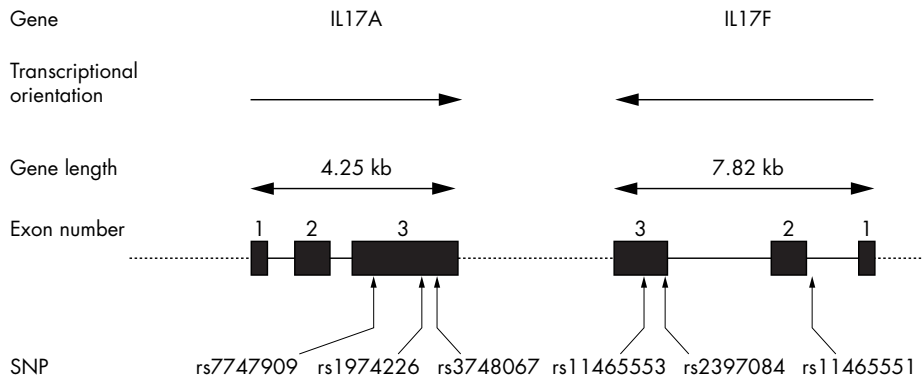

Figure 1 The position of the six SNPs genotyped. Black boxes represent exons, continuous lines represent introns and dotted lines represent intergenic regions. Arrows point toward the position of each SNP. The two genes are aligned according to their physical order, from 6p-telomere to centromere. The horizontal arrows demonstrate the transcriptional orientation of each gene. SNPs rs7747909 and rs11465551 are 49.6 kb apart.

rs2397084). Genotyping of the six SNPs in our probands and controls showed that none were associated with OA at $p \leqslant 0.05$. The SNPs genotyped encompass a genomic distance of 49.6 kb (fig 1; rs7747909 through to rs11465551). None of the pairwise haplotypes or any of the more complex haplotypes, which were constructed from all combinations of 3–6 SNPs, were associated with OA (data not shown).

We focused our analysis on the probands from the families that had provided us with the linkage and the association with chromosome 6. In this way we attempted to maximise our chance of detecting an association with IL17A and/or IL17F, if any such association existed. Our analysis did not provide any evidence of association of either gene. Our investigation does not therefore support IL17A or IL17F as coding for the OA susceptibility that we had previously identified on chromosome 6.

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Competing interests: None.

Ethical approval for the study was obtained from the Oxfordshire Clinical Research Ethics Committee and informed consent was obtained from all subjects.

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Rituximab in Churg-Strauss syndrome

M Koukoulaki, K G C Smith, D R W Jayne

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Churg-Strauss Syndrome (CSS) is a small vessel systemic vasculitis, characterised by asthma, peripheral eosinophilia, neuropathy, pulmonary infiltrates, and sinus abnormalities.[1] Conventional treatment with corticosteroids and cyclophosphamide[2] controls disease activity; however, relapse is frequent and the treatment is toxic. Alternative treatments include plasma exchange,[3] interferon alfa,[4] and intravenous immunoglobulin.[5] B cell depletion with rituximab has proved effective in autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and antineutrophil cytoplasmic antibody (ANCA) associated vasculitis.[6] We present two cases of patients with refractory CSS who were successfully treated with rituximab.

A 37 year old woman (case 1) presented with an 8 month history of nasal congestion, hearing loss, lymphadenopathy, rash, breast inflammation, peripheral neuropathy, abdominal

