

Churg-Strauss syndrome successfully treated with rituximab

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Abstract Churg-Strauss syndrome (CSS) is characterized by small-vessel vasculitis, extravascular granulomatous inflammation, and massive eosinophilia in tissues and blood, and is often accompanied by a history of preclinical asthma and/or allergic rhinitis lasting several years before the syndrome develops its full clinical picture. Corticosteroids, often in combination with cytotoxic agents, comprise standard therapy; however, a number of patients appear to be resistant to treatment and there is a need for more effective regimens. B cell depletion may be an effective treatment option for CSS. Here, we describe two patients resistant to conventional therapy who were treated with rituximab and experienced a rapid and substantial decrease in disease activity and asthmatic symptoms and an increase in physical capacity.

Keywords Vasculitis · B cell depletion · Eosinophilia · Treatment

Introduction

Churg-Strauss syndrome (CSS) is characterized by granulomatous inflammation of the respiratory tract accompanied by blood eosinophilia, eosinophilia in affected tissues, and necrotizing vasculitis in small blood vessels. CSS develops almost exclusively in patients with pre-existing asthma [1]. Historically, corticosteroids in combination with cytotoxic agents have been the most effective treatment. However, some patients do not respond to conventional regimens and newer biological agents, like tumour necrosis factor- α inhibitors, have been tried with limited success. Based on several reports concerning the effect of the B cell-depleting agent rituximab for treating various chronic inflammatory diseases, we treated two patients who had treatment-resistant CSS with rituximab [2–7].

Case 1

A 50-year-old man was diagnosed with asthma in 2000. During the spring, he developed nasal polyposis and recurring sinusitis. Biopsy of a nasal polyp revealed nonspecific inflammation. The patient responded well to prednisolone but his asthma worsened as soon as prednisolone doses were reduced. Conventional antiasthmatic drugs had poor or no effect. After 1 year, he was treated with montelukast with no obvious effect. Three months later, he presented with fever, skin rash, and deterioration of his asthmatic symptoms. Peripheral blood count showed strong eosinophilia (31%). Montelukast was suspected as a provoking factor and was discontinued [8, 9]. Repeat nasal biopsy demonstrated eosinophilic infiltration. Routine immunological tests, including those for antineutrophil cytoplasmatic antibodies (ANCA), anti-nuclear

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antibodies (ANA), rheumatoid factor, cryoglobulins, and complement factors C3 and C4, were normal. Urinalysis was normal. The patient was diagnosed with CSS based on a history of asthma, recurring sinusitis, non-fixed pulmonary infiltrates, blood eosinophilia, and a skin biopsy showing intense inflammatory cell infiltration, including increased numbers of eosinophils and some areas with small-vessel vasculitis.

Initially, immunosuppressive treatment with azathioprine and prednisolone had good effect, but after a few months, sinusitis reoccurred, his asthma deteriorated, and the patient developed bilateral hearing loss. The lack of a sustained response to azathioprine and prednisolone required a change to methotrexate. The initial effect was good, but the patient again experienced hearing loss. Cyclosporine was added in the summer of 2002; no sustained response manifested. Infliximab therapy was initiated in the spring of 2003. After 5 months, the patient developed resistance to infliximab and anakinra was tried. The response was insufficient and infliximab was reintroduced. Infliximab treatment was ceased permanently when the patient developed intolerance in the spring of 2005, and his condition continued to deteriorate (Table 1).

Rituximab therapy was started in February 2007. The patient received two cycles of 1,000 mg given 2 weeks apart, followed by 1,000 mg every 6 months. Four weeks after starting rituximab, the patient reported feeling almost fully recovered, experienced less asthmatic symptoms, and had nearly normal hearing. After receiving his fourth round of rituximab in March 2008, the patient felt completely recovered and experienced no limitations in physical capacity. Peripheral CD 19 and CD 20 cell counts demonstrated complete B cell depletion with normal T cell counts. As of September 2008, the patient had received his fifth rituximab treatment and he remains in remission. The patient is currently receiving 7.5 mg methotrexate per week, 5 mg prednisolone per day, and has no need for antiasthmatic medication.

