Intra-articular anti-tumor necrosis factor α antibody in recalcitrant arthritis of Behçet's disease

Sirs,

Infliximab, a chimeric monoclonal antibody against TNFα, has been used successfully in the management of rheumatoid arthritis (RA) (1), Chron's disease (2), psoriasis (3) and psoriatic arthritis (4),ankylosing spondylitis (5) and, recently, in refractory cases of Behçet's disease (BD) (6, 7). Anecdotal reports on the effect of intra-articular (IA) administration of this biologic agent suggest its efficacy in cases of refractory inflammatory arthritis (8, 9). However, the effect of infliximab administered either intra-articularly or systemically on the arthritis of BD has never been reported. In this report we describe our impressively favorable experience with the intraarticular injection of infliximab, in a case of recalcitrant bilateral knee synovitis in a patient with Behçet's disease, both on his arthritis and the severe orogenital ulcerative lesions.

Our patient was a 32-year-old Caucasian male who first presented in 1995 with a 4-year history of recurrent arthritis of the knees, oral and scrotal ulcers, panniculitis and skin folliculitis. Paracentesis of the right knee yielded an inflammatory fluid with 34,000 white cells, of which 97% were polymorphonuclears (PMNs), and negative cultures. A mild normocytic normochromic anemia was present, his ESR was 45 mm, the serologic profile was negative, whereas HLA typing disclosed the B5 alloantigen. Based on the above, the diagnosis of Behçet's disease was made and the patient was placed on colchicine 0.5 mg b.i.d. and methylprednizolone 6 mg per day, later reduced to 4 mg daily. Since then, and under this treatment, supplemented at several intervals with non-steroidal anti-inflammatory medications (NSAIDs), he had been experiencing recurrent episodes of severe bilateral knee synovitis (white cell count up to 80,000/μL with 95% PMNs), recurrent scrotal ulcerations and mouth aphthae, and skin folliculitis. On several occasions, long acting steroid injections had been administered IA with only brief (less than 15 -20 days), periods of relief of the synovitis, In December 2001 methotrexate was added to the regimen without remission of the arthritis.

In March 2002,he presented with severe bilateral knee synovitis (32,000 WBCs in the fluid and normal glucose) and recurrence of the orogenital ulcers. ESR was 40 mm and CRP 8.5 mg/dl (normal up to 0.6 mg/dL). A decision was made to give IA 100 mg of infliximab (Remicade) in each knee, after informed consent was obtained. Three weeks later the patient was re-evaluated. He reported disappearance of the synovitis and the orogenital lesions within 2 days following the infusion. His knees were completely normal and there were no ulcers in his mouth and scrotum; his ESR was 10 mm and his CRP was normal. Methylprednizolone was decreased to 2 mg/day and one month later to 2 mg every other day.

Five months following the injection,the patient was seen and he reported having been free of symptoms for 3 months, after which time there was a recurrence of the arthritis and the orogenital lesions. A crop of mouth and scrotal ulcerations was noted, and both knees were swollen, warm and painful. ESR was 80 mm and CRP 11.5 mg/dL. Sixty μl of inflammatory fluid was removed from the right knee and 100 mg of infliximab was injected locally. The left knee was not evacuated but 3 cc of fluid was removed and the same amount of Remicade was injected. This was done in order to study the effect of the biologic agent upon the inflammatory synovitis and to compare it between the two joints,the one being almost dry and the other full of fluid. The right knee effusion had a WBC count of 42,000/μl with 98% PMNs, and the left a count of 25,500/μL with 97% PMNs. Three days later upon re-evaluation, the patient presented in excellent condition, and reported disappearance of the synovitis from both knees and the orogenital ulcers within 24 hours following the injections. Arthrocentesis of the left knee yielded, with great difficulty, only 1.5 cc of fluid, containing 1,653 WBCs with 6% PMNs and 94% lymphocytes. ESR was 35 mm and CRP 1.1 mg/dL. Discontinuation of methotrexate and methylprednizolone was recommended, and re-evaluation after one month was scheduled.

There is no information in the literature regarding the effect of anti-TNFα in refractory cases of arthritis of BD. Furthermore, no such information exists regarding IA injection of this agent in the above clinical condition. At the same time, IA administration of infliximab has been anecdotally suggested for refractory cases of inflammatory synovitis (8, 9), but no firm data in the literature have confirmed its efficacy.

Our young patient with BD and recalcitrant arthritis responded dramatically, although not permanently, to the IA injection of the forementioned substance. Several important comments can be made from this case. Firstly, that the intractable inflammatory synovitis of BD responds dramatically and for a reasonably long period to inta-articular anti-TNFα. Consequently, this modality can be used in refractory arthritis of this disease. But, perhaps even more importantly, refractory or persistent inflammatory synovitis in other Th1 mediated conditions such as RA,in one or two joints in an otherwise controlled disease, may very successfully respond to the described method.

Secondly, the fact that, following the IA injection, the mouth and scrotal ulcers disappeared promptly, in a way similar to that observed after the systemic administration of anti-TNFα antibody, suggests that this agent is well absorbed into the systemic circulation from the joint space. Data on the kinetics of infliximab following its IA administration are not available but appropriate studies may confirm our observation.

Finally, the dramatic response of both the synovitis and orogenital lesions to anti-TNFα suggests that TNFα may be the major cytokine involved in their pathogenesis. This is rather to be expected, since the activated γδT cells in this disease produce large amounts of TNFα (10). This favorable response, along with the reported similar responses of severe uveitis (6) and severe gastrointestinal involvement (7) to anti-TNFα, may indicate that infliximab could be a very effective global treatment for a disease with protean and often serious manifestations occurring concomitantly and for each one of which, so far, individual drugs have been recommended, with the exception of central nervous system disease.

In conclusion, by no means do we suggest that IA infliximab be the treatment of choice for the synovitis of Behçet's disease. However, we suggest that refractory arthritis may respond well to this agent,and this may control other concomitant minor manifestations of the disease, whereas for major manifestations the systemic administration of infliximab may be indicated.

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