

Should We Be Using Intraarticular Tumor Necrosis Factor Blockade in Inflammatory Monoarthritis?



Persistent inflammatory monoarthritis is a common clinical problem that is often difficult to treat. Local therapies such as intraarticular steroids or chemical, radionuclide, or surgical synovectomy commonly offer limited efficacy and short duration of action. Systemic immunosuppression is not an attractive option for the patient with limited disease and is not always effective. Yet persistent monoarthritis may be debilitating and destructive, and may ultimately necessitate joint replacement surgery as a consequence of either acute joint destruction or later secondary osteoarthritis. Now that the efficacy of systemic anti-tumor necrosis factor (TNF) therapy is established in several inflammatory arthritides, the prospect of local anti-TNF treatment, at substantially less cost and risk, appears attractive. Several authors have reported experience with intraarticular administration of anti-TNF agents. Although the sum total of published experience is very limited and publication bias is possible, these reports beg the question of whether there is a place for intraarticular anti-TNF treatment in clinical practice. We have reviewed available data to see what rational conclusions can be drawn.

Each of the 3 currently available anti-TNF agents, infliximab, etanercept, and adalimumab, is administered parenterally, with varying half-lives following a single dose of 8 days, 2.8 days, and 14 days, respectively¹. Clearance of infliximab appears to decrease with concomitant administration of methotrexate (MTX). Intraarticular therapy is attractive, as injections are quick and familiar to rheumatologists. However, an inherent problem of the intraarticular route is that most compounds are rapidly absorbed from an inflamed joint into systemic circulation. Indeed, intraarticular corticosteroids are generally dependent on being complexed as salts for retention in the joint and clinical efficacy. Small molecules such as MTX can be found in the opposite knee 10–15 minutes following knee injection². The rate of systemic absorption falls as molecular weight increases and solubility decreases, and is more influenced by total area of exposed synovium than by dose³. Reports of systemic improvement following intraarticular administration of anti-TNF agents suggest there is significant systemic absorption of drug from the joint^{4,5}.

Bokarewa and Tarkowski injected knees of 6 patients with differing underlying diagnoses but with persistent knee synovitis⁶. Following aspiration, a single 100 mg dose of infliximab was administered. Five patients relapsed within 2 weeks, and it was concluded that infliximab offered no benefit over intraarticular corticosteroid. In contrast, Nikas, *et al* studied 5 patients with rheumatoid arthritis (RA) receiving disease modifying antirheumatic drugs (DMARD; unspecified) with persistent inflammation in one large joint⁷. Two 100 mg injections were given 24 hours apart, with good results at 6 weeks' followup. A similar regimen gave a good result after 4 weeks in 3 patients with RA⁴. Recently, 3 patients with ankylosing spondylitis and refractory knee monoarthritis, whose disease did not justify parenteral anti-TNF, received single 100 mg injections. Remission of knee symptoms had lasted 3 months in 2 patients and 4 months in the third patient when the report went to press⁸. Disparity between these studies may relate to dose, underlying disease, presence of DMARD, or decreased systemic absorption from the second dose via reduction in vascular endothelial growth factor-induced vascular permeability and endothelial dysfunction⁹. Benefit has been reported with 6-weekly injections to persistently inflamed joints in patients with RA and spondyloarthropathies already receiving intravenous infliximab¹⁰. A pharmacokinetic rationale exists, given the low volume of distribution with infliximab (3 to 5 liters). Prolonged remission of resistant knee monoarthritis in a patient with spondyloarthropathy was recently reported following a single 100 mg dose. Scintigraphy with ^{99m}Tc-infliximab prior to treatment showed intense uptake in the affected knee, indicating high levels of TNF¹¹.

There are fewer published data relating to etanercept. Osborn performed a small, placebo-controlled study of 20 patients with acute RA, comparing one 12.5 mg dose with saline in a single swollen joint¹². Some patients continued to show benefit at 16 weeks. Efficacy has been reported with smaller doses, accompanied by a reduction in vascularity on Doppler ultrasound¹³. Long-lasting benefit following injection of 25 mg etanercept into the wrist of a patient with sarcoidosis and monoarthritis has been described¹⁴.

We are not aware of any data regarding adalimumab. Toxicity seems rare, although injection site reactions¹⁵ and septic arthritis secondary to intraarticular TNF blockers have been reported¹⁰.

Should we be using anti-TNF drugs intraarticularly? Clearly the answer to this question is not discernible from current literature, although available data seem encouraging, especially regarding peripheral spondyloarthritis. It is an important question, as the clinical problems can be substantial and, on the face of it, intraarticular anti-TNF is a plausible form of treatment. A number of issues need to be clarified and the sooner the better. Are there subgroups of patients who benefit? Are all the current anti-TNF drugs equally effective or ineffective? How much drug should be administered intraarticularly? How many times? Should oral DMARD be given concomitantly, to improve efficacy or reduce risk of allergic reactions following repeated administration of infliximab? Is intraarticular therapy safe? The latter question includes the necessity for tuberculosis screening and the possibility of injection reactions akin to those seen with subcutaneous etanercept. Strict aseptic technique and close surveillance for infection would be advisable given such limited clinical experience. Perhaps most critically, can drug developments be made that will prolong local activity within the joint? Liposomal delivery might be one such possibility, but the uptake of liposomes by macrophages might remove anti-TNF from its site of action and diminish the beneficial effect; subsequent processing could even be detrimental. Larger studies are clearly warranted, and pharmacokinetic study is desirable, in particular to clarify the degree of systemic absorption. We are mindful that 50 years after the advent of intraarticular steroids, optimal doses are still unclear and randomized, controlled trials few.

There is a great need for effective, long-lasting local treatment for persistent monoarthritis. Intraarticular therapy with anti-TNF drugs or their development might have a place in this context and is worthy of systematic evaluation.

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