\mu$ L for longer than 6 months; (ii) lack of evidence of any known cause of eosinophilia; and (iii) evidence of organ system involvement. Many diseases are associated with various degrees of eosinophilia.<sup>2</sup> The present patient had no history of allergy, no clinical or serological evidence of a parasitic infection and no evidence of connective tissue disease, neoplastic disease, leukemia or immunodeficiency.

Various therapeutic strategies for HES have been reported. Prednisolone has been the drug of choice if the patient manifests significant symptomatology. In the present patient, the blood eosinophilia was rapidly suppressed by a short course of prednisolone. However, 2–4 months after cessation of the steroid, the eosinophil count increased again. In an attempt to decrease the steroid dose, CEPH treatment was started in February 1997. Cepharanthin is a partially purified alkaloid

preparation of *Stephania cepharantha* Hayata and is mainly composed of six alkaloids.<sup>4</sup> Cepharanthin has been shown to be effective for increasing platelet counts in patients with chronic idiopathic thrombocytopenic purpura and is used as a drug for reducing the steroid dose required.<sup>6</sup> By using CEPH in the present case, it seemed that the dose of the steroid could be decreased, but still steroid therapy could not be discontinued.

The administration of CEPH together with AZE in April 1998 led to a decrease in the slightly elevated eosinophil count and this was maintained while the patient was on AZE single therapy; however, a relapse occurred 11 months after its cessation. In April 2002, the reinstatement and doubling of the doses of CEPH and AZE again led to maintenance of a normal eosinophil count. However, the role of CEPH in achieving this is unclear. No data suggesting the suppressive effect of CEPH on Th2 cells have been reported.

Azelastine HCl, which was given by an otolaryngologist, was unexpectedly effective in the present case. The efficacy of AZE seemed to be apparent for the following reasons: (i) after starting administration of this drug, a normal eosinophil count was maintained for 3.5 months, in contrast with the relapse that occurred in the 1–2 month interval without AZE during the period of therapy with CEPH and prednisolone; (ii) stopping the administration of this drug led to an increase in the eosinophil count; (iii) reinstatement of therapy with AZE plus CEPH, followed by AZE alone, led to a normal eosinophil count that was maintained for the next 29 months; (iv) in April 2002, after reinstatement and doubling of the doses of AZE and CEPH, a normal eosinophil count was maintained again; and (v) in January 2003, reinstatement of therapy with AZE plus CEPH led to a normal eosinophil count.

Interleukin (IL)-5 in humans is restricted to stimulating eosinophil production. In the present case, the serum IL-5 level was high at the time of the first visit and, thereafter, the increased number of eosinophils in the blood correlated high serum IL-5 levels. In March 1988, when the eosinophil count had risen to 5655 / $\mu$ L, the serum IL-5 level was 114 pg/mL. One week later, the eosinophil count rose to > 25 000 / $\mu$ L, probably due to exposure to high levels of IL-5 in the circulation. One week after treatment, the serum IL-5 level was 46 pg/mL. Two weeks later, the eosinophil count went down to 1870 / $\mu$ L and the IL-5 level was < 5 pg/mL. Konno *et al.*<sup>7</sup> have reported that IL-2, IL-3, IL-4 and IL-5 production from blood leukocytes was strongly suppressed when the cells were cultured in the presence of anti-allergic agents, such as AZE, terfenadine, ketotifen, oxatomide and sodium cromoglycate; a significant decrease in blood eosinophil counts was observed after the administration of AZE.<sup>8</sup> Therefore, it is likely that AZE may have suppressed the secretion of eosinophilopoietic cytokines in the present case.

As shown in Table 1, the increased percentage of OKDR-positive lymphocytes in the bone marrow and the high level of serum IL-5 in this patient suggest the presence of activated Th2 cells. The increased number of mature eosinophils exhibiting occasional hypodense phenotypes is suggestive of eosinophil activation. The clonal proliferation of Th2 cells secreting IL-4 and IL-5 may contribute to the eosinophilia in HES,<sup>9,10</sup> although it could be due to an immune reaction triggered by an as yet unknown antigenic stimulus leading to the release of IL-2, IL-3, IL-4 and IL-5 by activated T cells, resulting in stimulation of eosinophilopoiesis.<sup>3</sup>

Analyses of circulating CD25<sup>+</sup> T cells showed that both CD4<sup>+</sup>CD25<sup>+</sup> T cells and CD3<sup>+</sup>CD25<sup>+</sup> T cells were present at 9%; this is consistent with T cell activation, which may, in turn, have induced the eosinophilia. Recently, IL-5-producing T cell subsets have been identified in some patients with HES;<sup>11</sup> however, such abnormal clones were not identified in the present case.

In the present study, no adverse effects were observed during AZE therapy, with or without CEPH. Therefore, AZE with or without CEPH may be useful in preventing eosinophil-induced organ damage and, secondarily, in preventing the side-effects of long-term corticosteroid

therapy, which may otherwise be required. Further studies are necessary to evaluate this novel beneficial effect of AZE with or without CEPH in HES patients. Future trials should also focus on other anti-allergic agents that may inhibit the secretion of eosinophilopoietic cytokines.

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