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)-α 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-α 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-α concentrations in culture media from mitogen-activated mononuclear cells.

The use of blood TNF-α 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-α 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-α 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-α (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-α or any other cytokine could generate confusion with the risk of misleading implications for clinical practice.

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References

1. GIACOMELLI R, CIPRIANI P, MATUCCI CERINIC M *et al.*: Combination therapy with cyclosporine and methotrexate in patients with early rheumatoid arthritis soon inhibits TNFα production without decreasing TNFα mRNA levels. An *in vivo* and *in vitro* study. *Clin Exp Rheumatol* 2002; 20: 365-72.
2. FEKADE D, KNOX K, HUSSEIN K *et al.*: Prevention of Jarisch-Herxheimer reactions by treatment with antibodies against Tumor Necrosis Factor-α. *N Engl J Med* 1996; 335: 311-15.
3. KAPLANSKI G, GRANEL B, VAZ T, DURAND JM: Jarisch-Herxheimer reaction complicating the treatment of chronic Q fever endocarditis: Elevated TNF-alpha and IL-6 serum levels. *J Infect* 1998; 37: 83-4.
4. COOPER PJ, FEKADE D, REMICK DG, GRINT P, WHERRY J, GRIFFIN GE: Recombinant human interleukin-10 fails to alter proinflammatory cytokine production or physiologic changes associated with the Jarisch-Herxheimer reaction. *J Infect Dis* 2000; 181: 203-9.
5. BREEDVELD FC: Therapeutic monoclonal antibodies. *Lancet* 2000; 355: 735-40.
6. SCALLON BJ, MOORE MA, TRINH DM, GHRAYEB J: Chimeric anti-TNF-α monoclonal antibody, cA2, binds recombinant transmembrane TNF-α and activates immune effector functions. *Cytokine* 1995; 7: 251-9.
7. KRIEGLER M, PEREZ C, DeFAY K, ALBERT I, LU SD: A novel form of TNF/Cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. *Cell* 1988; 53: 45-53.

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 limps, 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/μl; 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-