

Letters to the Editor

Blood TNF- α and combination therapy for rheumatoid arthritis

Sirs,

I believe that the report by Giacomelli and colleagues (1) leaves some questions open regarding what the study actually demonstrated and how the findings should be applied.

The authors suggest that the greater decrease of circulating tumor necrosis factor (TNF)- levels in the group given combination therapy with prednisone, methotrexate, and cyclosporine A reflected a more potent immunosuppressive and anti-inflammatory effect of the treatment as compared to patients who received prednisone and methotrexate without cyclosporine A. However, blood concentrations of TNF- did not correlate with any clinical or laboratory parameter of disease activity at baseline nor, it may be assumed, throughout the study even though data have not been shown. To confuse the issue further, expression of messenger RNA for the cytokine was not affected by either of the therapeutic regimens despite the decreased TNF- concentrations in culture media from mitogen-activated mononuclear cells.

The use of blood TNF- as a surrogate marker of disease activity in immune diseases remains questionable. Except for the Jarisch-Herxheimer reaction (2-4) or the "cytokine-release syndrome" associated with the *in vivo* administration of therapeutic monoclonal antibodies such as OKT3 and Campath-1H (5), there is no other convincing evidence from studies published in peer-reviewed journals that measuring blood levels of TNF- or other pro-inflammatory cytokines may represent a helpful tool for monitoring the clinical activity of inflammatory diseases or the response to treatment. This view is reinforced by clinical experience with anti-TNF- monoclonal antibodies. Indeed, treatment with infliximab down-modulates inflammation and improves the clinical course of patients with rheumatoid arthritis or Crohn's disease by eliminating TNF-producing cells rather than neutralizing blood TNF- (6, 7).

In my opinion, when equivalence in terms of efficacy and safety has been demonstrated between two different therapeutic regimens for rheumatoid arthritis, any further statement favoring either regimen that is based solely on blood concentrations and *in vitro* production of TNF- or any other cytokine could generate confusion with the risk of misleading implications for clinical practice.

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The successful use of i.v. gammaglobulin for Guillain-Barré syndrome following gold therapy in an RA patient

Sirs,

A 28-year-old woman suffering from rheumatoid arthritis (RA) received treatment with injectable gold 50 mg weekly for the first time. After 10 weeks of therapy she complained of the progressive onset of the following symptoms: numbness and tingling dysesthesia of the hands and feet starting from the tips of her toes and spreading up her lower legs, a "wooden" feeling in the feet and rapidly progressive, symmetric, ascending motor weakness. Fever and constitutional symptoms were absent. Gold therapy was stopped and she was admitted to our service. She had no history of smoking, alcohol abuse, toxin exposure or recent vaccination. Her past medical history was negative.

Neurological examination showed generalized motor weakness in both the upper and lower limbs, gait ataxia, difficulty walking

on her heels, foot drop, hypesthesia in the distal portions of all extremities and deep tendon areflexia. Plantar responses were normal. The rest of the physical examination was unremarkable.

Laboratory studies revealed no abnormalities. Blood and urine cultures were sterile. Immunological tests and antibodies to CMV, EBV, VZV, HIV, HCV, HBV and *Borrelia burgdorferi* were negative. Cerebrospinal fluid (CSF) analysis revealed: cells 0/ μ l; glucose 57 mg/dl; LDH 76 U/l; protein 487 mg/dl; IgG index and protein electrophoresis normal; gram stain negative; and CSF cultures negative. Nerve conduction tests on the first day of hospitalization showed no pathologic findings. Magnetic resonance imaging of the brain and of the cervical, thoracic and lumbar spine revealed no abnormalities.

On the basis of the characteristic clinical pattern of rapidly evolving, symmetric, ascending motor weakness, areflexia and sensory impairment, and the distinctive CSF findings (albumino-cytologic dissociation), the diagnosis of Guillain-Barré syndrome (GBS) was made. Intravenous gammaglobulin (IVGG) (400 mg/kg daily) for 5 days was administered. At the end of the treatment course, the patient was able to walk and her sensory disturbance gradually improved. No other treatment for GBS was administered. One year later the patient remains in an excellent clinical condition with no pathological findings on physical examination.

In this report a female patient with RA developed neurological manifestations 3 months after initiation of gold therapy. The diagnosis of GBS was confirmed by the characteristic clinical and CSF findings. GBS as a neurological complication due to gold therapy is very rare. It has been reported only in 7 case reports in the English and French literature (1-7). In our patient GBS developed soon after starting gold treatment. In other reports the cumulative gold dosage and the interval between the initiation of therapy and the onset of GBS manifestations varied greatly (1.5 months to 1 year) (4,7). The pathogenetic mechanisms that have been proposed for gold-induced GBS are a direct toxic effect of gold on the nerves or an immunological hypersensitivity reaction (4,6,7). We consider the immunological mechanism to be the more likely pathogenetic theory.

