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REVIEW ARTICLE

Treatment for Churg-Strauss Syndrome: Induction of Remission and Efficacy of Intravenous Immunoglobulin Therapy

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ABSTRACT

Churg-Strauss syndrome (CSS) is characterized by the presence of asthma, eosinophilia, and small-vessel vasculitis with granuloma. It is a distinct entity, as determined from all classifications of systemic vasculitis. The poor prognostic factors in CSS are renal insufficiency, cardiomyopathy, severe gastrointestinal (GI) tract, and central nervous systems (CNS) involvement. The initial management of CSS should include a high dose of a corticosteroid: prednisone at 1 mg/kg/day or its equivalent for methylprednisolone with tapering over 6 months. In patients with severe or rapidly progressing CSS, the administration of methylprednisolone pulse at 1 g/body/day for 3 days is recommended. When corticosteroid therapy does not induce remission, or when patients have poor prognostic factors, immunosuppressive cytotoxic therapy is indicated. However, some patients with severe CSS often show resistance to conventional treatment. We think that IVIG therapy is a hopeful candidate for second-line treatment for CSS patients, particularly in the case of neuropathy and/or cardiomyopathy, which are resistant to conventional therapy. However, there is not much evidence supporting the effectiveness of IVIG in CSS, and the mechanisms underlying the action of IVIG remain unclear. Now we are performing clinical trials of IVIG therapy for CSS patients who are resistant to conventional treatment, through a nationwide double-blinded placebo-controlled study in Japan.

KEY WORDS

Churg-Strauss syndrome, intravenous immunoglobulin therapy

INTRODUCTION

Churg-Strauss syndrome (CSS) is characterized by the presence of asthma, eosinophilia, and small-vessel vasculitis with granuloma.[1,2] It is a distinct entity, listed separately in the classifications of systemic vasculitis.[2,3] The syndrome was named after the two pathologists, J. Churg and L. Strauss, who first described it in 1951 as a disease that is similar to but clearly distinct from polyarteritis nodosa (PAN).[1] Eosinophilic infiltration and/or ischemic damage due to vasculitis are often detected in the lungs, skin, GI tract, heart, and peripheral neurons.[1-7]

In 1990, the American College of Rheumatology (ACR) proposed six classification criteria for CSS (Table 1).[8] CSS is one of typical members of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, that also include Wegener's granulomatosis (WG) and microscopic polyangitis (MPA), and clearly distinct from classical PAN, which involves medium-sized arteries and is usually not associated with ANCA. The type of ANCA in CSS is mainly anti-myeloperoxydase (MPO) antibody, which is also common in MPA.

The natural history of CSS is, first, the appearance of eosinophilic rhinosinusitis, followed several years later by the development of severe asthma with marked peripheral blood eosinophilia, and finally the

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Table 1 1990 American College of Rheumatology Criteria for the Classification of Churg-Strauss Syndrome

Criterion	Definition
1. Asthma	History of wheezing or diffuse, high-pitched rales on expiration
2. Eosinophilia	Eosinophilia > 10% of white blood cell differential count
3. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (*i.e.*, glove/stocking distribution) attributable to vasculitis
4. Pulmonary infiltrates, nonfixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis
5. Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness, or radiographic opacification of the paranasal sinuses
6. Extravascular eosinophils	Biopsy including artery, arteriole or venule, showing accumulations of eosinophils in extravascular areas

For classification purposes, a patient with vasculitis shall be said to have Churg-Strauss syndrome if at least four of these six criteria are present.

The presence of any four or more criteria yields a sensitivity of 85% and a specificity of 99.7%. (Adapted from Masi *et al.*[8])

development of systemic vasculitis. In the series of patients studied by Guillevin *et al.*, 97.9% of the patients had asthma and 37.5% had pulmonary infiltrates on chest X-ray.[3]

Various CSS therapies can markedly alter the course of CSS: 50% or fewer of those who are untreated die within 3 months of diagnosis, whereas treated patients have a 10-year survival rate of more than 70%. Many CSS patients respond rapidly to corticosteroids. With treatment, remission is obtained in more than 80% of CSS patients.[4] However, patients with moderate to severe CSS do not respond to corticosteroids well. Cardiac involvement is the primary cause of death of CSS patients,[1-3,9-11] who do not fully respond to conventional treatment. Moreover, almost all CSS patients show long-lasting and steroid-resistant neuralgia and muscle weakness due to peripheral neuropathy.

