

Letter to the Editor

Induction of severe systemic lupus erythematosus by TNF blockade and response to anti-IL-6 strategy

To the Editor:

TNF and IL-6 induce a wide range of proinflammatory effects. Infliximab, a TNF-blocking mAb, is used to control systemic autoimmune diseases, such as rheumatoid arthritis (RA).¹ Tocilizumab, an mAb that blocks the effects of IL-6, is also licensed to treat RA.² Because these 2 biologic agents share many characteristics, they are prescribed in identical clinical situations. Our case impressively unveils fundamental biological differences of the TNF and IL-6 pathways on a clinical level and provides information about a differential indication for these anti-cytokine antibodies in patients with systemic autoimmune diseases.

The patient, a 70-year-old retired plasterer, was hospitalized because of relapsing fever and a steady increase in systemic inflammation (C-reactive protein, 160 mg/L; erythrocyte sedimentation rate, 120 mm/h). Medical history and clinical examination were unremarkable. In particular, he never used over-the-counter supplements and was not exposed to toxic materials. Apart from vaccinations as proposed by the Swiss regulatory authorities (Swissmedic) for Swiss citizens, he was never vaccinated and did not have any side effects. He received one tooth implant 30 years before the start of relapsing fever. Silica and asbestos exposure as a cause for induction of an autoimmune disorder could be excluded as far as possible.^{3,4}

Laboratory examinations excluded a wide range of infections. Anti-nuclear antibodies (ANAs) of 1:80 were the only hint of a possible autoimmune disease. HLA class II molecules were DR3⁺DR2⁻ (DR17(3)/DR52, DR4/DR53). Using FACS analysis, we documented normal CD3⁺, CD4⁺, and CD4⁺/CD25⁺ forkhead box protein 3–positive lymphocyte populations in peripheral blood (see Fig E1 in this article's Online Repository at www.jacionline.org). Results of positron emission tomographic/computed tomographic body imaging, transesophageal echocardiography, bone scintigraphy, colonoscopy, gastroscopy, and mediastinal lymph node biopsy were unremarkable. A monoclonal gammopathy with polyclonal bone marrow B lymphocytes was of unknown significance, showing negative amyloid stains. Temporal artery biopsy showed no signs of vasculitis.

The patient had a nonnecrotizing anterior scleritis of the left eye (Fig 1, A) accompanied by intraorbital and retrobulbar inflammation (Fig 1, B and C). Scleral histology showed minimal edema with few lymphocytes; conjunctival histology demonstrated interstitial inflammation with signs of granuloma but without vasculitis, eosinophilia, or necrosis. Immunosuppression with methylprednisolone boli (500 mg/d administered intravenously for 3 days), followed by oral prednisone (1 mg/kg body weight) was initiated and followed by prompt improvement of scleritis and resolution of systemic inflammation. However, during tapering of prednisone, the right eye had an anterior scleritis as well. Prednisone was increased again (50 mg/d), and azathioprine (1.5 mg/kg body weight) was introduced with a steroid-sparing

