A Pilot Study of Tumor Necrosis Factor Inhibition in Erosive/Inflammatory Osteoarthritis of the Hands

MOLLY D. MAGNANO, ELIZA F. CHAKRAVARTY, CORRIE BROUDY, LORINDA CHUNG, ARIELLA KELMAN, JENNIFER HILLYGUS, and MARK C. GENOVESE

ABSTRACT. ***Objective.*** To determine if anti-tumor necrosis factor (TNF) therapy (adalimumab) can safely improve symptoms of erosive/inflammatory osteoarthritis (EOA).

Methods. This was an open-label pilot trial in 12 patients with EOA. Patients > 45 years old with EOA of the hands defined by ≥ 2 tender and ≥ 2 swollen joints (distal interphalangeal, proximal interphalangeal, first carpometacarpal) despite nonsteroidal antiinflammatory drug therapy were eligible. Patients were excluded for autoimmune arthritis, recent disease modifying antirheumatic drug use, prior use of anti-TNF therapy, infection, malignancy, or poorly controlled medical conditions. All patients received adalimumab 40 mg every other week for 12 weeks. Safety was assessed 4 weeks after the final dose. Primary endpoints included safety and American College of Rheumatology (ACR) response.

Results. Patients were predominantly female with a mean age of 60 years and 12 years of arthritis. All patients completed the study and safety followup. Adverse events were mild without necessitating discontinuation of study drug. After 12 weeks, there was a statistically significant improvement in the number of swollen joints compared to baseline ($p < 0.01$). One patient achieved an ACR20 response and 42% achieved an OMERACT-OARSI response. Although we detected no statistically significant improvement in the number of tender joints, grip strength, disability, pain, or global disease assessments, trends suggested modest improvement in all efficacy measures.

Conclusion. This small open-label study of patients with EOA demonstrated that adalimumab was well tolerated. Treatment with adalimumab for 3 months did not significantly improve the signs and symptoms of EOA and most patients did not achieve an ACR20. Trends suggested improvement and individual patients had some benefit. Factors limiting interpretation of this study include the lack of a control group, outcomes chosen, number of patients treated, and the duration of treatment. (First Release May 15 2007; J Rheumatol 2007;34:1323–7)

Key Indexing Terms:
OSTEOARTHRITIS TUMOR NECROSIS FACTOR TREATMENT CYTOKINE

Osteoarthritis (OA) is a heterogeneous group of conditions with defective integrity of articular cartilage and changes in underlying bone. The pathogenesis of OA is multifactorial and involves a complex interplay of genetic, metabolic, biochemical, and biomechanical factors with variable components of inflammation. A subset of patients with OA develop an inflammatory and erosive form of the disease. Erosive osteoarthritis (EOA) is clinically recognized in peri-menopausal female patients who develop synovitis in the distal and proximal interphalangeal (DIP, PIP) joints of the hands. The classic radiological changes of EOA are characterized by a combination of bony proliferation and central erosions resulting in the classic "gull-wing deformity." In clinical studies, the diagnosis of EOA is accepted only for patients meeting American College of Rheumatology (ACR) clinical criteria for OA of the hand and showing radiographic aspects of articular surface erosions[1].

A growing body of evidence supports the theory that aberrant cytokine biology is important to the pathophysiology of OA. Morphological changes observed in OA include cartilage erosion as well as variable degrees of synovial inflammation. Cartilage from equine osteoarthritic knees demonstrates levels of interleukin 1ß (IL-1ß), tumor necrosis factor-α (TNF-α), and numerous matrix metalloproteinases (MMP) above those found in normal joints[2]. This cytokine milieu signals synoviocytes and chondrocytes to express metalloproteinases that destroy the structural integrity of synovial cartilage[3]. In response to this inflammatory environment, chondrocytes show a diminished capacity to self-repair in response to growth factors, resulting in irreversible cartilage damage[4].

From the Division of Immunology and Rheumatology, Stanford University, Palo Alto, California, USA.

Supported by Abbott Pharmaceuticals and grant 5 M01 RR000070 from the National Center for Research Resources, National Institutes of Health.

M.D. Magnano, MD, Postdoctoral Fellow; E.F. Chakravarty, MD, Assistant Professor; C. Broudy, MD, Postdoctoral Fellow; L. Chung, MD, Assistant Professor; A. Kelman, MD, Adjunct Clinical Professor, Stanford University, Medical Director, Genentech Inc.; J. Hillygus, Research Assistant; M. Genovese, Associate Professor of Medicine, Division of Immunology and Rheumatology, Stanford University.