In this article, we review the recent reports on the management of CSS and the induction remission and efficacy of intravenous immunoglobulin therapy.

PROGNOSTIC FACTORS

The outcome of CSS depends on the extent of disease dissemination and the severity of visceral involvement. In a prospective study of 342 patients with CSS or PAN, Guillevin *et al*. evaluated several clinical, biological, immunological, and therapeutic factors and identified poor prognostic factors, namely, proteinuria, renal insufficiency, cardiomyopathy, and severe GI tract involvement.[9] Moreover, previous reports showed that old age and CNS involvement are also poor prognostic factors.[3,10] The majority of CSS patients without these factors show a good response to corticosteroids and survive for a long time.

CONVENTIONAL TREATMENT OF CSS

CORTICOSTEROIDS

CSS patients respond rapidly to corticosteroids, but sometimes they must be administered together with cytotoxic agents, which are useful for patients with severe CSS. The initial management of CSS should include a high dose of corticosteroid: prednisone at 1 mg/kg/day, or its equivalent for methylprednisolone with tapering over 6 months. In patients with severe or rapidly progressing CSS, the administration of methylprednisolone pulse at 1 g/body/day for 3 days is recommended.[3,6,7] Corticosteroids are often highly effective and clinical symptoms and eosinophilia improves dramatically. Vasculitis remission is obtained in most patients with mild to moderate CSS with corticosteroids alone (Table 2). After the improvement of clinical symptoms and the normalization of blood parameters (ESR, CRP, LDH, CK, ANCA titer and eosinophil count), the tapering of the prednisone dose can begin. The tapering of prednisone is as follows: 10 to 15% decrease at one- to two-week intervals with monitoring of peripheral eosinophilia and clinical symptoms. In the stable condition and remission stage after an intensive therapy, CSS in the majority patients can be controlled with low doses of prednisone (mean dose: 8.85 ± 6.8 mg/day), together with inhaled corticosteroid.[10]

CYTOTOXIC AGENTS

Asthma symptoms, pulmonary infiltration, and skin lesions are usually resolved after corticosteroid therapy. Although most CSS patients respond well to corticosteroid therapy, some organ impairments are not easily resolved; cardiac, GI, and neurological involvement do not respond well to treatment with a corticosteroid alone. Moreover, from our experience, patients with moderate to severe CSS, or CSS patients with prominent peripheral neuropathy, such as gait disturbance, often show resistance to treatment with corticosteroids alone.

When corticosteroid therapy does not induce remission, or when patients have a poor prognostic factor such as cardiac, GI, renal, or CNS involvement, immunosuppressive cytotoxic therapy is indicated. Patients with systemic vasculitis syndrome, including those with WG and MPA, respond well to cytotoxic

Table 2 Summary of treatment options for Churg-Strauss vasculitis

Diagnosis	Treatment	Indications	Dose	Comments
Churg-Strauss vasculitis	Corticosteroids	First-line therapy	1 mg/kg with taper over 3-6 mo	Corticosteroid monotherapy controls most patients' symptoms acutely but only rarely induces lifelong remission
	Cyclophosphamide	In addition to corticosteroids for treatment of refractory disease, relapse, or acute disease with involvement of $\geq$ 2 extrapulmonary organs	Monthly intravenous or daily oral	Monthly intravenous administration is better tolerated, no difference in survival but decreased incidence of relapse with addition of cyclophosphamide
	Other cytotoxic agents (including azathioprine, methotrexate)	Consider as alternative corticosteroid - sparing agents for maintenance therapy, treatment of relapse, or both	Escalate dose as tolerated based on side effects	Little published data, high rate of relapse with methotrexate
	Immunomodulatory agents (including IFN-α, mycophenolate mofetil, TNF blockers, and IVIG)	Consider as alternative corticosteroid - sparing agents for maintenance therapy, treatment of relapse, or both	NA	Little data to support use in CSS, leukoencephalopathy reported in 2/12 patients treated with long-term IFN-α
	mAbs (including anti-IL-5,anti-IgE [omalizumab])	Unknown	NA	No published data in CSS and uncertain efficacy for the underlying vasculitis, anti-IgE therapy reduces exacerbations and symptoms in severe asthma
	Routine asthma management	Should be used as adjuvant therapy in all patients with asthma symptoms	Variable	Leukotriene modifier use in CSS is controversial, although data to date do not support a causative role for these agents in the development of CSS