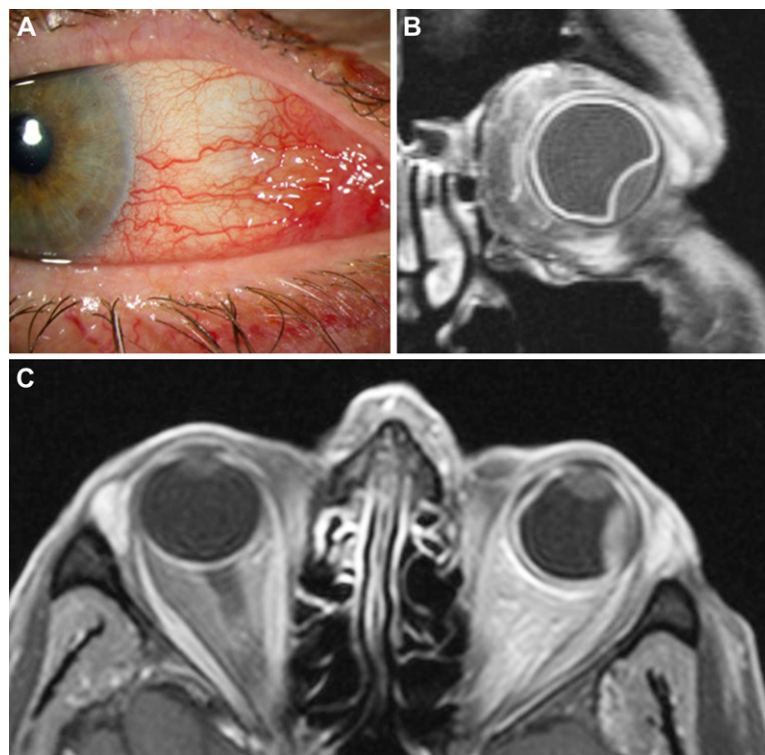


FIG 1. A, Scleritis of the left eye. B and C, Magnetic resonance imaging with contrast agent. The frontal view shows diffuse inflammation around the bulb, as well as lateral detachment of the chorioidea. The sagittal view documents concentric retinal and choroidal detachment and retrobulbar inflammation.

intention. A few months later, therapy resistance led to use of cyclophosphamide (1000 mg every 4 weeks). Despite increased cyclophosphamide (1200 mg), only partial remission was achieved after 6 cycles.

On the basis of our reports and our own experience with the TNF-blocking antibody infliximab in patients with cyclophosphamide-resistant systemic inflammatory disorders and in patients with granulomatosis with polyangiitis (Wegener disease),^{5,6} we decided to introduce infliximab (400 mg every 3 weeks) combined with methotrexate (15 mg/wk administered subcutaneously) and prednisone (10 mg/d). This resulted in rapid and complete remission of local and systemic inflammation. Prednisone was tapered and discontinued. After the seventh infusion of infliximab, the patient had leukopenia (leukocytes, 1.6 g/L; lymphocytes, 0.3 g/L; and neutrophils, 1.0 g/L). Further analysis documented the presence of anti-neutrophil antibodies, a highly positive ANA result, positive double-stranded DNA (dsDNA) antibody in ELISA and *Crithidia* species assays, diminished C3 and C4 concentrations, and increased muscle enzyme levels. The patient complained about fever and polyarthritides. Within days, the situation deteriorated, with pericarditis and a sudden mitral valve insufficiency caused by papillary muscle necrosis demanding emergency valve replacement. Histology showed Libman-Sacks endocarditis (Fig 2). Diagnosis of systemic lupus erythematosus (SLE) induced (or precipitated) by TNF blockade had to be made.

Methylprednisolone boli (500 mg for 3 days) and rituximab (4 × 500 mg in weekly intervals) stabilized SLE, followed by decreasing doses of prednisone. However, scleritis relapsed, and systemic inflammation increased again. On the basis of refractory disease, persistent systemic inflammation, autoantibodies, polyclonal B lymphocytes in the bone marrow, and histology of the mitral valve, we decided to choose an anti-IL-6 strategy.⁷ The therapeutic response to tocilizumab was striking: systemic inflammation vanished within a few weeks (normalization of C-reactive protein and erythrocyte sedimentation rate), complement components normalized, autoantibody results became negative, and local inflammation subsided. Medication could be substantially reduced. Because of neutropenia (1.2 g/L), the interval of infusions was prolonged from 4 to 6 weeks. The patient has continued to have lasting and complete remission for more than 1 year.

The patient's history and clinical findings, together with extensive laboratory examinations and imaging methods, did not allow an undisputable diagnosis at first presentation. The emergence of a localized inflammation with signs of granuloma formation together with the findings in magnetic resonance imaging suggested a localized granulomatosis with polyangiitis (Wegener disease). This interpretation was supported by the lack of immunoglobulin, complement deposits, or both in biopsy specimens. Because the disease did not respond to treatment with cyclophosphamide, we finally introduced infliximab to block the TNF pathway. In line with published data,^{5,6,8} this strategy was successful, and local and systemic inflammation subsided within a few weeks.

TNF inhibition promotes immunologic features of a T_H2 response, as characterized by an increase in or development of autoantibodies, particularly ANAs and dsDNA antibodies. Rarely, these immunologic changes evolve into full-blown SLE.⁹ In this case autoantibodies (ANAs and dsDNA), reduction in levels of the complement components C3 and C4, symmetric polyarthritides,