Address reprint requests to Dr. M. Genovese, Division of Immunology and Rheumatology, Stanford University, 1000 Welch Road, Suite 203, Palo Alto, CA 94304. E-mail: genovese@stanford.edu

Accepted for publication February 26, 2007.

Several experiments suggest that neutralizing TNF-α may suppress cartilage degradation in arthritis. Animal models of OA reveal increased staining for TNF-α in diseased cartilage and elevated levels of TNF-α in the synovial fluid compared to normal controls[5,6]. In human OA samples, chondrocytes produce more TNF-α and TNF-α convertase enzyme than normal cartilage and express higher quantities of the p55 TNF-α receptor[7]; consequently, OA cartilage may be more susceptible to damage resulting from TNF-α. These data, in addition to a report of successful treatment of OA with TNF inhibition[8], raise the possibility that anticytokine therapy with a TNF-α inhibitor may be effective treatment for OA; its effects may be most pronounced in the inflammatory EOA subset.

Therapeutic strategies designed to modulate the imbalance between anabolic and catabolic pathways in OA are needed. Investigating the role of cytokines in the progression of articular cartilage damage may offer new insight into the biology of OA and provide relief to patients. This pilot study investigated if cytokine blockade with a fully human TNF-α monoclonal antibody (adalimumab) can safely improve the symptoms and signs of EOA.

MATERIALS AND METHODS

Patient population. This was an open-label trial of adalimumab in patients ≥ 45 years of age with moderate to severe EOA of the hands, defined by ≥ 2 tender joints and ≥ 2 swollen joints (assessment included DIP, PIP, and first carpometacarpal joints). All patients met ACR clinical criteria for OA of the hands, had an inadequate response to nonsteroidal antiinflammatory drugs (NSAID), and had prior radiographs showing ≥ 1 articular surface erosion at the DIP and/or PIP joints. Concomitant use of NSAID and/or analgesic medications during the study was permitted at stable doses for at least 4 weeks prior to the baseline visit. The study received local institutional review board approval and all patients provided written informed consent prior to participation.

Patients were excluded for evidence of an autoimmune cause of arthritis, history of psoriasis or systemic lupus erythematosus, or neurologic symptoms suggestive of multiple sclerosis or other central nervous system demyelinating diseases. Medication exclusions included any prior anti-TNF-α therapy or use of any disease modifying antirheumatic drugs within 4 weeks of baseline. Patients with other clinically significant medical conditions including active infection or known malignancy requiring treatment were ineligible.

Assessments and drug administration. Prior to study enrollment, each patient underwent a clinical evaluation including medical history, physical examination, laboratory studies, PPD skin test, and review of concurrent medications. Laboratory tests required for eligibility included a negative urine pregnancy test, hepatitis B surface antigen, anti-hepatitis C antibody, and normal complete blood count (CBC), alanine aminotransferase (ALT), and serum creatinine.

Enrolled patients received 6 biweekly subcutaneous injections of 40 mg adalimumab over 12 weeks. Patients were assessed at baseline and at Weeks 4, 8, and 12 of treatment. Evaluations at each visit included an interval history and physical examination; tender (TJC) and swollen (SJC) joint counts; grip strength (kg) using a standardized dynamometer; the Health Assessment Questionnaire Disability Index (HAQ-DI); the Western Ontario McMaster University OA index (WOMAC; total score); physician and patient assessments of global disease activity by 100 mm visual analog scale (VAS) score; and patient assessment of pain by 100 mm VAS. Laboratory studies at each visit included a CBC, ALT, serum creatinine, and erythrocyte sedimentation rate (ESR).

All patients underwent a final safety assessment 30 days after the Week 12 visit.

Outcome measures. The co-primary outcomes were safety and efficacy after 12 weeks of treatment. Patients were monitored for adverse events (AE), serious AE, and clinically significant changes in vital signs and laboratory tests. Efficacy was measured by the proportion of patients with an ACR20 response at 12 weeks. An ACR20 response indicates a decrease of at least 20% in the TJC and SJC (20 joints were assessed for tenderness and swelling) as well as a 20% improvement in at least 3 of the following: patient's global assessment of disease activity; patient's assessment of pain; physical function as assessed by the HAQ-DI; physician's global assessment of disease activity; and ESR.

