Efficacy of imatinib mesylate in a case of Churg–Strauss syndrome: evidence for the pathogenic role of a tyrosine kinase?

Sr., Churg–Strauss syndrome (CSS) is a systemic vasculitis with eosinophilia, associated with anti-neutrophil cytoplasmic antibodies (ANCAs) in 40% of patients. Its pathophysiology remains unknown, but activated eosinophils could be the effector cells in this vasculitis. We report the case of a patient with CSS who responded well to a prolonged course of imatinib mesylate, suggesting the pathogenic role of a tyrosine kinase (TK) in CSS.

The patient, a 26-year-old woman, was treated between 2001 and 2002 with prednisone and mesalazine for recurrent bloody diarrhoea associated with elevated transaminases attributed to Crohn’s disease with auto-immune hepatitis. In 2003 she was hospitalized for bloody diarrhoea, facial oedema, cutaneous vasculitis and new-onset asthma. Blood tests showed an elevated peripheral eosinophil count of 13,500/μl. Colonoscopy revealed pancolitis, with marked eosinophilic infiltration on histology. Although an extensive blood workup failed to establish the diagnosis of myeloproliferative or lymphoid variant of hypereosinophilic syndrome (HES), she was treated with IFN-α then hydroxy carbamide, with poor results. She reported worsening asthma and frequent sinusitis. Imatinib mesylate 400 mg/day was introduced in 2004, with rapid efficacy on clinical symptoms and eosinophil count, allowing prednisone withdrawal (Fig. 1). She stopped imatinib mesylate in July 2008 and was admitted 15 days later in our internal medicine department because of fatigue, high-grade fever, generalized oedema and dyspnoea. On examination she showed upper and lower limb purpuric patches, wheezing, abdominal pain and arthritis of the right ankle. The peripheral eosinophil count was 27,000 × 10⁶/l. A CT scan revealed a dysmorphic liver with thrombosis of two hepatic veins and ascites. A skin biopsy showed leucocytoclastic vasculitis. The search for a JAK2 V617F mutation and FIP1L1-PDGFRα fusion gene were negative. The bone marrow karyotype (45XX-21/46XX) did not show any translocation involving chromosome 5. Complete sequencing of exons of the KIT and PDGFRα genes revealed no significant mutation. A repeated search for ANCA was negative. She was diagnosed with CSS and Budd–Chiari syndrome and therapy with prednisone, AZA and anticoagulants led to rapid clinical and biological remission, which has persisted ever since.

This case, which meets the 1990 ACR criteria for CSS, is the first report of imatinib mesylate efficacy in this disease [1]. This drug acts as a specific inhibitor of TK enzymes by blocking the acquired kinase activation induced by bcr-abl, c-kit and PDGF-R mutations. Its efficacy in our case and the relapse after withdrawal both suggest possible, yet unproven, involvement of TK in CSS pathogenesis that might be responsible for an uncontrolled expansion of eosinophils, as seen in the myeloproliferative form of HES [2]. The concomitant Budd–Chiari syndrome, which has been reported in association with idiopathic HESs, but also described in CSS [3, 4], could be secondary to a pro-thrombotic state linked to the eosinophil granule proteins or to a latent myeloproliferative disorder associated with a TK mutation as seen in patients with JAK2 mutations. The reported case also meets the criteria for HES published by Chusid [5], although new-onset asthma and sinusitis strongly suggest a diagnosis of CSS. Moreover, after 11 years of follow-up, our patient does not exhibit clinical or biological signs of a myeloproliferative or lymphoid disorder. Based on this case report, we hypothesize that an imatinib mesylate-sensitive TK could be involved in the pathogenic mechanism underlying CSS.

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Laurence Josselin-Mahr1, Anabelle Werbrouck-Chiraux2, Laurent Garderet3 and Jean Cabane1

1Department of Internal Medicine, 2Department of Pathology and 3Department of Haematology, Hospital Saint-Antoine, Groupe Hospitalier Paris Est, University Pierre et Marie Curie, Assistance Publique–Hôpitaux de Paris, Paris, France.

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Correspondence to: Laurence Josselin-Mahr, Department of Internal Medicine, Hospital Saint Antoine, 184 rue du Faubourg Saint Antoine, 75012 Paris, France.

E-mail: laurence.josselin@sat.aphp.fr

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Fig. 1 Between 2004 and 2008, imatinib mesylate 400 mg/day controlled eosinophilia in this CSS case.

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Successful treatment of refractory anti-signal recognition particle myopathy using abatacept

Sinn, Anti-signal recognition particle (SRP) antibodies have been associated with severe and refractory myopathy. In this letter we present the experience of a patient with intractable anti-SRP-positive myopathy who achieved remission following treatment with abatacept.

In 2007 a 58-year-old Japanese man developed rapidly progressive shoulder and hip girdle weakness. Serum creatine kinase (CK) levels of this patient were found to be 6871 U/l (normal 62–287 U/l). A muscle biopsy revealed necrotizing myopathy and his sera was found to be negative for antinuclear and Jo-1 antibodies, following which we confirmed the presence of anti-SRP antibody. After a dramatic initial clinical response to high-dose prednisone, CK levels decreased to 554 U/l, but continued treatment with prednisone at more than 30 mg/day was required to prevent relapse. In 2009, steroid pulse therapy, i.v. CYC and i.v. immunoglobulin (IVIG) were administered, which produced varying but short-lived benefits. In 2010, MTX, tacrolimus, mizoribine and infliximab were sequentially administered, which produced little effect, and his CK levels again increased to 1994 U/l. Since August 2010, etanercept, in combination with MTX, has resulted in partial clinical improvements, and CK levels again decreased to 751 U/l, though myalgia and muscle weakness continued. The subject’s CK levels increased again to 1527 U/l after discontinuation of MTX because of herpes simplex, and subsequently CK increased to 2285 U/l after discontinuation of etanercept because of upper respiratory infection (Fig. 1). These observations suggest that MTX enhanced the effect of etanercept. In March 2012, both clinical and serological deterioration was observed after 1 month of tocilizumab treatment. Thus abatacept was administered at 750 mg/month, prednisone doses were increased to 30 mg/day and MTX and IVIG treatments were resumed. Under this regimen a positive clinical response was observed, with restoration of CK levels to normal. In September 2012, at 15 mg/day of prednisone, increased CK levels (440 U/l) were observed, accompanied by aggravated muscular manifestations. To manage these symptoms we reintroduced tacrolimus with the hope that it would exert a synergistic action with abatacept. His muscular symptoms completely disappeared, his CK levels returned to normal, and for the first time since disease onset the patient felt well and had increasing muscle power.

Previous studies have distinguished anti-SRP myopathy from PM, DM and other idiopathic inflammatory myopathies by its clinical features and histopathology [1–3].

**Fig. 1** Clinical course.

![Diagram](https://example.com/diagram.png)

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PSL: prednisone; ETN: etanercept; TAC: tacrolimus; TCZ: tocilizumab; ABT: abatacept.