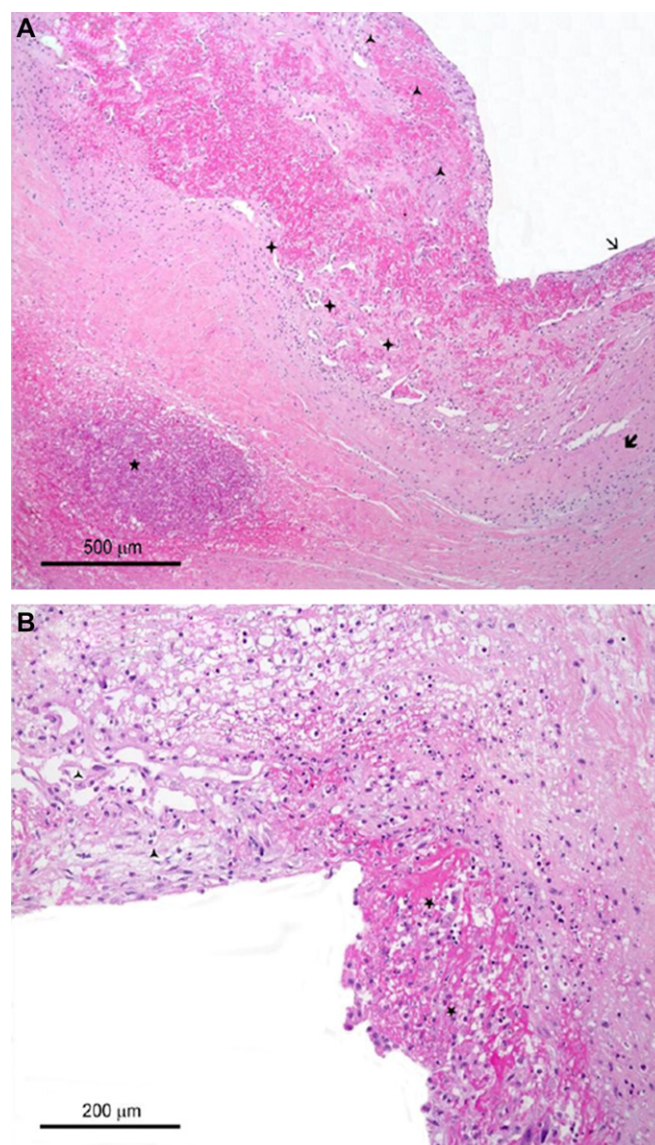


FIG 2. A, Endocarditis with vegetations consisting of an outer exudative layer ($\blacktriangle$) of fibrin and platelets and an inner organizing layer ($+$) of proliferating capillaries (neovascularization) and fibroblasts with sparse mononuclear inflammatory cells. $\star$, Fibrinoid necrosis of the valvular stroma; $\blackarrow$, endocardial surface; $\blacktriangle$, valvular stroma. Magnification $\times 40$. Scale = 500 μ m. B, Exudative layer of fibrin and platelets ($\star$); organizing layer of proliferating capillaries and fibroblasts ($\blacktriangle$). Magnification $\times 100$. Scale = 200 μ m.

pericarditis, myositis, and Libman-Sacks endocarditis documented the diagnosis of SLE, fulfilling the American College of Rheumatology criteria of 1997. Histology of the replaced valve provided additional proof. Correlation between disease evolution and infliximab treatment strongly argues for a decisive role of TNF blockade in the development of SLE in this case.

From a pathogenetic standpoint, systemic inflammation and formation of autoantibodies and polyclonal plasma cells in bone marrow argue for an IL-6-driven disorder. Of note, IL-6 was formerly named B cell-stimulating factor 2. We therefore hypothesized that IL-6 blockade might control lupus-like features.⁷ Blocking the IL-6 receptor α chain with tocilizumab and thereby inhibiting the IL-6 pathway was highly effective, leading

to a rapid and lasting remission and allowing reduction of glucocorticoids. Persisting leukopenia during tocilizumab might reflect a side effect or a remaining disease feature.¹⁰

Blockade of the TNF and IL-6 pathway is very effective in suppressing systemic and local inflammation and is regarded as equivalently effective in patients with RA. This case highlights that knowledge of the differential effects of proinflammatory cytokines on the adaptive immune system might become highly important in a specific clinical setting. With the growing number of biologic agents, pathogenetic considerations are likely to become more important in clinical decision making.

In conclusion, we strongly believe that clinical reasoning should involve consideration of the molecular effects of therapeutic interventions. Drug prescription based on diagnostic labels is too simplistic. The traditional approach bears the risk of overlooking potentially fatal side effects in a given in-label indication but also impedes prescription of a potentially effective drug in an off-label situation.

