
TNF involvement and anti-TNF therapy of reactive and unclassified arthritis

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ABSTRACT

A growing body of evidence shows that tumor necrosis factor (TNF) alpha, a pro-inflammatory cytokine involved in the pathogenesis of rheumatoid arthritis (RA), is also involved in the pathogenesis of reactive and unclassified arthritis. Elevated levels of TNF- α and other pro-inflammatory cytokines are seen in these inflammatory arthropathies. The clinical effect on a potential underlying infection is not known, but several studies have suggested at least short-term effectiveness and safety of anti-TNF- α therapy in reactive and unclassified arthritis.

I. Background

Tumor necrosis factor α (TNF- α) is a key factor in synovial inflammation and is an attractive target for several biologic agents approved for use in rheumatoid arthritis (RA) (1). Traditional therapy against RA may also work in part by affecting TNF- α production and secretion. For instance, low doses of methotrexate (MTX) suppress TNF- α production by T cells from RA patients (2). With the advent of specific therapy against TNF- α , we can now more directly assess the response to altering this cytokine. TNF- α blockade can be achieved therapeutically with biologic agents, including anti-TNF- α monoclonal antibodies such as infliximab and soluble TNF- α receptors. Etanercept, an injectable soluble tumor necrosis factor (TNF) receptor protein, decreases the inflammation seen in RA and improves patients' symptoms. However, investigation in other inflammatory arthritides has only begun. TNF- α has been detected in CT-guided biopsies of sacroiliac joints in patients with spondyloarthropathies, which has led to investigation of this cytokine as a therapeutic target (3). For example, Van den Bosch and colleagues have shown effectiveness of infliximab in patients

with active spondyloarthropathy (SpA) (4). Enthesal pathology in resistant SpA has also responded to etanercept, (5) as well as has morning stiffness, fatigue, and axial and peripheral arthritis (6). Clinical and experimental evidence exists that TNF- α blockade also suppresses other inflammatory mediators, such as IL-1, IL-6, and IL-8, so that the impact of TNF- α suppression goes well beyond an effect on this one cytokine (7).

II. TNF- α involvement in reactive arthritis

Reactive arthritis (ReA) is an inflammatory arthropathy that occurs in response to several characteristic infections (8). The typical pattern of involvement includes peripheral oligoarticular arthritis generally prominent in the lower extremities and frequently accompanied by sacroiliitis. Extra-articular manifestations often involve the skin, eyes, entheses, and tendons.

Typically ReA occurs after a gastrointestinal or genitourinary infection. *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter* (with enteric infection), *Chlamydia* and *Ureaplasma* (with genital infection) have been implicated as inciting organisms. Other bacteria may be involved in causing ReA, but these have not been well characterized. The exact pathogenesis of reactive arthritis remains unclear, as cultures of synovial fluid (SF) are generally negative for organisms. Despite negative cultures, microbial antigens and nucleic acids have been identified in some but not all patients with reactive arthritis (9). Although *Chlamydia* are often not culturable, evidence exists that viable and metabolically active bacteria may persist in synovium and specifically in monocytes (10). Indeed, *Chlamydia trachomatis* may persist in joint tissue despite clinical improvement after antibiotic treatment, as shown by *in situ* hybridization techniques (11,12). Pres-

ence of chlamydia was more commonly detected in synovial tissue than in SF of patients with ReA (13).

Cytokines and their soluble receptors in the joints of inflammatory arthropathies likely play a role in response to infectious triggers. They can be detected in synovial tissue by highly sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) techniques (14). TNF- α is readily detected in synovium of early ReA (15). Notably, patients with culture-proven bacterial arthritis have higher levels of synovial TNF- α than patients with osteoarthritis or with other inflammatory arthritides, including gouty arthritis and RA (16). Lichten *et al.* developed a rat model whereby arthritis was induced by intra-articular injection of a polysaccharide from group A streptococci. After the arthritis resolved, experimentally-induced small bowel overgrowth reactivated the arthritis (17). Reactivation of arthritis was prevented by anti-TNF- α antiserum and interleukin 1 receptor antagonist, suggesting important roles for these cytokines.