IVIG, Intravenous immunoglobulin; *NA*, not applicable. (Adapted from Kilon *et al.*[7])

therapy included in the standard regimen.[12] The standard treatment for severe CSS includes cyclophosphamide at various dosages is continued for 6 months to 1 year during remission (Table 2). Oral administration of cyclophosphamide (2 mg/kg/day) was previously reported. However recently, monthly intravenous pulse cyclophosphamide (400–800 mg/body/day) has been used for the treatment of CSS and has been found to be better tolerated. The most effective route of cyclophosphamide administration has not been confirmed.[3,6,7] However, from our experience, intravenous cyclophosphamide pulse often shows dramatic effect in CSS patients. Guillevin *et al.* also recommended intravenous cyclophosphamide pulse in their review article. Other cytotoxic agents, which include methotrexate or azathioprine, may be used; however, they may not be as efficient as cyclophosphamide in inducing remission. Remission rate within 1 year is about 90% to 95%. A small percentage (5% to 6%) of patients show no response to conventional therapy (corticosteroid and cyclophosphamide), and the overall mortality rate in CSS patients is 20% to 25% over 5 to 10 years.[4,10]

OTHER TREATMENT OPTIONS

IMMUNOMODULATORY AGENTS

When CSS patients are resistant to corticosteroid and cyclophophamide, or when patients are unable to effectively taper the corticosteroid dose, several immunomodulatory agents might be effective.

Intravenous Immunoglobulin (IVIG)

Over the past 20 years, the intravenous administration of exogenous pooled human immunoglobulin has become an important therapy in clinical medicine.[13] Intravenous administration of a high dose of human immunoglobulin (IVIG) has shown beneficial results in some autoimmune diseases and inflamma-

Table 3 Immunomodulatory activities of IVIG

1. Alterations in the populations of lymphocytes in the circulation and in lymphoid tissues
2. Inhibition of lymphocyte (and other leukocyte) activation as determined by proliferation, cytokine production, or expression of activation markers (eg, adhesion molecules), mediated by:
   a. IVIG interaction with cell surface proteins
   b. IVIG binding to cytokines or other soluble mediators
3. FcγR blockade
4. Induction of inhibitory FcγR
5. Interaction with the complement pathways
6. Idiotype network interactions

(Adapted from Binstadt *et al.*[15])

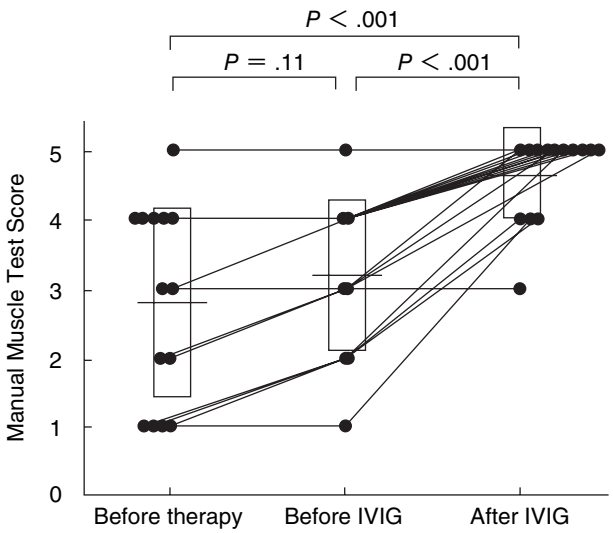

Fig. 1 Manual muscle test. Before therapy indicates before treatment with corticosteroids with or without cyclophosphamide; IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD. (Adapted from Tsurikisawa *et al.*[22])

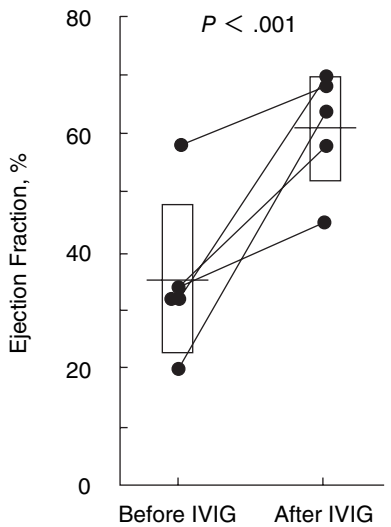

Fig. 2 Ejection fraction of echocardiography. IVIG, intravenous high-dose immunoglobulin therapy. Bars and boxes represent the mean ± SD. (Adapted from Tsurikisawa *et al.*[22])

tory disorders, including idiopathic thrombocytopenic purpura, Kawasaki disease, and Gullain-Barré syndrome. The mechanisms underlying the action of IVIG therapy remain unclear. Some established or proposed mechanisms of the therapeutic effects of IVIG therapy are listed in Table 3.[14,15]

