Successful treatment of hypereosinophilic syndrome with azelastine hydrochloride and Cepharanthin®

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好酸球増多症候群のアゼラスチンとセファランチンによる治療

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好酸球増多症候群（HES）に対してアゼラスチン（AZE）単独、またはAZE、セファランチン（CEPH）併用による治療が有効であった第1例目としての症例を報告する。9才男児が発熱と蕁麻疹にて紹介された。ヘモグロビン値正常、白血球数66,400で95%が成熟好酸球であった。アレルギー性疾患、寄生虫、結合組織病、悪性新生物、白血病、免疫不全症は認められなかった、患児はプレドニソロン治療で急速に寛解した。CEPHおよび低用量ステロイドで6.5か月間治療されたが、最終的にステロイドを中止できなかった。AZEが耳鼻科にて通年性鼻炎として処方されたが、予想外に好酸球数を正常域に減少させた。患児はAZE、CEPH併用、その後AZE単独にて3.5か月治療、それから薬剤を中止した。中止5週間後、好酸球数は25,000以上と上昇した。AZE、CEPH併用療法を再開し、その後AZE単独治療で30か月間、患児は寛解状態となり、薬剤を中止した。

薬剤中止11か月後、好酸球数が再度上昇した。AZEとCEPH併用療法の再開後、患児は7か月間寛解したため、薬剤を中止している。

AZEおよびCEPHは好酸球増多症候群に対して有効な薬剤で、ステロイド長期治療による副作用を回避できうるとも推測される。

Abstract

This is a first report in which azelastine hydrochloride (AZE) with or without cepharanthin (CEPH) has appeared to be effective in a patient with hypereosinophilic syndrome (HES). A 9-year-old boy was referred to our hospital because of fever and cutaneous eruption. Blood count showed normal hemoglobin level with a leukocytosis of 66,4000/μl with 95% mature eosinophils. There was no history of allergy, no clinical or serological evidence of a parasitic infection. There was no evidence of connective tissue disease, neoplastic disease, leukemia, or immunodeficiency. He was treated with a prednisolone, which induced a rapid remission. The CEPH was used with a low-dose steroid for 6.5 months, and eventually the steroid could not be discontinued. AZE, which was prescribed by otolaryngologist for perennial rhinitis, unexpectedly reduced and maintained the eosinophil count to normal level. The patient had been doing well on AZE with CEPH followed by single AZE for 3.5 months, then we discontinued the AZE. Five weeks after the discontinuation, the eosinophil count rose to >25,000/μl. After reinstitution of AZE with CEPH followed by single AZE, the patient had been doing well for 30 months, then we stopped AZE. Eleven months after the discontinuation, the eosinophil count rose up again. After reinstituting of AZE with CEPH, the patient had been doing well for 7 months, then we stopped AZE with CEPH. AZE and CEPH might be effective in HES patients, and minimize the adverse effects of long-lasting therapy with steroids.

Introduction

Hypereosinophilic syndrome 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.[1,2] Various modalities have been used to treat HES, including corticosteroids, hydroxyurea, leukopheresis, vincristine, 6-mercaptopurine, cyclosporine, recombinant interferon alpha, and allogeneic bone marrow transplantation.[1-3] This paper reports the first case of HES that responded well to the drug azelastine hydrochloride (AZE; Eisai co., Tokyo, Japan) and cepharanthin (CEPH; Kaken Shoyaku Co. Ltd., Japan).

Case report

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 leukocytosis (18,800/μl) and marked eosinophilia (10,500/μl or 56%). He was referred to our hospital on April 25, 1996. His birth weight was 3,250g, and his birth 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. Physical examination findings were unremarkable except for small cervical lymphnodes.

