Biologic Therapy for Systemic Sclerosis: 
A Systematic Review

VEERAPONG PHUMETHUM, SHAHIN JAMAL, and SINDHU R. JOHNSON

ABSTRACT. Objective. Biologic agents are increasingly used in the rheumatic diseases. Their role in patients with systemic sclerosis (SSc) is uncertain. Our aim was to evaluate the effectiveness and safety of biologic agents in SSc. We review the evidence for the use of biologic agents to improve inflammatory arthritis, disability, and skin score, and we review adverse effects with biologic agents in patients with SSc.

Methods. A systematic literature review was performed to identify studies evaluating the use of biologic agents in SSc. Medline, Embase, CINAHL, and Cochrane Database of Systematic Reviews were searched. A standardized abstraction form was used to extract biologic agent, study design, sample size, treatment effect, and adverse effects.

Results. A total of 23 studies from 1413 citations were evaluated. Three studies evaluated infliximab, 3 evaluated etanercept, 3 evaluated antithymocyte globulin, 3 evaluated imatinib, 6 evaluated rituximab, and 1 study each evaluated interferon-\(\gamma\) (IFN-\(\gamma\)), IFN-\(\alpha\), relaxin, delipidated, deglycolipidated Mycobacterium vaccae, human anti-transforming growth factor \(\beta\)1 antibody, and oral type I collagen. Studies of etanercept and infliximab suggest improvements in inflammatory arthritis and Health Assessment Questionnaire Disability Index (HAQ-DI). None of the other biologic agents demonstrated reproducible, statistically significant improvements in joint count, HAQ-DI, or skin score.

Conclusion. Anti-tumor necrosis factor-\(\alpha\) agents may improve inflammatory arthritis and disability in SSc. The effect on skin score is uncertain. Adequately powered trials are needed to evaluate efficacy, and longitudinal studies are needed to evaluate longterm safety of these agents in SSc. (First Release Nov 1 2010; J Rheumatol 2011;38:289–96; doi:10.3899/jrheum.100361)

Key Indexing Terms: SCLERODERMA SYSTEMIC SCLEROSIS BIOLOGIC ANTI-TUMOR NECROSIS FACTOR-\(\alpha\)

Systemic sclerosis (SSc) is a disease characterized by immune activation and inflammation that leads to fibrosis. It commonly affects the skin, blood vessels, and internal organs. Inflammatory arthritis is an increasingly recognized manifestation of SSc, with a prevalence of 10% to 25% \(^1,2\). Using the European League Against Rheumatism Scleroderma Trials and Research Group database, the prevalence of synovitis is 16% \((1191/7286)\) \(^3\). Synovial biopsy studies have shown histological evidence of inflammation with lymphocytic and plasma cell infiltration. On electron microscopy there are prominent microvascular alterations and abundant immature collagen fibrils. Late in the course of the disease there can be evidence of severe synovial fibrosis \(^4\).

In a retrospective cohort study evaluating the use of magnetic resonance imaging (MRI) in patients with SSc who have joint pain, 59% of patients had synovitis, erosions, joint effusion, or tenosynovitis \(^5\). Rheumatoid factor and anticyclic citrullinated peptide (anti-CCP) antibodies were present in only 40% and 11% of patients with inflammatory MRI findings, respectively \(^5\). Whether erosive, inflammatory arthritis is a direct manifestation of SSc or reflects an overlap syndrome with rheumatoid arthritis (RA) is controversial \(^3\). The low frequency of anti-CCP antibodies in multiple studies of patients with SSc who have an erosive inflammatory arthritis (estimates ranging from 1.5% to 11%) suggest that the condition is a direct manifestation of SSc \(^5,6,7\).

Tumor necrosis factor (TNF) is an important proinflammatory cytokine that has been shown to play a pivotal role in the pathogenesis of other autoimmune diseases including RA, psoriatic arthritis (PsA), and ankylosing spondylitis \(^8\). However, its role in the pathogenesis of SSc is unclear. In
vivo animal studies demonstrate that antagonists of TNF-α can significantly reduce the accumulation of extracellular matrix and prevent the development of fibrosis in mouse models of silica-induced and bleomycin-induced pulmonary fibrosis. Studies in mice lacking TNF-1 or both TNF receptors demonstrated that inhibition of TNF signaling can prevent organ fibrosis. Conversely, the majority of in vitro studies show antifibrotic effects of TNF, in that it suppresses the production of collagen, reduces the expression of tissue inhibitor of metalloproteinases, and stimulates the release of matrix metalloproteinase, thereby preventing the accumulation of extracellular matrix and preventing the development of fibrosis.

The efficacy of TNF antagonists in inflammatory diseases such as RA, spondyloarthropathies, and Crohn’s disease has been demonstrated in clinical trials. Despite much interest in the use of anti-TNF agents in the treatment of SSc, there is no consensus on their potential therapeutic benefit. There is also some concern about using anti-TNF therapy in SSc because of a potential for worsening disease. A case report indicated that adalimumab was associated with fibrosing alveolitis in a patient with SSc. Similarly, infliximab has been associated with fibrosing alveolitis in patients with RA. Further, anti-TNF agents have also been associated with the development of autoantibodies and drug-induced lupus erythematosus, which may be a potential concern in patients with SSc.

Given the potential benefits of biologic therapies in SSc and their demonstrable efficacy in other rheumatic diseases, our systematic review aims to evaluate the effectiveness and safety of biologic therapies in patients with SSc. In particular, we reviewed the evidence for the use of biologic agents to improve inflammatory arthritis, disability, and skin score, and reviewed the adverse effect profile of these agents in SSc.