Secondary outcomes included improvements in each component of the ACR20 and in symptoms of OA, as measured by grip strength and total WOMAC score.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI) recently published novel criteria for a response to treatment in randomized controlled trials (RCT) of OA[9]. An OMERACT-OARSI response is classified as an improvement in pain or function of at least 50% and a decrease of at least 20 mm on the VAS for pain or function, or occurrence of at least 2 of the following: decrease in pain of at least 20% and at least 10 mm on the VAS; improvement in function of at least 20% and a decrease of at least 10 mm on the VAS; and an increase in the patient's global assessment score by at least 20% and at least 10 mm on the VAS. As data were collected on function, pain, and patient's global assessment of disease activity, the OMERACT–OARSI response index is also reported as a secondary outcome.

Statistical analysis. Because this was an uncontrolled open-label pilot study, only descriptive analyses were performed. The sample size was determined by what was felt to be feasible at a single institution. The proportion of patients achieving an ACR20 response and an OMERACT-OARSI response was calculated for each timepoint. Comparisons of each clinical measure were made between Weeks 12 and baseline using Student t tests.

RESULTS

Patient population. Demographic and baseline characteristics of the 12 patients are summarized in Table 1. The majority of

Table 1. Demographic and baseline characteristics of 12 patients with erosive/inflammatory OA.

Variable	Mean (%)	Range
Age, yrs	60	45–75
Disease duration, yrs	12	3–49
Women, n (%)	11 (92)	NA
Prior DMARD use, n (%)	6 (50)	NA
DMARD withdrawal 4 weeks prior to study, n (%)	4 (33)	NA
Current NSAID users, n (%)	7 (58)	NA
Current glucosamine/chondroitin users, n (%)	5 (42)	NA
Right grip strength, kg	25.2	16–40
Left grip strength, kg	23.7	17–39
Tender joint count (0–20)	9	4–16
Swollen joint count (0–20)	7.8	3–13
Erythrocyte sedimentation rate, mm/h	8.8	0–29
Disability index of the HAQ (0–3)	0.97	0.125–1.5
Patient global assessment of disease activity, mm on VAS (0–100)	48.6	10 – 80
Physician global assessment of disease activity, mm on VAS (0–100)	40.1	21–68
Patient pain assessment, mm on VAS (0–100)	40.1	2–83
Western Ontario McMaster University OA Index (WOMAC) (0–1000)	479.4	92–1410

the patients were women (11/12) with a mean age of 60 years and greater than 10 years of arthritis. Patients had active disease at baseline with a high number of swollen and tender joints.

Clinical efficacy. After 12 weeks of treatment with adalimumab, only one patient achieved the primary endpoint of an ACR20 response (Table 2). A second patient achieved an ACR20 response at 8 weeks, but the benefit was not sustained through 12 weeks.

Analysis of change in the individual components of the ACR20 revealed a statistically significant improvement in the number of swollen joints ($p = 0.01$). Although we detected no statistically significant improvement in the number of tender joints, hand grip strength, serum markers of inflammation, disability, pain, physical function, or patient or physician global disease assessment, there were trends suggesting modest improvement in all efficacy measures. Mean grip strength improved by 1.2 kg in each hand ($p = 0.44$), and mean combined WOMAC scores decreased by 81 units ($p = 0.60$) at 12 weeks. Unfortunately, the WOMAC OA index could not discriminate between symptoms directly related to OA of the hands versus OA in other anatomic locations such as the knee or hip. Retrospective analysis revealed an OMERACT-OARSI response in 42% of patients.

Safety. All enrolled subjects completed 12 weeks of treatment. Adalimumab was relatively well tolerated: all AE were graded as mild to moderate in severity and none required withdrawal from the study (Table 3). Consistent with the experience of adalimumab in other diseases, injection site reactions were the most commonly reported AE. One patient experienced a rise in serum ALT level at Week 8 that did not require withdrawal from the study and remained elevated 30 days after study completion.

A total of 6 mild infectious AE were experienced by 4 patients; 3 required oral antibiotics. No patient was hospitalized during the study.

DISCUSSION

OA is the leading cause of longterm disability in the United States[10]. The impact of OA is expected to grow exponentially as the population increases and ages in the coming decades. The most common idiopathic form of OA occurs in the interphalangeal (IP) joints of the hands and results in pain, deformity, and functional impairment. These symptoms have great financial and psychological ramifications: in 2003, the total cost for medical care and lost wages for arthritis was $128 billion[11]. At present, treatment is limited to analgesics, intraarticular steroids, NSAID, and physical therapy. Surgical options for the treatment of OA of the hands are generally ineffective and often result in decreased range of motion, decreased dexterity, and a loss of grip strength. The limited efficacy of available therapies underscores the need for improved and more targeted therapies.

Table 3. Adverse events during 12 weeks of treatment.