Laboratory tests showed: hemoglobin 12.0 g/dl; WBC count 66,400/μl with 1% banded neutrophils, 4% lymphocytes and 95% eosinophils; platelet count 270,000/μl; erythrocyte sedimentation rate 66mm/h; a normal leukocyte alkaline phosphatase level; and no chromosomal abnormalities. A bone marrow aspirate was normocellular with 70% mature eosinophils. No abnormal cells were present. Immunoglobulin G (IgG), 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 April 25 1996, oral prednisolone (2 mg/kg per day) was begun (Fig 1). The eosinophil count began to decrease on day 2, and had decreased to 124/μl on day 6. The steroid was tapered and discontinued within the next 2 weeks. The patient had been doing well without any therapy until October 1996, at which time the eosinophil count was found to have risen to >20,000/μl. Prednisolone (1 mg/kg per day orally) was restarted. The eosinophil count decreased rapidly, and the steroid was tapered and stopped within the next 10 days. This was repeated again 2 months later. In February 1997, 9.5 months after the treatment was started, a fourth episode of worsening of eosinophilia was encountered. CEPH[4] treatment was begun in oral doses of 70 mg (1.5 mg/kg) per day in an attempt to decrease his steroid dose. The parents gave their informed written consent for the patient's participation in using CEPH. The CEPH together with a short course of low-dose prednisolone (0.05-0.5 mg/kg per day for 14days) was started. Because of increasing eosinophil counts and the development of an urticarial rash, this combination therapy was repeated four times at intervals of 1-2 months.

In October 1997, 17.5 months after the patient was first seen, AZE in oral doses of 1mg twice daily was given by an otolaryngologist because of perennial rhinitis. AZE [4-(p-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepine-4-yl)-1-

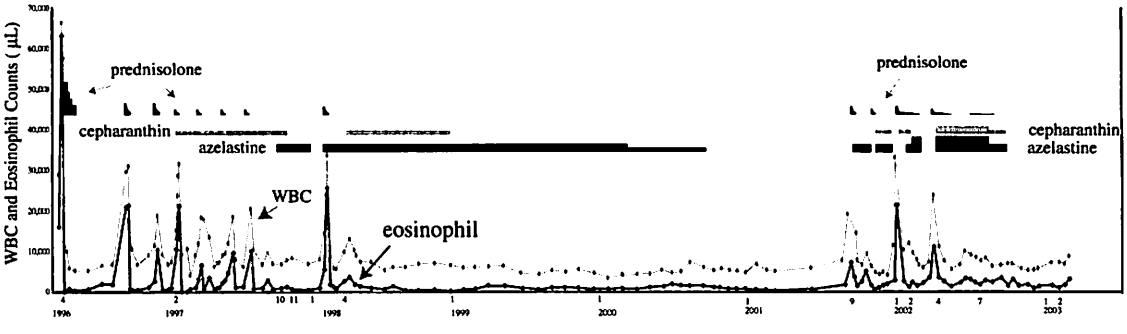

Fig.1 Clinical course of a 9-year-old boy with hypereosinophilic syndrome

(2H)-phthalazione hydrochrolide] is an anti-allergic drug that inhibits the release of various chemical mediators from mast cells, and it has been widely used in Japan.[5] Surprisingly, two weeks after starting administration of AZE, the eosinophil count of 3,038/μl had decreased to 710/μl. Since the patient did well for the next 5 weeks on AZE and CEPH, we stopped the CEPH. On AZE single therapy, the eosinophil count was well controlled for the next 2.5 months, then we discontinued the AZE in January, 1998. Five weeks after the discontinuation of AZE, the eosinophil count had risen to >25,000/μl. AZE with low-dose prednisolone was restarted, and the steroid was tapered and stopped. The CEPH was restarted in April, because of a slight increase in eosinophil count while on AZE single therapy. The disease was well controlled for 10 months after reinstituting AZE and CEPH, and again CEPH was discontinued in January 1999. On AZE single therapy, the patient did well for next 21 months, then we stopped AZE. Eleven months after the discontinuation of AZE, the eosinophil count had risen to >7,965/μl. AZE with low-dose prednisolone was restarted, and the steroid was tapered and stopped. The CEPH was added, because of an increase in eosinophil count. In April 2002, AZE dose was increased to 2mg twice daily, and CEPH to 140mg per day. The disease was well controlled for next 7 months after increasing the doses of AZE and CEPH, then AZE and CEPH were decreased the doses and stopped. 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.[1] are: (1) a persistent eosinophilia of 1,500/μl for longer than 6 months; (2) lack of evidence of any known cause of eosinophilia; and, (3) evidence of organ system involvement. Many diseases are associated with various degrees of eosinophilia[2]. Allergic diseases cause minor degrees of eosinophilia. The perennial rhinitis in our patient was eosinophilic non-allergic rhinitis according to the criteria; nasal eosinophilia, normal serum IgE concentration, and negative allergy evaluations. Our patient had no clinical or serological evidence of a parasitic infection. There was no evidence of connective tissue disease, neoplastic disease, leukemia, or immunodeficiency.

