Long-term safety and effectiveness of tumour necrosis factor inhibitors in systemic sclerosis patients with inflammatory arthritis

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ABSTRACT

Objectives. *To assess the long-term safety and effectiveness of tumour necrosis factor (TNF) inhibitors in the treatment of systemic sclerosis (SSc) patients with inflammatory arthritis.*

Methods. *SSc patients who fulfilled the ACR criteria and had inflammatory arthritis followed in The Scleroderma Programme at the Mount Sinai and Toronto Western Hospitals, Toronto, Canada who received a TNF inhibitors for 12 months or more were retrospectively reviewed. Safety outcomes included development of TNF inhibitor related side effects, malignancy and death. Effectiveness outcomes included swollen joint count, tender joint count, skin score, and self-reported pain score at 12 months, compared to baseline.*

Results. *Ten SSc patients were identified: 7 (70%) were female and 6 (60%) had diffuse disease with a median skin score of 6. Six patients (60%) had ILD. At 12 months, the median swollen joint count and tender joint count significantly decreased from 10 to 0 ($p<0.01$) and 15 to 3 ($p=0.02$), respectively. The median pain score decreased from 6 to 3.5 ($p=0.10$). The median skin score remained unchanged at 6 months. The FVC and DLCO changed from 86% and 65% respectively, to 80% and 75% respectively. One patient developed uncomplicated herpes zoster. After 30 months, 3 patients (30%) developed malignancy. No death or other adverse events were observed.*

Conclusion. *TNF inhibitors appear to be effective in the treatment of SSc-associated inflammatory arthritis. Skin score and lung function did not change significantly with therapy. However, malignancy occurred in one third of patients. Further studies are required to confirm these findings.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by progressive fibrosis of the skin and internal organs. Inflammatory arthritis is an increasingly recognised feature of SSc with a prevalence of 10 to 25% (1, 2). More recent data using the European League Against Rheumatism (EULAR) Scleroderma Trial and Research Group (EUSTAR) Database, estimated the prevalence of synovitis at 16% (1191/7286) (3).

Available therapies for the treatment of SSc with proven efficacy are few (4). Tumour necrosis factor (TNF) inhibitors are novel targeted therapies in the treatment of autoimmune disease with remarkable success (5). Tumour necrosis factor is an important proinflammatory cytokine that plays a central role in the pathogenesis of immune mediated inflammatory diseases. TNF inhibitors have been used successfully in the treatment of rheumatoid arthritis, spondylarthropathies and Crohn's disease (6). Adverse events related to TNF inhibitors are well documented in the rheumatoid arthritis and spondyloarthropathies literatures (5) including reactivation of tuberculosis (7), increase risk of serious bacterial infection (7), drug induced lupus (8), demyelinating diseases (9). There are conflicting data regarding the increased rates of malignancy with TNFI in randomised controlled trials (RCT) and observational of RA patients (10, 11).

We recently systematically reviewed the literature evaluating the safety and effectiveness of TNF inhibitors in the treatment of SSc (12). Five studies reported the use of TNF inhibitors in SSc; however all were short-term (6-months or less) in duration (13-17). In the short term, TNF inhibitor use in SSc appears safe. In an observational study of 18

SSc patients treated with etanercept in the United States, 1 patient developed a lupus-like reaction, and another patient had a decline in lung function (13). Ellman *et al*. reported another observational study evaluating etanercept in 10 SSc patients. One patient developed digital ischaemia (14). Marie *et al*. reported the development of *Actinomyces meyeri* pneumonia in a SSc patient in France after 2 weeks of treatment with infliximab (15). Denton *et al*. reported an observational study of 16 SSc patients treated with infliximab for 16 weeks. No serious adverse events were reported, and 44% developed infusion reactions (16).

The ability to make inferences about the effectiveness of TNF inhibitors on SSc-associated inflammatory arthritis is limited by the paucity of data. Of the 5 studies evaluating the use of TNF agents in SSc, only one study reported joint symptoms as an outcome. Lam *et al*. reported that 15 of 18 SSc patients treated with etanercept had a significant decrease in the signs and symptoms of joint inflammation/synovitis. The joint count was not reported. The mean health assessment questionnaire disability index (HAQ-DI) score decreased from 1.08±0.70 to 0.74±0.56 (p=0.13) (13).