TNF responses may well be genetically determined. Within the TNF gene region, several microsatellites have been identified. Susceptibility to ReA may be predicted by expression of polymorphisms within the gene region. Tuokko *et al.* found that several TNF- α alleles were increased in patients with ReA (18). The increase in the c1 allele was independent from HLA-B27, suggesting that it might be a unique susceptibility marker for the disease.

T helper 1 (Th1) cytokines such as interferon gamma (IFN- γ) and TNF- α appear from a variety of experiments to be able to inhibit chlamydial growth and are potentially helpful in eradicating chlamydia and some other intracellular bacteria (19, 20). Th2 cytokines (IL-4 and IL-10) may prevent a complete Th1 response and favor persistence of these organisms.

In the synovial fluid (SF) of patients with ReA, an impaired T cell response to a triggering microbe may result in abnormal cytokine release (21). Thiel *et al.* identified antigen specific T cells in SF of ReA patients and investigated SF T cell responses from patients with

Chlamydia- and Yersinia-induced ReA after stimulation with proteins from each organism. TNF- α and IFN- γ positive CD4 cells were present, but in addition there was antigen specific expression of IL-10, which could have an inhibitory effect on IFN- γ and TNF- α secretion (22).

Kotake *et al.* used RT-PCR for synovial tissue cytokine message analysis from patients with ReA, unclassified arthritis, and RA (23). Cytokine mRNA profiles revealed elevated TNF- α , as well as other type 1 pro-inflammatory cytokines. Lower levels of cytokine mRNA expression in those on corticosteroids or disease-modifying-anti-rheumatic medication (DMARD) compared with those off of therapy suggested that drug therapy may inhibit cytokine secretion. A greater amount of IFN- γ and IL-2 was seen in patients with ReA than RA, suggesting that underlying pathogenesis of the diseases may differ. Since IFN- γ may alter chlamydial development in a dose-dependent fashion, it is of interest that atypical reticulate bodies (RB) of *C. trachomatis* have been found in fibroblasts and macrophages of patients with ReA despite antibiotic treatment (23). *In vitro* exposure to IFN- γ inhibited transformation of metabolically active RBs into smaller infectious elementary bodies (19, 20). Kotake *et al.* found relatively high IL-10 amounts along with IFN- γ in synovium from patients with unclassified oligoarthritis and chlamydia, and suggested that the IL-10 may inhibit development of sufficient IFN- γ to eradicate the organisms (22).

A majority of patients with ReA experience a self-limited course that runs 3-12 months. However, approximately 15% of patients continue to have chronic often destructive and disabling arthritis or enthesitis (24). The nature of the immune system response may explain why disease persists in some persons. Can the TNF or other response help by eradicating the organism or might the response induce a resistant phase of the infection and contribute to the symptoms? Braun *et al.* showed that ReA patients with a disease duration of ≥ 6 months secreted a lower level of TNF- α than patients with a disease

duration of < 6 months. In addition, a higher frequency of B27 positive patients had a chronic course. The authors suggested that a low TNF- α secretion might contribute to bacterial persistence in ReA patients, but it is not yet established if the lower TNF- α levels were a cause or result of the course (25).

Chlamydia-induced cytokine release from synovial fibroblasts may contribute to the development of joint inflammation. Rodel *et al.* demonstrated that IFN- γ production was stimulated by TNF- α in Chlamydia trachomatis-infected synovial fibroblasts (26). In response to Chlamydia infection and synoviocyte treatment with interferon-gamma (IFN- γ), TNF- α was released (27). A separate study showed that recombinant TNF- α acted synergistically with IFN- γ to inhibit the growth of Chlamydia trachomatis in human laryngeal carcinoma cells (28). This inhibition may have occurred through catalyzing the degradation of essential tryptophan. Persistent infection may have developed through this alteration of intracellular growth (29).