Adverse Event	No. of Events	No. Patients Experiencing Event
Noninfectious adverse events	13	7
Injection site reaction	5	2
Rash	1	1
Alopecia	1	1
Pruritis	1	1
Nausea	1	1
Abdominal pain	3	2
Elevated ALT	1	1
Infectious adverse events	6	4
Upper respiratory infection	3	3
Urinary tract infection	2	2
Folliculitis	1	1

Table 2. Results after 12 weeks of adalimumab, mean (standard deviation).

Variable	Baseline	Week 4	Week 8	Week 12	p, Week 12
ACR 20 Response	NA	0/12	1/12	1/12	NA
Tender joint count	9.0 (4.4)	7.7 (5.1)	9.4 (5.6)	8.1 (5.0)	0.64
Swollen joint count	7.8 (3.2)	6.0 (2.7)	5.9 (2.3)	5 (1.7)	0.01
ESR	8.8 (8.3)	5.6 (7.4)	7.9 (7.8)	8.5 (9.3)	0.92
HAQ-DI	0.97 (0.5)	1.0 (0.6)	0.85 (0.5)	0.82 (0.4)	0.45
Pain assessment (VAS)	40.1 (24.7)	40.5 (30.8)	32.3 (23.4)	34.3 (20.6)	0.55
Physician global assessment (VAS)	40.1 (16.2)	37.9 (12.8)	35.9 (15.3)	30.2 (13.4)	0.12
Patient global assessment (VAS)	48.6 (23.1)	45.4 (22.3)	39.6 (30.2)	38.5 (22.3)	0.3
Right grip strength, kg	25.2 (7.3)	26.0 (7.8)	26.2 (7.1)	27.5 (7.1)	0.44
Left grip strength, kg	23.7 (6.1)	25.6 (6.5)	24.3 (5.9)	24.9 (12.2)	0.75
WOMAC OA Index	479 (360)	488 (405)	395 (386)	399 (384)	0.6
OMERACT-OARSI responder index	NA	2/12	4/12	5/12	NA

ESR: erythrocyte sedimentation rate, HAQ-DI: Health Assessment Questionnaire-Damage Index, VAS: visual analog scale, NA: not applicable.

The objective of this open-label study was to investigate the safety and efficacy of anticytokine therapy in patients with EOA. Patients enrolled in the study had longstanding erosive disease with demonstrable inflammation in the PIP and DIP joints despite stable NSAID use. After 12 weeks of treatment with adalimumab, we detected significant improvement in the number of swollen joints and trends suggesting modest improvement in the number of tender joints, disability score, pain score, and patient and physician global assessments. However, the primary outcome of an ACR20 response was not met in the majority of participants.

There are several potential explanations for the lack of treatment effect in this study. First, this cohort had longstanding arthritis with documented erosions. A cohort with earlier EOA might have had a more robust response to biologic therapy; arguably, the most compelling indication for an anti-TNF-α agent in OA would be to prevent or retard radiographic joint deformities in this population. Second, in contrast to the primary immune activation that occurs in rheumatoid joints, the inflammation in OA joints may be a secondary phenomenon; thus, inflammatory cytokines such as TNF-α and IL-1 may be elevated in response to joint damage, rather than perpetrators of arthritis. Similarly to our report, a trial of anakinra, an IL-1 receptor antagonist, failed to yield a significant benefit in patients with knee OA[12]. Although these trials are small and inconclusive, the disappointing results of 2 unique biologic response modifiers suggest that proinflammatory cytokines may not be effective treatment strategies for established OA.

Finally, when interpreting the lack of a treatment effect seen in this study, it is important to understand limitations inherent in the efficacy assessments that were measured. Because there were no validated response criteria in EOA when this protocol was written, efficacy was primarily defined as the achievement of an ACR20 response as well as improvement in the individual ACR criteria, grip strength, and WOMAC score. It must be recognized that the ACR responder indices were designed to detect changes in disease activity in clinical trials for rheumatoid arthritis (RA), which has a high degree of systemic inflammation and joint involvement. In contrast, subjects with active EOA often have a limited number of swollen and tender joints, without significant elevations of markers of acute inflammation. The bony abnormalities and fixed joint deformities of OA may be more refractory to pharmacologic intervention. Therefore, distinguishing clinically meaningful changes in disease activity and function may be difficult using the ACR20 as a primary outcome measure.

The WOMAC questionnaire is the most commonly used measure of functional activity in generalized OA studies and was chosen to facilitate comparison with other OA therapeutic trials. Since the writing of this protocol in 2002, several responder indices have emerged as valid measures of treatment effect in hand OA, including Bellamy's AUSCAN Hand OA index and Dreiser's index[13,14]. These newer scales are likely to be more sensitive tools for detecting symptom response in patients with EOA of the hands.