Despite being on the market for many years, the long-term safety and effectiveness of using TNF inhibitors in SSc associated inflammatory arthritis has not been assessed. All the published studies are limited in their small sample sizes and duration of follow-up (12). The primary objective of this study is to evaluate the long-term safety of TNF inhibitors in SSc. We secondarily evaluated the long-term effect of TNF inhibitors on SSc-associated inflammatory arthritis.

Methods

Patients

The Toronto Scleroderma Programme is a longitudinal, research-protocol based, cohort where patients are followed at the Mount Sinai and Toronto Western Hospitals. The SSc patients fulfilling the American College of Rheumatology classification criteria for systemic sclerosis (18) were screened. Patients who 1) had inflammatory arthritis defined as the presence of synovitis or effusion of the joints on physical examination; 2) received any TNFI (s); and 3) followed for at least 12 months were included in this study.

A standardised abstraction form was used to collect sex (male, female), age at initiation of first TNF inhibitor, SSc disease duration at initiation of first TNF inhibitor, SSc subtype at the time of diagnosis (limited, diffuse), modified Rodnan skin score (MRSS), serology (antinuclear antibody, Scl-70, anticentromere antibody, double stranded DNA, rheumatoid factor (RF), anti-cyclic citrullinated protein (CCP) antibody), first TNF inhibitor, concomitant immunosuppressive therapies and pulmonary function test before and after exposure to TNF inhibitor.

Outcomes

The safety outcomes included infection, admission to hospital or need for intravenous antibiotics, allergic reaction to TNF inhibitor, development of new neurologic symptoms, malignancy, development of drug induced lupus, the development of lupus manifestations (skin rash, oral ulcers, arthritis and serositis, serology of anti-double stranded DNA, anti-Smith or anti-histone antibodies), development of congestive heart failure, exacerbation of interstitial lung disease and death. Malignancy was confirmed by pathology.

The effectiveness outcomes included swollen joint count, tender joint count, and patient self-reported pain rating on a numeric analogue scale (0–10, 0 indicates no pain, 10 indicates worst pain in their life) at 12 months, compared to baseline. The modifies Rodnan skin score (MRSS) was documented prior and after therapy.

Exposure

The exposure was the use of any TNF inhibitor after the diagnosis of SSc. This included infliximab (Remicaide), etanercept (Enbrel) or adalimumab (Humira).

Analysis

Descriptive statistics were used to summarise the data. The Wilcoxon signed rank test was used to test the median difference the 12-month scores compared to baseline. Analyses were performed using R (version 2.2.1, The R Foundation for Statistical Computing).

Research ethics board approval was obtained prior to the conduct of this study.

Results

Patients

Of the 969 SSc patients screened, 10 SSc patients had inflammatory arthritis and were treated with TNF inhibitors for 12 months or more. SSc patients who had inflammatory arthritis successfully treated with traditional DMARDS, and patients treated with TNF inhibitors for less than 12 months were not included in this study. Patient's clinical characteristics, serologic profile and background immunosuppressives are summarised in Table I. Inflammatory arthritis was the only indication for initiating the TNF inhibitor. None of the patients had an overlap condition. The MRSS was documented at the time of TNF inhibitor initiation. Three patients with the diffuse subtype had softening (spontaneous or with DMARDs) of their skin between the time of SSc

Table I. Baseline characteristics of SSc patients with inflammatory arthritis.

Characteristics	Number (%) n=10
Female sex	7 (70%)
Age (median, IQR)	49 (45, 52.5) years
SSc duration (median, IQR)	24 (12, 35.5) years
Diffuse	6 (60%)
Limited	4 (40%)
Serology	
Antinuclear antibody positive	10 (100%)
ScL-70 antibody positive	7 (70%)
Anti-centromere antibody positive	1 (10%)
Anti-DS DNA antibody positive	0
Rheumatoid factor positive	4 (40%)
CCP antibody positive	0
Background DMARDs	
Methotrexate	3 (30%)
Leuflunomide	1 (10%)
Hydroxychloroquine	2 (20%)
Mycophenolate mofetil	2 (20%)
Azathioprine	6 (60%)

IQR inter-quartile range, CCP cyclic citrullinated protein, DMARD's disease-modifying anti-rheumatic drugs.

diagnosis and the measurement of the MRSS prior to TNF inhibitor initiation. Two of the patients with limited disease were ScL-70 positive. Six patients had interstitial lung disease confirmed by CT scan and pulmonary function tests. Four of 10 patients had baseline MRI of the upper extremities and all detected abnormalities including: synovitis n=4, erosions n=3, and bone marrow oedema n=2. Seven patients had radiographs which demonstrated erosions n=4 and joint space narrowing n=2. Other SSc related radiographic changes included soft tissue calcification and osteolysis.