In our patient, treatment with high dose IVGG was used for gold-induced GBS and resulted in a dramatic clinical improvement in a short time. In previous case reports the therapy consisted of corticosteroids or a course of plasmapheresis. In randomised trials IVIG therapy has been shown to be as effective as plasma exchange in GBS treat-

ment (8).

In conclusion, this is the first case reporting the successful treatment of GBS following gold therapy with high dose IVIG.

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Cutaneous vasculitis associated with mixed cryoglobulinemia in adult Still's disease

Sirs,

Adult Still's disease (ASD) is a systemic inflammatory disorder of unknown origin, characterized by high spiking fever, arthralgias or arthritis, sore throat, and an evanescent rash often occurring during the fever spikes (1-3). We describe a 47-year-old man fulfilling the diagnostic criteria of ASD (1, 3, 4) who is unique in having developed mixed cryoglobulinemia, leukocytoclastic cutaneous vasculitis and mild mesangial glomerulonephritis during the phase of

active disease.

Our patient had a 10-day history of high fever ($> 39.5^{\circ}\text{C}$), diffuse arthralgias and myalgias, and an evanescent salmon pink rash prior to admission, as well as a one month history of sore throat, low-grade fever, mild abdominal pain and weight loss of 5 kg. Remarkably, at the age of 6 and 8 years he had two episodes of high fever and arthralgias which fully resolved after a 3-month treatment with high doses of aspirin. On admission he also had hepatosplenomegaly, anemia, leukocytosis, strikingly elevated C-reactive protein and ferritin levels, mild liver dysfunction and normal renal function. Serum immunoglobulins IgG and IgA were elevated, IgM was normal, while complement levels were at the lower limit of normal. Rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies and an extensive work-up for infection were all negative. Of note, cryoglobulins were detectable as polyclonal IgG, IgA, and IgM.

On the second day of hospitalization a mild migratory, itchy, maculopapular rash appeared on the head, upper trunk, back, buttocks and groins. The rash evolved into purpuric plaques after two days and disappeared soon after. On the fifth day several annular purpuric plaques on the ankles and dorsal area of the feet and a symmetric confluent purpuric plaque on the shins were observed (Fig. 1). Skin biopsy findings were compatible with leukocytoclastic vasculitis. In the following days his general condition deteriorated to the point that he was unable to walk, cutaneous lesions became fixed, and renal dysfunction demonstrated by the presence of granular casts, mild pyuria and hematuria and elevated serum urea, was observed. Renal biopsy revealed rare vessel hyaline deposits, mesangial alterations and mild hypercellularity with C_3 and IgM deposits on immunofluorescence. Bone marrow and liver biopsy findings were unremarkable. At the 10th day methylprednisolone (72 mg/day) and methotrexate (17.5 mg/week) were started (5); during the



Fig. 1. Demarcated annular purpuric plaques with a palpable border and clearing in the center, without necrosis or ulceration; smaller 3-5 mm purpuric papules surround the plaques.

following days a dramatic clinical response, including remission of skin vasculitis, was observed. By the seventh week he had resumed all of his daily activities, treatment was discontinued at the 14th month and he did extremely well during the following 6 months. Laboratory examinations, including repeated determination of cryoglobulins, were unremarkable.

Clearly, our patient fulfilled the diagnostic criteria of ASD (1, 3, 4), which was confirmed during the 20-month follow-up. Because of his childhood episodes of fever and arthralgias the diagnosis of Still's disease of childhood onset is tempting; however, since he denied any similar episodes for the next 40 years, he was classified as having an adult-onset disease (1, 6, 7). We systematically excluded viral infections, sepsis, tuberculosis, sarcoidosis, malignancies, systemic connective tissue diseases (1, 2), and Schnitzel's syndrome (8), not only because ASD is a relatively rare disease, but also because of the atypical coexistence of both skin and renal involvement. Cutaneous vasculitis and glomerulonephritis in the course of ASD have been described only once and twice in the past, respectively (9, 10). To the best of our knowledge no previous cases of ASD associated with mixed cryoglobulinemia have been reported. Perhaps clinicians are overlooking a possibly not uncommon aspect of this disease, since during the course of a severe, acute inflammatory response such as ASD transient cryoglobulin formation is not unexpected. This case suggests that ASD should be included in the list of systemic conditions that may be complicated with mixed cryoglobulinemia.

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