The OMERACT-OARSI responder index was published as a measure of response to treatment of OA. Since we had collected data on each component in the index, we were able to detect a 42% OMERACT-OARSI response rate. Although this responder index was not a prespecified outcome measure, we believe that, along with trends toward improvements in individual measures of joint counts, disability, and global assessments of disease, it provides evidence of a modest therapeutic benefit of anti-TNF treatment in this patient population. It is important to note that the OMERACT-OARSI index was designed to measure a treatment effect in RCT of generalized OA and has not been validated in open-label studies specific to hand OA.

There were several limitations to our study. Due to the design as a pilot study, we were limited in sample size and therefore did not have significant numbers of subjects that would enable detection of statistically significant benefits of therapy. We limited our analysis to a single treatment group in order to maximize the number of patients treated; however, the lack of a control group and an independent assessor hindered the ability to discriminate placebo effects from true therapeutic effects. In addition, stable background use of NSAID was permitted, to reflect realistic analgesic use by arthritis patients, and as the dose was kept stable it should not have interfered with our clinical assessments.

Although the duration of our study was short, we chose 3 months of treatment since responders to adalimumab in RA trials achieved a clinical response by 12 weeks[15]; however, it is unknown whether a longer duration of therapy would have led to any difference in outcome.

In summary, treatment with adalimumab for 3 months did not significantly improve the signs and symptoms of EOA in this cohort of patients using the ACR responder index, although modest benefit was observed using the OMERACT-OARSI responder index. It is noteworthy, however, that a trend toward improvement was seen in all outcome measures and that substantial benefit was seen in a few individual patients. A future longterm randomized, placebo-controlled study to assess effects on structure (based on radiographic or magnetic resonance imaging results) in addition to efficacy of anticytokine therapy in both early and established EOA may be warranted. The development of specific efficacy outcome measures for this disease will help facilitate future study of therapeutic agents.

REFERENCES

1. Punzi L, Ramonda R, Sfriso P. Erosive osteoarthritis. Best Pract Res Clin Rheumatol 2004;18:739-58.
2. Tung JT, Fenton JI, Arnold C, et al. Recombinant equine interleukin-1ß induces putative mediators of articular cartilage degradation in equine chondrocytes. Can J Vet Res 2002;66:19-25.
3. Westacott CI, Sharif M. Cytokines in osteoarthritis: mediators or

markers of joint destruction? Semin Arthritis Rheum 1996;25:254–72.
4. Ghosh P, Smith M. Osteoarthritis, genetic and molecular mechanisms. Biogerontology 2002;3:85-8.
5. Kammermann JR, Kincaid SA, Rumph PF, et al. Tumor necrosis factor-alpha (TNF-alpha) in canine osteoarthritis: Immunolocalization of TNF-alpha, stromelysin and TNF receptors in canine osteoarthritic cartilage. Osteoarthritis Cartilage 1996;4:23-34.
6. Venn G, Nietfeld JJ, Duits AJ, et al. Elevated synovial fluid levels of interleukin-6 and tumor necrosis factor associated with early experimental canine osteoarthritis. Arthritis Rheum 1993;36**:**819-26.
7. Fernandes JC, Martel-Pelletier J, Pelletier JP. The role of cytokines in osteoarthritis pathophysiology. Biorheology 2002;39:237-46.
8. Grunke M, Schulze-Koops H. Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade. Ann Rheum Dis 2006;65:555-6.
9. Pham T, van der Heijde D, Altman R, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12:389-99.
10. Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults — United States, 1999. MMWR Morb Mortal Wkly Rep 2001;50:120-5.
11. Centers for Disease Control and Prevention. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions — United States, 2003. MMWR Morb Mortal Wkly Rep 2007;56:4-7.
12. Chevalier X, Goupille P, Beaulieu AD, et al. Results from a double blind, placebo-controlled multicenter trial of a single intra-articular injection of anakinra (Kineret®) in patients with osteoarthritis of the knee [abstract]. Arthritis Rheum 2005;52 Suppl:1339.
13. Hochberg HC, Vignon E, Maheu E. Clinical assessments in hand OA. Osteoarthritis Cartilage 2000;8 Suppl:S38-40.
14. Allen KD, Jordan JM, Renner JB, et al. Validity, factor structure, and clinical relevance of the AUSCAN Osteoarthritis Hand Index. Arthritis Rheum 2006;54:551-6.
15. Weinblatt ME, Keystone EC, Furst DE. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concurrent methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.