Safety

One cutaneous infection with herpes zoster was reported in a patient who was on concomitant prednisone 5 mg daily and azathioprine. After 30 months on TNF inhibitor therapy, 3 out of ten (30%) patients developed malignancy: breast carcinoma n=1, basal cell carcinoma (BCC) n=1, and chronic myelogenous leukaemia (CML) n=1. The characteristics of these patients are summarised in Table II. Two of 3 patients discontinued the TNF inhibitor after the diagnosis of malignancy. No serious infection, reactivation of tuberculosis, allergic reactions, development of new neurologic symptoms, development of drug induced lupus, development of congestive heart failure, nor death were reported.

Skin score and lung function

The median skin score remained unchanged at 6 months. The FVC and DLCO changed from 86% and 65% expected to 80% and 75% respectively. None of the patients developed acute exacerbation of their ILD during exposure to TNFI.

Inflammatory arthritis

All of the patients had an improvement in the number of tender and swollen joints, respectively, at 3-months. At 12 months the median swollen joint count and tender joint count significantly decreased from 10 to 0 ($p<0.01$) and 15 to 3 ($p=0.02$), respectively. The median pain score decreased from 6 to 3.5 ($p=0.10$) (Table III).

Table II. Characteristics of patients who developed malignancy after initiation of TNF inhibitor.

Patient	Sex	Disease type	TNFI	Malignancy	Duration of TNFI	Concomitant Immunosuppressive
Patient 1	Female	Diffuse	Adalimumab	Breast	24 months	MTX
Patient 2	Female	Limited	Infliximab	CML	19 months	Azathioprine
Patient 3	Male	Diffuse	Etanercept	Basal cell carcinoma	30 months	MTX, HCQ, Mycophenolate mofetil

MTX: Methotrexate; CML: Chronic myelogenous leukaemia; HCQ: Hydroxychloroquine.

Table III. Long-term effect of TNF inhibitors on inflammatory arthritis, skin score and pulmonary function.

	Baseline	3 months	6 months	9 months	12 months	*p*-value[b]
Swollen joint count: Median (IQR)	10 (7, 11)	3 (0, 8)	1 (0, 5)	2 (1, 5)	0 (0, 2)	<0.01
Tender joint count: Median (IQR)	15 (9, 19)	8 (5, 12)	5 (2, 10)	5 (2, 10)	3 (0, 11)	0.02
Pain [a] median (IQR)	6 (5.75, 8)	5.5 (4.3, 6)	3.5 (3, 6.3)	7 (4.5, 7.5)	3.5 (3, 4.75)	0.10
MRSS	6 (5.5, 12.5)	N/A	N/A	N/A	6 (4, 12)	0.42
FVC (% of expected value)	86 (74, 94)	N/A	N/A	N/A	80 (70, 88)	0.55
DLCO (% of expected value)	65 (49, 78)	N/A	N/A	N/A	75 (56, 86)	0.99

IQR Inter-quartile range, MRSS modified rodnan skin score, FVC functional vital capacity, DLCO diffusion capacity of carbon monoxide.
[a] Pain reported on a numeric analogue scale, 0: no pain; 10: worst pain; [b] The Wilcoxon signed rank test was used to test the median difference the 12-month scores compared to baseline.