Jayne *et al.* reported in 1991 that IVIG is effective in seven patients with ANCA-positive systemic vasculitis including WG and MPA.[16] Hamilos and Christensen first reported in 1991 that a 33-year-old man with CSS, who was resistant to conventional steroid treatment, showed a marked improvement of vasculitis symptoms and normalization of eosinophil count after IVIG therapy.[17] However, there had been only a few reports on the use of IVIG therapy for CSS.[18-20] In 1994, we encountered a 53-year-old Japanese man with CSS, who was admitted to Fujita Health University Hospital and complained severe gait disturbance despite corticosteroid and cyclophosphamide therapy, but showed a marked improvement of neurological involvement immediately after the administration of IVIG.[21] Since this experience, we had been attempting to evaluate the efficacy of IVIG therapy in CSS. In our preliminary study, we were able to confirm the efficacy of IVIG therapy particularly on neurological and cardiac involvement in the majority of patients with CSS who did not respond well to conventional therapy. In 2004, we reported that neurological and cardiac manifestations in 15 patients with CSS, who were not responsive to corticosteroids with or without cyclophosphamide, were significantly improved after IVIG therapy.[22] IVIG improved motor neuropathy within 1 week in 13 of the 15 patients. The manual muscle strength test showed that IVIG therapy improved muscle performance, whereas the conventional treatment before IVIG did not (Fig. 1).[22] Cardiac function was improved by IVIG therapy in all 5 patients with heart failure. The ejection fraction of the left ventricle markedly increased (Fig. 2).[22]

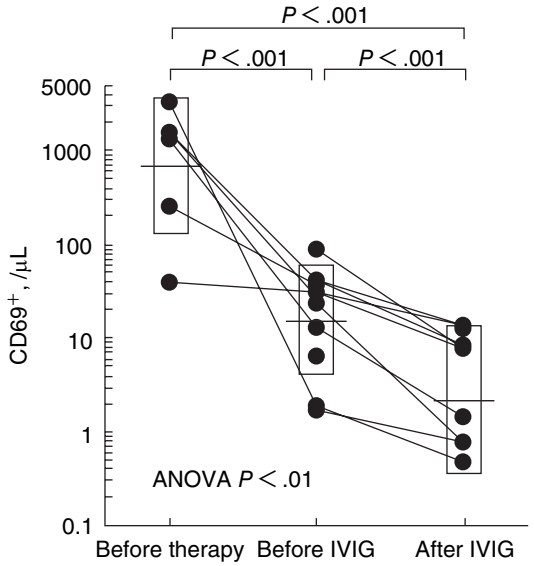

Fig. 3 The effect of intravenous high-dose immunoglobulin therapy (IVIG) on $CD69^+$ eosinophils. The CD69 cell number is expressed in a logarithmic scale. ANOVA, analysis of variance. Bars and boxes represent the mean ± SD. (Adapted from Tsurikisawa *et al.*[22])

Eosinophils in the peripheral blood composed less than 10% of the white blood cell count after the therapy with corticosteroids with or without cyclophsophamide. IVIG treatment decreased the number of CD-69-expressing activated eosinophils from 27.5 to 5.9/μl ($p < .01$), whereas the number of peripheral eosinophils did not change (Fig. 3).[22] Recently, Danieli *et al.* reported that complete clinical and functional recovery with a long-term remission by IVIG with plasmapheresis in 18 patients with CSS.[23] Takigawa *et al*. presented that IVIG with conventional therapy resulted in a significant improvement in one alveolar hemorrhage patient with severe CSS.[24] These results suggest that IVIG therapy may be a hopeful second-line treatment for CSS patients, particularly in the case of neuropathy and/or cardiomyopathy, which are resistant to conventional therapy. However, there is not much evidence supporting the effectiveness of IVIG therapy in CSS, and the mechanisms underlying the action of IVIG remain unclear. Now we are evaluating the mechanisms underlying this action and performing clinical trials of IVIG therapy for CSS patients who are resistant to conventional treatment, through a nationwide double-blinded placebo-controlled study in Japan.

