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Successful treatment of cerebral vasculitis in an HIV-positive patient with anti-CD25 treatment

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A 33-year-old HIV-seropositive man presented with recurrent oral candidiasis, weight loss, and lymphadenopathy.¹ CD4 count was 73 cells/ml, and viral load was 296 000 copies/ml. Zidovudine, lamivudine and efavirenz were started, after which the patient showed an increase in CD4 count to 444 cells/ml. In the following weeks he developed progressive paresis of his left arm, left-sided facial weakness, bulbar dysarthria and dysphagia, which remitted when highly active antiretroviral therapy (HAART) was discontinued. However, his condition worsened again on resumption of HAART. Laboratory results showed a CD4 count of 441 cells/ml, a viral load of 105 copies/ml, a C reactive protein concentration of 18 mg/l and a sedimentation rate of 107 mm in the first hour. Serological tests for hepatitis B, hepatitis C and syphilis were negative, as were those for ANA, ANCA, rheumatoid factor and cryoglobulins. Complement (CH50) was normal. Magnetic resonance imaging of the brain showed bilateral hyperintense lesions on T2 images in the frontoparietal cortex. Brain biopsy showed lymphocytic vasculitis,² mainly of small vessels, with predominantly CD3 cells, some CD68 macrophages and some CD20 plasma cells. Giant cells were absent, and specific staining for fungi, acid-fast bacilli, cytomegalovirus, human simian virus, Fe and p24 antigen was negative. Polymerase chain reaction was positive for *Mycobacterium chelonae*, but cultures remained negative. Abavavir, lamivudine and nelfinavir were continued. The patient was treated with 1000 mg/day solumedrol for 3 days, followed by 40 mg prednisone, with an initially good response. When prednisone was tapered to 25 mg, his symptoms recurred. To exclude mycobacterial immune restoration vasculitis, the patient received clarithromycin 1000 mg/day for 10 weeks, without any neurological improvement. Subsequently, he was treated with prednisone with mycophenolate mofetil 1000 mg twice daily for 6 months, prednisone with azathioprine 2 mg/kg for 6 months, and prednisone with azathioprine and ciclosporin A 2 mg/kg. Under each regimen, his symptoms recurred when prednisone was tapered to 25 mg. Phenotypic analysis of PBMCs under immunosuppression showed 443 CD4 cells/ μ l (normal 224–1471 cells/ μ l) with 50%

CD25 positivity (normal 2.4–35.2%), and 1157 CD8+ cells/ μ l (normal 158–648 cells/ μ l) with 20% CD25 positivity (normal 0–10.5%). We postulated that activated, CD25-expressing T cells played an important part in the pathogenesis of his immunerestoration cerebral vasculitis. Therefore, we started treatment with daclizumab after the patient gave informed consent. Treatment consisted of 1 mg/kg on days 1 and 14, whereas prednisone, ciclosporin A and azathioprine were tapered. Single-dose infusions (1 mg/kg) were given 8 and 12 months after initial treatment. Subsequently, prednisone could be stopped. CD4 cell counts stabilised to between 400 and 600 cells/ml, whereas CD25 T cells dropped dramatically after each infusion (fig 1). Viral load and autoantibodies were undetectable. The disease course was complicated by cutaneous varicella zoster infection (2 years after neurological symptoms), condylomata acuminata (after 3 years) and verrucae vulgaris.

Daclizumab is a human immunoglobulin G1- κ recombinant antibody that binds CD25, the IL2 α -chain expressed on activated T cells. It interferes with T cell proliferation and survival, and has been successful in steroid-free anti-rejection regimens in renal allografts and in several immunological disorders, including autoimmune uveitis,³ graft-versus-host disease,⁴ pemphigus vulgaris,⁵ a hemophagocytic lymphohistiocytosis,⁶ ulcerative colitis⁷ and multiple sclerosis.⁸

Daclizumab interferes either by promoting death by antagonising the anti-apoptotic effect of IL2 or by competitive binding for the receptor, leading to cytokine-starvation-induced death. In HIV, CD25 is up regulated during reconstitution of the CD4 compartment on HAART. Recall responses to persistent (auto)antigens are reconstituted and associated with increased production of IL2.⁹ This might explain the development of immune restoration cerebral vasculitis on starting HAART, as well as the development of other forms of autoimmunity after immune reconstitution in patients infected with HIV. CD25 is also expressed on regulatory T cells; thus, daclizumab treatment might be complicated by autoimmune phenomena, as autoimmunity has been described in animal models where regulatory T cells

Figure 1 CD4CD25 + and CD8CD25 + cell counts after each infusion.

are depleted.¹⁰ However, we did not detect autoantibodies associated with atrophic gastritis, pernicious anaemia or thyroiditis.

Anti-CD25 treatment induced long-term steroid-free remission in our patient. However, further studies are needed to evaluate the long-term efficacy of anti-CD25 antibody treatment in this and other forms of vasculitis.

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Neutropenia while receiving anti-tumour necrosis factor treatment for rheumatoid arthritis

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Anti-tumour necrosis factor (TNF) α treatment has had a tremendous effect on the management of rheumatoid arthritis, but it needs to be monitored closely. Guidelines state that haematological complications are rare, so regular full blood counts are not recommended.^{1,2} We noticed that a minority of our patients with rheumatoid arthritis receiving

anti-TNF treatment developed neutropenia ($<2 \times 10^9/l$). Table 1 summarises the demographics of 133 patients with rheumatoid arthritis. Of these, 14.3% of patients had at least one episode of neutropenia, with no obvious cause other than the anti-TNF treatment. The lowest neutropenic episodes had counts that ranged from 1.02 to 1.94 (8/19 patients had an episode with