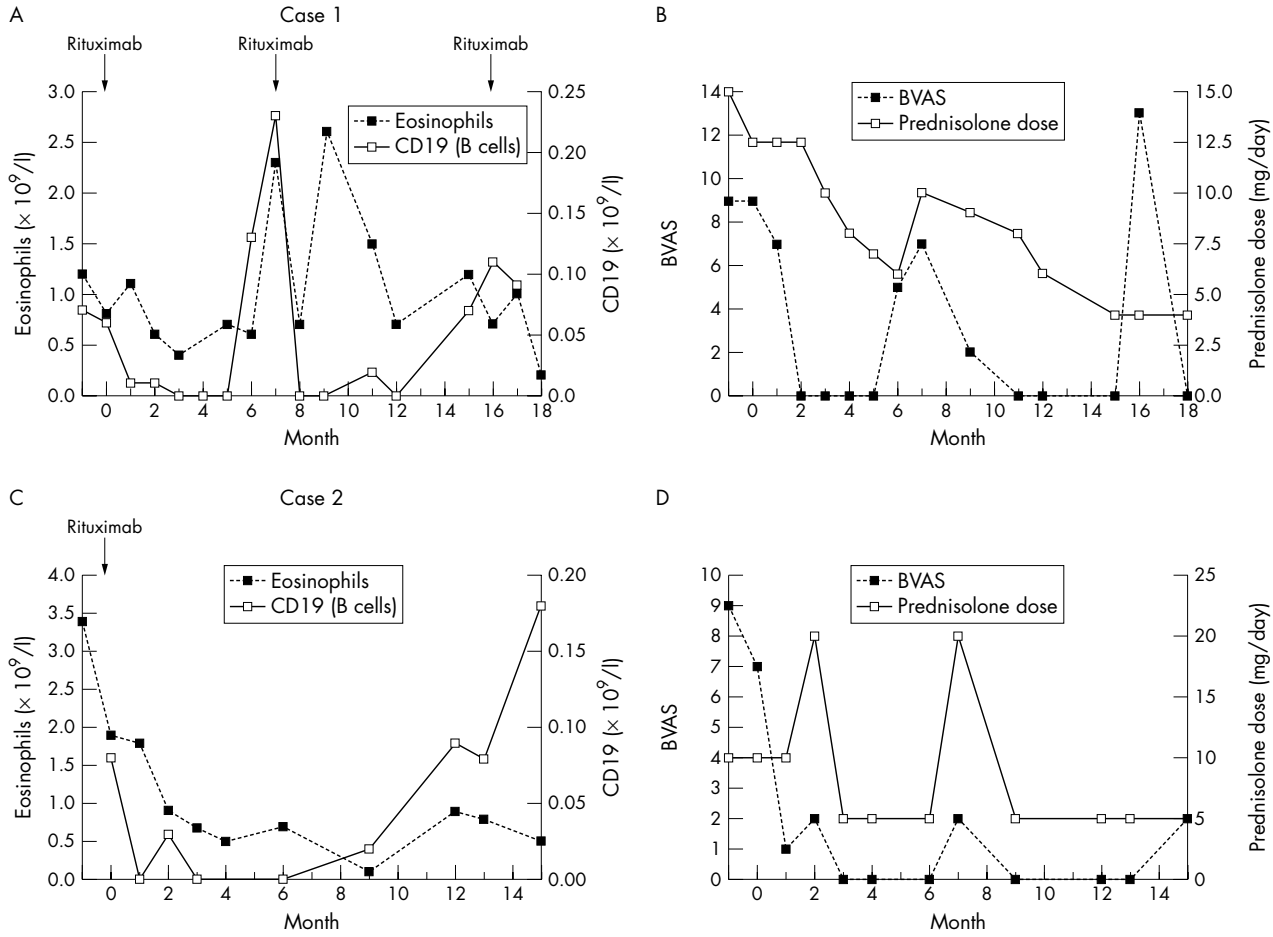

Figure 1 Case 1: (A) sequential eosinophil and CD19 counts and (B) Birmingham Vasculitis Activity Score (BVAS) and prednisolone dose after rituximab administration. Case 2: (C) sequential eosinophil and CD19 counts and (D) BVAS and prednisolone dose after rituximab administration.

pain, malaise, and weight loss. Tachydysrhythmias with poor left ventricular function on echocardiogram suggested cardiac vasculitis. Bone marrow nasal and skin biopsies demonstrated prominent eosinophil infiltration, and a chest computed tomography scan showed pulmonary infiltrates. There was a peripheral eosinophilia (7.4×10^9/l), and raised C reactive protein 48 mg/l; ANCA were negative. CSS was diagnosed.

Initial treatment with intravenous (IV) cyclophosphamide and oral prednisolone induced temporary remission, but subsequent relapses were treated with IV methylprednisolone, high dose pooled IV immunoglobulin, mycophenolate mofetil, and alemtuzumab, (Campath-1H, anti-52 monoclonal antibody). Five months after a third course of alemtuzumab her disease relapsed, presenting with malaise, nasal obstruction, asthma, and peripheral neuropathy. She received treatment with rituximab (as four, weekly, doses of 375 mg/m^2). The patient received further rituximab at 7 and 16 months in response to a return of eosinophilia, nasal symptoms, and asthma after B cell reconstitution (figs 1A and B).

A 35 year old woman (case 2) with known CSS presented in January 2004 with relapsing disease reflected by malaise, fatigue, asthma, peripheral neuropathy, night sweats, polyarthritis, multiple subcutaneous nodules, and an erythematous rash. The original presentation at the age of 21 was additionally characterised by respiratory failure and gastrointestinal involvement. Previous treatment included cyclophosphamide, azathioprine, mycophenolate mofetil interferon alfa, and alemtuzumab. Repeat skin biopsy confirmed granulomatous infiltrates with necrotising foci and eosinophils. She failed to respond to further alemtuzumab and developed deteriorating respiratory symptoms, nasal congestion, and breast inflammation.

Rituximab was given as two infusions of 1000 mg 2 weeks apart. During the follow up period, the patient had two respiratory tract infections, which were treated with temporary increases in prednisolone dose and oral antibiotics. B cell counts recovered 9 months after rituximab without reappearance of an eosinophilia or disease relapse (figs 1C and D).

The diagnoses of CSS were based on disease manifestations and biopsy findings, which disclosed eosinophil infiltrates according to the criteria of the American College of Rheumatology[1] and the Chapel Hill consensus disease definitions. Corticosteroids and cyclophosphamide were initially effective in controlling disease activity. Both our patients had long histories of relapsing disease activity, despite continuous immune suppressive treatment and alternative immunotherapies.

In CSS, eosinophil activation is mainly responsible for disease manifestations, and cytokines produced by T lymphocytes, such as interleukin (IL) 4, IL5,[7] and IL13,[8] are increased in active CSS. This suggests that hypereosinophilia is secondary to T cell involvement in the disease pathogenesis. T cell autoreactivity has been shown to be B cell dependent in certain experimental models,[9 10] and this dependency has been proposed to explain the therapeutic response to rituximab in human autoimmunity. We therefore suggest a hierarchy of dysregulation in CSS, linking B cells with the eosinophilia through autoreactive T cells.

Rituximab was successful in controlling disease activity both on initial presentation and during a flare in our patients. B cell depletion was achieved and the eosinophil count decreased to normal levels. B cell depletion may be an alternative treatment for other patients with refractory CSS.

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