Chlamydia are not the only organisms causing ReA that can trigger inflammatory mediators in various ways. Kirveskari *et al.* evaluated peripheral blood mononuclear cells (PBMC) for inflammatory cytokines in patients with Salmonella infection. Those with ReA due to Salmonella produced TNF- α , along with IL-10, IL-8, and IL-6. During disease amelioration in these patients treated only with NSAIDs, most cytokine levels fell, but TNF- α decreased in only 1 of 4 (30). More studies on the joints are needed.

TNF- α may also be able to destroy various intracellular organisms. Both IL-1b and TNF- α destroyed Yersinia enterocolitica in human fibroblast cells. In contrast, IL-4 significantly supported bacterial survival. Huppertz *et al.* concluded that cytokines, found in the joints of patients with Yersinia arthritis, were able to affect intracellular survival (31).

III. Why address unclassified arthritis?

Undifferentiated arthritis or unclassi-

fied (unspecified) inflammatory arthritis are terms that have been used to describe inflammatory arthritides that do not fit into any well-known clinical diseases category. Such patients typically have rheumatoid factor negative mono- or oligoarthritis that closely resembles ReA, except for the absence of evidence for an associated infection. If there is also inflammatory back pain, uveitis, and enthesitis, patients may be considered as having undifferentiated spondyloarthropathy (UspA).

Between 25-50% of patients with inflammatory arthritis presenting to outpatient rheumatology clinics are given the diagnosis of unclassified arthritis. It is unclear whether cases described as unclassified arthritis represent: (1) an early stage of a known type of inflammatory arthritis which has yet to fully manifest itself, (2) an incomplete manifestation of a "specific" inflammatory arthritis such as ankylosing spondylitis, (3) an overlap syndrome between several different diseases that cannot be yet be differentiated, or (4) a syndrome or syndromes that will eventually be found to have specific mechanisms (32). The report by Hulsemann and Zeidler (33) showed that the majority of patients with undifferentiated arthritis remained with unclassified disease after two years, although the prognosis was generally good with about half

achieving remission. Our own experience has been similar (22,23,34). Self-limited inflammatory oligoarthritis has also been described for years in various populations. One example of generally resolving oligoarthritis is in the Navajo Indians (35, 36). One other series showed that 55% of patients with unclassified arthritis developed a specific inflammatory joint disease, and 42% were termed rheumatoid arthritis, which was consistently mild at the end of 60 months. Resolution of all inflammatory joint symptoms occurred in 28% of cases (37).

Despite extensive testing to search for bacterial infection, including standard microbiologic procedures, serology, urogenital smears, and stool cultures, no causative infection is usually found in unclassified cases. However, several studies showing bacterial nucleic acids in SF from patients with undifferentiated arthritis suggested a common etiologic process with reactive arthritis (38). Clinically, the high rate of mono- and oligoarthritis, the high frequency of HLA-B27, the predominance of synovitis in the lower limbs, and the good prognosis all characterize a condition similar to ReA. Silveria *et al.* found increased serologic evidence of chlamydial infection in unclassified patients with no known antecedent infection (39). Weyand and Goronzy found clini-

cally silent infections in many of their patients with unclassified oligoarthritis (40). Aggerwal *et al.* proposed that a certain percentage of patients termed uSpA may in fact have ReA. They found elevated IgA antibodies to *Salmonella flexneri*, *Salmonella typhimurium* and *Chlamydia trachomatis* (compared to levels for *E. Coli*) in patients with uSpA (41). More studies are needed, but it appears that unclassified arthritis, although often a cause of confusion, is common and offers many of the same opportunities and concerns as ReA (42, 43).