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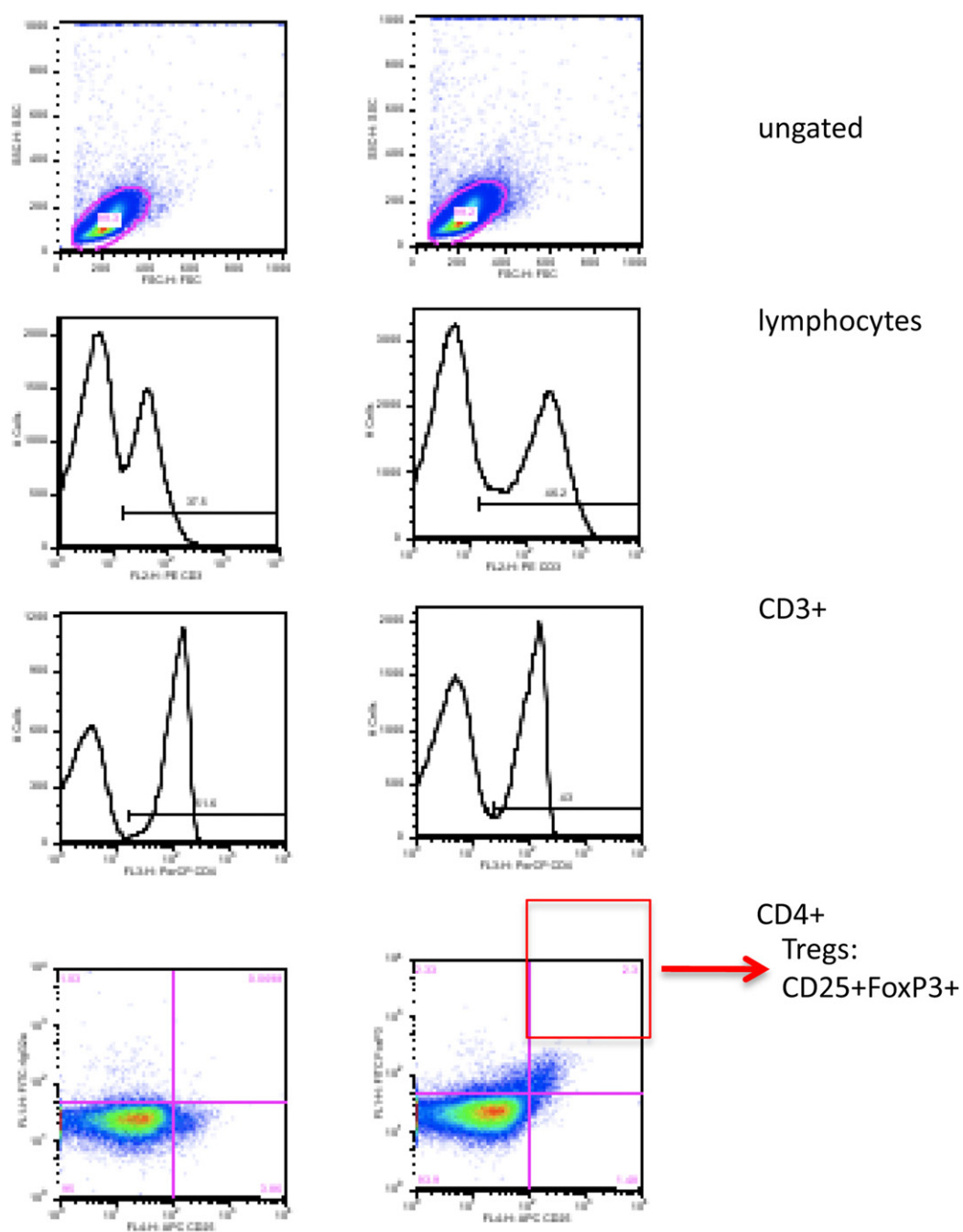
Disclosure of potential conflict of interest: P. M. Villiger has board memberships with Roche, Novartis, Pfizer, Merck Sharp & Dohme, Abbott, Bristol-Myers Squibb,

UCB, and Grünenthal; is employed by the University of Bern; and has received grants from the Swiss National Science Foundation and Lichtensteinstiftung. The rest of the authors declare that they have no relevant conflicts of interest.

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SLE by TNF-blocking agents and response to anti-IL-6

FIG E1. Normal population of CD25⁺ forkhead box protein 3 (FoxP3)⁺ regulatory T lymphocytes (Tregs) in peripheral blood. PBMCs were isolated and stained first for CD3, CD4, and CD25 and stained after fixation for FoxP3 (right panel) or the corresponding isotype (left panel), respectively. Flow cytometric analysis revealed normal populations of CD3⁺ T cells, CD4⁺ T cells, and CD25⁺FoxP3⁺ regulatory T cells.