Table 1 Selected variables in patients before and after treatment with rituximab

	Patient 1		Patient 2	
	Before Rx	After Rx	Before Rx	After Rx
Eosinophils (%)	19.5	2	19	10
CD19 B cells (%)	6.1	<0.1	12.1	0.1
FVC (%/L)	80/3.67	103/4.63	66/2.38	70/2.50
FEV1 (%/L)	53/1.98	70/2.56	52/1.62	67/2.10
FEV1/FVC (%)	54	55	68	84

Rtx rituximab, FVC forced vital capacity, FEV1 forced expiratory volume in one second

Case 2

A 35-year-old woman with asthma had been treated with montelukast for 3 years. After the introduction of montelukast, she suffered from increasing problems of the paranasal sinuses. Chest radiography in June 2003 showed bilateral pulmonary infiltrates, and blood tests showed elevated C-reactive protein (CRP; 152 mg/L) and eosinophilia in peripheral blood (36%, peaking at 47%). ANCA and ANA tests were negative. Computed tomography (CT) scan of the paranasal sinuses demonstrated mucosal thickening; pulmonary CT showed widespread bilateral infiltrates, abnormal masses in the mediastinum, and small amounts of bilateral pleural effusions. Urinalysis was normal. Based on her history of asthma, sinusitis, fever, eosinophilia, and pulmonary infiltrates not responding to antibiotics, CSS was suspected. Prednisolone and azathioprine were started and montelukast removed. The patient responded well to this regimen. Mediastinal biopsy and biopsy from nasal mucosa demonstrated eosinophilia but did not prove small-vessel vasculitis.

Five months later, the patient reported increasing paranasal symptoms but her chest radiograph was normal. Her erythrocyte sedimentation rate and CRP levels were normal, and the results of spirometry were satisfactory. Over the next 3 years, the patient's condition gradually deteriorated, and in March 2006, spirometry demonstrated a forced vital capacity (FVC) of 45%, a forced expiratory volume in 1-s (FEV1) of 30%, and an FEV1/FVC of 58%.

Due to a lack of response to azathioprine and prednisolone, rituximab infusions were initiated in April 2008. Initially she received 1,000 mg of rituximab every 2 weeks. Five months after initiating rituximab treatment, minor asthmatic symptoms remained but her physical capacity had increased. There were substantial improvements in spirometry values, with an almost 1-l increase in FVC and a 0.4-l increase in FEV1. After 6 months, she received another 1,000 mg of rituximab and continued to improve. At the end of October 2008, the patient was receiving 50 mg azathioprine twice daily, 5 mg prednisolone once daily, sprays with salmeterol/fluticasone, salbutamol, and mometasone furoate, and 10 mg loratadine once daily. The patient reported a substantial improvement in her physical capacity over the preceding 6 months.

Discussion

Rituximab had a remarkable positive effect on these two patients who were resistant to conventional immunosuppressive treatment. These results suggest that B cell depletion is an effective treatment option for this sometimes difficult to treat disease. B cell depletion has been

reported successful for treating several other chronic inflammatory autoimmune diseases, including rheumatoid arthritis [7], systemic lupus erythematosus [2, 6, 7] primary Sjögrens syndrome [2, 7], vasculitis [2, 6, 7], thrombocytopenic purpura [2], and myositis [2, 7].

There are only a few reports concerning the use of rituximab in CSS [3–6] and it is unknown whether the mechanism of action is general immunosuppression due to B cell depletion or whether other specific mechanisms may be involved. Based on the hyper-eosinophilia that accompanies CSS, it has been postulated that the drug works through the inhibition of T cell interleukin 5 production, which is known to be a key mediator in eosinophil activation [3].

The role of montelukast or other leucotriene receptor antagonists as potential provokers or inducers of CSS in susceptible individuals remains under debate [8, 9]; however, in the two cases described herein, montelukast was removed early in the disease course due to such a suspicion. Cessation of montelukast therapy did not lead to improvement in either patient, and the long post-montelukast observation time showing gradually worsening CSS prior to the initiation of rituximab treatment indicates that any improvements in the conditions of these patients were not due to cessation of montelukast.

CSS is a chronic disease that is often complicated by serious and even disabling morbidity despite early treatment with conventional therapies. Such regimens, which often include cytotoxic agents, show limited therapeutic effect and are associated with significant toxicity and a potential for inducing malignancies [10]. Therefore, B cell depletion should be evaluated as an early intervention for CSS. Multi-centre, controlled studies are required to

determine the appropriate place for rituximab in the treatment arsenal for CSS.

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