Various therapies for HES have been reported, including corticosteroids, hydroxyurea, leukopheresis, vincristine, 6-mercaptopurine, α-interferon, cyclosporine, and allogeneic bone marrow transplantation.[2,3] Prednisone has been the drug of choice if the patient manifests significant symptomatology. In our patient, blood eosinophilia was rapidly suppressed by a short course of prednisolone. However, 2-4 months after the cessation of the steroid, the eosinophil count was found to increase again. In an attempt to decrease his steroid dose, CEPH treatment was started in February 1997. CEPH is a partially purified alkaloids preparation of Stephania cepharantha Hayata and mainly composed of six alkaloids.[4] This drug has been shown to have antiinflammatory, antiallergic, and immunomodulatory activities *in vivo*[6]. By using CEPH in our patient, it seemed that the dose of the steroid could be decreased, but still the steroid could not be discontinued. CEPH was recently known to be effective for increasing platelets counts in patients with chronic idiopathic thrombocytopenic purpura (ITP), and is used as a drug for reducing of steroid dosage.[7] However, the precise mechanism to increase the platelet count in ITP patients is unclear. The administration of CEPH together with AZE in April 1998 seemed to lead to a decrease in the slightly elevated eosinophil count while on AZE single therapy. However, the efficacy of CEPH appeared to be unclear.

AZE, which was given by an otolaryngologist, was unexpectedly effective in this patient. The efficacy of AZE seemed to be apparent for the following reasons; 1) after starting administration of this drug a normal eosinophil count was maintained for 3.5 months, in contrast to the relapse that occurred in the 1-2 month interval without AZE during the period of therapy with CEPH and prednisolone, 2) stopping administration of this drug led to an increase in eosinophil count, 3) reinstitution of therapy with AZE plus CEPH, followed by single AZE, led to a normal eosinophil count maintained for the next 17 months.

Raghavachar et al.[8] suggested that T-lymphocyte control of human eosinopoiesis might be a pathogenetic mechanism of HES. Interleukin (IL)-5 in humans is restricted to stimulating eosinophil production. The clonal proliferation of type 2 helper T cells secreting IL-4 and IL-5 might contribute to the eosinophilia in HES[9,10]. T cells in HES have been shown to produce IL-5 after in vitro stimulation with IL-2[11]. Konno et al.[12] 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. Furue et al. reported that AZE had potent immunosuppressive effects. They reported that AZE exerted its in vitro immunosuppressive activity preferentially by interfering with IL-2 responsiveness with partial inhibition of IL-2 production, and conversely tacrolimus acted as a strong inhibitor of IL-2 production without prominent effect on IL-2 responsiveness.[13] All of these phenomena observed in vitro might also be operative in vivo.

The eosinophilia in HES might be initially caused by an immune reaction triggered by an as yet unknown antigenic stimulus. This would lead to release of IL-2, IL-3, IL-4, and IL-5 by activated T cells and would result in a persistent stimulation of eosinopoiesis.[3] In our patient, AZE seems to suppress the cytokines required for the persistent activation of eosinophils seen in HES. In the present study, no adverse effects were observed during AZE with or without CEPH therapy. In patients with allergic disorders who were treated with AZE, no major side effects have been reported. AZE might be useful to prevent eosinophil-induced organ damage and secondarily to prevent the side effects of long-term corticosteroid therapy. Further studies are necessary to evaluate this novel beneficial effect of AZE in HES patients. Future trials might focus on other anti-allergic agents, which might inhibit secretion of eosinophilopoietic cytokines.

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