Interferon-α

INF-α has a beneficial effect on patients with idiopathic hypereosinophilic syndrome (HES). INF-α has been shown to inhibit eosinophil production and the release of eosinophil cationic protein and eosinophil-derived neurotoxin. In CSS there have

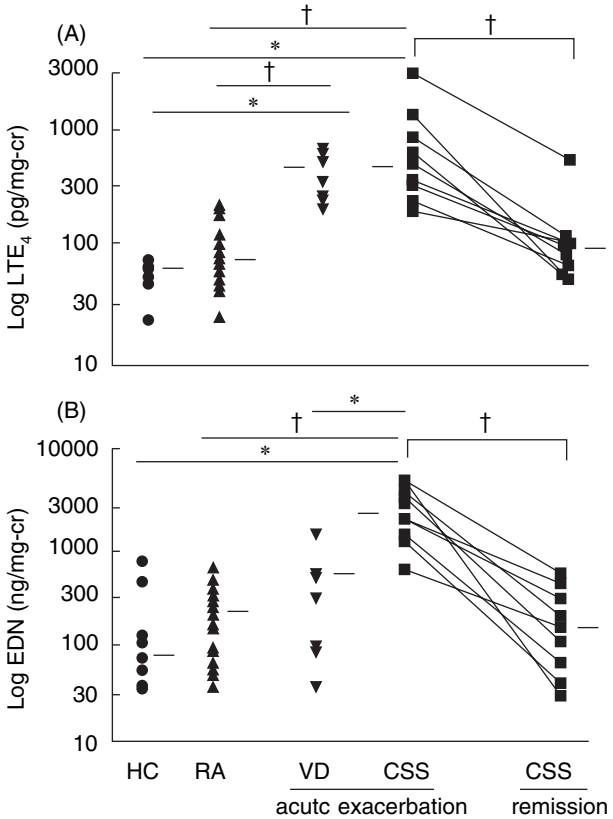

Fig. 4 Urinary LTE_4 (**A**) and EDN (**B**) concentrations in each group. Urinary concentrations are expressed by using the log scale. Patients with CSS, VD, and RA and HC subjects are denoted by *closed squares*, *closed triangles*, *open triangles*, and *open circles*, respectively. *Horizontal bars* indicate medians. * $P < .05$; † $P < .01$. HC: healthy control, RA: reumatoid arthritis, VD: non-eosinophilic vasculitides. (Adapted from Higashi *et al.*[29])

been several reports on the decrease in eosinophil count and disease activity in response to IFN-α. A good clinical response to a high dose of INF-α was observed in four patients with CSS, but most of them showed a relapse at the end of the therapy. Skin lesions have also been treated successfully with INF-α. Unfortunately, although INF-α was effective and tolerated for the induction of remission, patients followed up for more than one year continued to show relapses. From these results and a recent report on leukoencephalopathy in 2 of 12 patients with CSS who received INF-α for four years,[25] maintenance therapy with INF-α for CSS remains controversial.[7,13,26]

MONOCLONAL ANTIBODIES

A monoclonal antibody to TNF-α has been useful for rheumatic diseases and other immunological diseases. However, there are few published reports on antibodies to TNF-α for CSS. The effects of anti-TNF-

α are still unknown.[3,6,7]

An antibody to IL-5 has been shown to decrease eosinophil count in the blood and tissue of patients with HES. Theoretically, the anti-IL-5 antibody might be a useful additional therapy for CSS patients.[3,7] Total serum IgE level is also increased in patients with CSS in the acute stage. However, there are no reports of monoclonal antibodies to IL-5 and IgE for CSS.

Recently, Koukoulaki *et al*. reported that B cell depletion by rituximab (anti-CD 20) was effective in two patients with refractory CSS.[27] In the near future, the effect of these antibodies on CSS vasculitis should be evaluated.

PLASMA EXCHANGE

Several studies attempted to confirm the effect of plasma exchange on systemic vasculitis including CSS. However, there is no strong evidence that this treatment is effective for CSS patients.[28]

BIOMARKER OF DISEASE ACTIVITY

During the active stage or in the relapsing phase, the levels of common inflammatory markers, namely, CRP, ESR, WBC, and some acute phase reactants are elevated. However, these indicators do not correspond to disease activity and are not specific to CSS patients. Peripheral eosinophil count is one of good markers of disease activity, but this count easily normalizes in spite of persistent symptoms. Recently, we have found that urinary leukotriene (U-LT) E4 concentration is a good marker in the acute phase of CSS. U-LTE4 concentration significantly increases in not only eosinophilic vasculitides, including CSS, but also noneosinophilic vasculitides (Fig. 4).[29] U-LTE4 concentration may be used as a sensitive biomarker for monitoring physiological events involved in vasculitides.

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