IV. Treatment and future directions

Etanercept has already been shown to reduce the inflammation, improve symptoms and slow joint damage in RA. To the extent that similar mechanisms underlie reactive and unclassified arthritis, suppressing TNF- α would likely provide a similar benefit. Alternatively, if TNF- α is necessary or important for microbial eradication, altering TNF- α levels could potentially change the cytokine milieu to favor a persistence of microbes, which could possibly worsen symptoms in a subset of patients with reactive or undifferentiated arthritis. It is unclear how current therapies used in reactive arthritis or unclassified arthritis affect the cytokine environment and the handling of microbial

Table I. Effectiveness of anti-TNF- α therapy in reactive and undifferentiated arthritis.

Disease	Author (reference)	Drug used	Outcome
Reactive and unclassified arthritis	Meador <i>et al.</i> (45)	Etanercept 25 mg SC twice weekly	Open label trial. Over a 6-month treatment period, Six patients (4 with uSpA, 2 with ReA) experienced improvement in global function as well as tender and swollen joints.
Undifferentiated spondyloarthropathy (uSpA)	Marzo-Ortega <i>et al.</i> (5)	Etanercept 25 mg SC twice weekly	Descriptive longitudinal study. Out of 10 patients with SpA treated for 6 months, one patient had uSpA. This patient sustained remission for 9 months.
Undifferentiated spondyloarthropathy (uSpA)	Van den Bosch <i>et al.</i> (4)	Infliximab 5 mg/kg	Randomized, double-blinded placebo controlled trial. Out of 40 patients with SpA treated with infliximab or placebo for 12 weeks, 2 had uSpA. One patient with unclassified arthritis was withdrawn from study because of dramatic synovitis after initial improvement (see text). In the other, significant improvement occurred in patient and physician global assessments of disease activity.
Undifferentiated spondyloarthropathy (uSpA)	Brandt <i>et al.</i> (46)	Infliximab 5mg/kg	Six patients were treated over 12 weeks. Improvement in spinal symptoms, quality of life, and enthesitis occurred after the first dose and lasted for 5/6 patients, although 5 mg/kg was more effective than 3 mg/kg. One patient with a normal CRP showed improvement with enthesitis but no improvement in spinal symptoms.

antigens. Steroids, both intra-articular and systemic, as well as sulfasalazine, methotrexate, and azathioprine, have been shown to provide some benefit in reactive arthritis patients. Prednisone and second-line drugs have seemed to lead to a decrease of Th1 cytokine levels in early synovitis (15). A small open label study (still in progress and now up to 9 patients) has demonstrated early safety and efficacy of etanercept in ReA and unclassified cases (44) (Table I). While inflammation clearly decreased clinically and on synovial biopsies performed after treatment initiation, some DNA evidence of organisms persisted in several patients. No clinical worsening was seen. More observations and longer follow up are needed. Recent studies with infliximab in spondyloarthropathies have included a few patients who had unclassified arthritis that need consideration here, and have suggested efficacy of anti-TNF treatment (Table I) (45). A recent study in 6 patients with uSpA treated with infliximab showed early and sustained improvement over a 12-week period (46). A 1-year follow-up of patients from a study by Van den Bosch (Table I) showed a sustained improvement in all disease manifestations, although as time passed, symptoms recurred in a larger percentage of patients before each re-treatment (46). Importantly, in a randomized double-blinded 12-week trial, 1 patient with unclassified arthritis of 1 knee improved initially, but 1 day after a synovial biopsy developed acutely increased synovitis with negative cultures and PCR (4). He recovered with IV antibiotics over 2 days. Could this have been activation of some occult infectious trigger? Follow-up will be of interest. Not all patients with reactive and undifferentiated arthritis have identical disease processes. For example, only some patients have identifiable bacterial antigens in joints.

Studying anti-TNF therapy in reactive and undifferentiated arthritis may allow us to determine how to predict which patients may respond best to treatment through characterization of subjects by bacterial nucleic acids and cytokines found before and after treatment. Clinical

and chemical similarities between these diseases and other inflammatory arthropathies suggest that biologic agents have some role in therapy. The potential for clinical deterioration, however, requires close monitoring. Larger and longer studies are needed to evaluate safety and efficacy of this remarkable therapy.

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