Discussion

Inflammatory arthritis is an increasingly recognised manifestation of SSc. It was described by Rodnan in 1961 where he studied the pathologic findings of the synovium of 29 patients with SSc. Fourteen patients had lymphocyte and plasma cell infiltration in focal aggregate or diffuse pattern associated with fibrin deposition at the surface membrane. Seventeen patients had synovial fibrosis similar to that found in skin biopsies (19). In a cohort of 120 patients, Avouac *et al*. found concomitant erosions and joint space narrowing in the hand radiographs of 18% of patients (20). Cuomo *et al*. examined the joints of 45 SSc patients with ultrasound (US) and detected effusion in 49%, and erosions in 5%. The prevalence of synovitis detected by US was higher than clinically detected (26 *vs*.15 out of 45 cases; $p=0.03$) (21). Low *et al*. detected inflammatory arthritis findings on MRI in 10 out 17 patients with joint pain or swelling. The changes included synovitis, erosions, effusion, and bone marrow oedema. Rheumatoid factor and anti-CCP were present in 40% and 11% of patients, respectively (22). Whether inflammatory arthritis is an inherent manifestation of SSc or reflects an overlap syndrome with rheumatoid arthritis is controversial. The described pathology and the low frequency of anti-CCP antibodies (1.5-11%) in multiple studies of patients with SSc who have erosive inflammatory arthritis argue against an overlap syndrome with RA. In either case, the controversy regarding the presence or absence of an overlap syndrome with RA does not affect the need for early diagnosis and intervention to avoid further disability which is already significantly present in SSc patients (23).

Our study adds evidence suggesting the effectiveness of TNF inhibitors in SSc associated inflammatory arthritis. Lam *et al*. reported the use of etanercept in 18 patients. (83%) had a positive response, with 'a significant decrease in signs of inflammation or synovitis on follow-up examination and complete resolution of joint symptoms.' Unfortunately, their study does not clearly

report the joint counts – well-accepted objective measures of inflammatory joint disease commonly used in rheumatoid arthritis clinical studies (13). Our study is the first to use joint counts a objective outcomes. It is important to note that joint count may be less sensitive in SSc patients (due to taught overlying skin). Therefore, swollen and tender joint counts need to be validated as outcome measures in SSc patients. Although joint pain improved in our study, it did not decrease significantly in our patients. This may be due to the fact that pain in the setting of SSc is multifactorial in origin. Digital pain due to poor blood flow, skin tightness, calcinosis, fibromyalgia and osteoarthritis are all additional sources of pain in SSc patients. SSc patients with joint involvement have been shown to have higher pain visual analogue scale scores than patients with rheumatoid arthritis (31). Given the multiple potential causes of pain, it is not surprising that we observed a reduction in pain but not complete resolution.

In our cohort the median skin score before starting the TNFI was 6 and remained unchanged after initiation of TNFI. Other studies evaluating the effect of TNFI on skin score did not show any significant improvement(12), except the one reported by Ellman *et al*. (14) which had a 44% response rate. The lung function in our patients remained stable during the exposure to TNFI without any documented exacerbation which was previously reported in the literature with different autoimmune diseases (32).

The major adverse event observed in this study was the development of malignancy in 3 patients. One patient was treated with combination azathioprine and infliximab, the second patient was treated with combination methotrexate and adalimumab, and the third patient was treated with combination of hydroxychloroquine, mycophenolate mofetil, etanercept, and methotrexate. These findings could be the result of a number of factors. The first relates to the risk of malignancy with SSc. Many studies have demonstrated that malignancy is a frequent cause of SSc-unrelated mortality (33). Frequently observed malignancies include lung and breast carcinoma (34). The occurrence of CML has been described in a case report were the patient had been exposed to penicillamine (35). Whether SSc is associated with an increased risk of malignancy is less certain. Studies have shown an increase risk of malignancy in SSc patients in comparison to the general population (36), with a standardised mortality ratio of 1.50, 95% confidence interval (CI) 1.03–2.11 (37), and standardised incidence ratio of 1.5 (95% CI 1.3–1.7) (35). However, at least one study did not corroborate this finding. Chatterjee *at el*. did not find evidence of increased incidence of cancer in SSc patients (with the exception of liver cancer) (38). They speculate that this may have been due to the high background rate of cancer in the local area. A second issue to consider is the risk of malignancy with the use of TNF inhibitors and concomitant immunosuppression. One study, which combined etanercept and cyclophosphamide in the treatment of granulomatosis with polyangitis, found a high rate of malignancy (39). One may speculate that there may be an increased risk of developing malignancy when treated with a TNF inhibitor and concomitant immunosuppression. The purpose of this report is hypothesis generating, and this finding needs to be further evaluated in an appropriately powered, long-term, prospective study.

In conclusion, TNF inhibitors appear to be effective in the treatment of SSc related inflammatory arthritis. However we observed the development of malignancy in 30% of our patients, all of which were treated with a TNF inhibitor and concomitant immunosuppression. Further studies are needed to evaluate these findings.

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