**RESULTS**

**Search results.** The search identified 1413 citations; however, screening of titles and abstracts resulted in the exclusion of 1390 citations, leaving 23 articles for full review. Citations were excluded because they were review articles, involved patients with rheumatic diseases other than SSc, were animal studies, or did not describe use of a biologic agent. Of the 23 citations selected, 5 were cohort studies, reporting on the use of anti-TNF therapy for treatment in SSc, and 18 studies described the use of other biologic agents in SSc. These included the evaluation of antithymocyte globulin (ATG), imatinib mesylate, interferon-γ (IFN-γ), IFN-α, recombinant human relaxin, delipidated, deglycolipidated Mycobacterium vaccae (PVAC), recombinant human anti-transforming growth factor-β1 (TGF-B1) antibody, type I collagen, and rituximab.

**Anti-TNF therapy in SSc.** Three observational studies evaluated infliximab and 3 observational studies evaluated etanercept. No randomized trials evaluating the use of anti-TNF therapy in SSc were identified (Table 1). Lam, et al report a retrospective cohort study of etanercept 25 mg twice weekly or 50 mg once weekly in 18 women with SSc. The primary outcome was a significant decrease in synovitis on examination and complete resolution of joint pain. The mean age was 44 years (range 25–71 yrs) with a mean duration of therapy of 30 months (range 2–66 mo). Fifteen (83%) of 18 patients treated with etanercept had a significant decrease in signs of inflammation or synovitis and resolution of joint symptoms. The mean HAQ-DI score decreased from 1.08 ± 0.70 to 0.74 ± 0.56 (p = 0.13). The mean Rodnan skin score decreased from 6.63 ± 6.35 to 3.94 ± 2.38 (p = 0.12). There were no opportunistic infections, anaphylaxis, hospitalizations, or deaths attributed to etanercept therapy. One patient developed a lupus-like reaction and another had a significant decline in lung function.
Denton, et al report an observational study of infliximab 5 mg/kg given at Weeks 0, 2, 6, 14, and 22 in 16 patients with diffuse SSc. Patients were included who had an increase of > 10% in skin score or an increase of 4 skin score units over a maximum 3-month period. Mean disease duration was 25.7 months (SD 19). The median baseline 17-site modified Rodnan skin score (MRSS) was 26. There was no significant change at 26 weeks (median MRSS 22, range 6–48). The median HAQ-DI score decreased from 1.63 (range 0–3) to 1.5 (0–2.63) at 26 weeks, and was reported as not statistically significant (p value not given). Seven (44%) of 16 subjects developed infusion reactions. Anti-infliximab antibodies developed in 5 patients and were associated with suspected infusion reactions.

Bosello, et al report 4 patients with SSc who were treated with infliximab 3 mg/kg administered at Weeks 0, 2, 6, and 14 with methotrexate (MTX), followed by etanercept 25 mg subcutaneously (SC) twice weekly without concomitant MTX. Infliximab was switched to etanercept to minimize patients’ time away from work. Individual baseline MRSS of 35, 12, 16, and 8 improved at 6 months with MRSS of 16, 7, 7, and 3, respectively. Baseline HAQ-DI scores of 1.575, 2.5, 2.25, and 1.75 improved at 6 months with HAQ-DI scores of 0.375, 1.5, 1.75, and 1.375, respectively. No adverse effects were reported with either infliximab or etanercept.

Ellman, et al report use of etanercept 25 mg SC twice weekly for 6 months in 9 patients with diffuse SSc. Four of the patients had a 44% improvement in the Rodnan skin score and 5 remained unchanged. The HAQ-DI score improved from 1.8 to 1.57. One patient discontinued therapy after 4 weeks because of new digital ischemia, while 3 patients with digital ulcers noted improvement.

Marie, et al report the case of a 44-year-old woman with diffuse SSc and erosive, anti-CCP-positive polyarthritis treated with 2 doses of infliximab (3 mg/kg). One month after the second infusion she developed Actinomyces meyeri pneumonia. The effects of infliximab on joint count, HAQ, or skin score were not reported.

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Other biologic agents in SSc. Three studies report use of ATG and 3 report use of imatinib mesylate in SSc (Table 2). Five observational studies and 1 randomized trial report the use of rituximab in SSc (Table 3). Grassegger, et al report a multicenter trial of recombinant IFN-α 100 µg SC thrice weekly for 12 months in 44 patients. Of them, 27 patients were randomized to treatment...
and 17 patients randomized to the control groups. Mean followup was 7–17 months. Skin scores tended to improve in the treatment group (p > 0.05; Table 4).

Black, et al report a randomized trial of IFN-α 13.5 x 10^6 units in divided doses in 35 patients with diffuse SSc. Because of a withdrawal of 13 patients, an interim analysis was performed. Three deaths and the lack of benefit in the treatment arm resulted in termination of further recruitment. A greater improvement in the placebo group skin score was observed (Table 4).

Seibold, et al report a randomized trial of recombinant relaxin 25 µg/kg/day, 100 µg/kg/day, or placebo for 24 weeks by SC infusion in 72 patients with diffuse SSc. Patients who received 25 µg/kg of relaxin per day had lower skin scores than those who received placebo (mean change, –3.6 at 4 weeks, p = 0.021; –7.5 at 12 weeks, p < 0.001; and –8.7 at 24 weeks, p = 0.040). Joint score was defined as the sum of swollen or tender metacarpophalangeal joints (as a unit), wrists, and knees. No effect on joint score or HAQ-DI was observed (Table 4).

Genovese, et al report a trial of PV AC in 18 patients with SSc randomized to 8 injections of 15 µg PV AC, 50 µg PVAC, or placebo at 3-week intervals. Patients who received PV AC 15 mg demonstrated improvement in MRSS [change score –4.3 (–20.6%)] at 24 weeks. Both the placebo and the PV AC 50 µg groups had worsening of skin disease.

Table 2. Summary of studies evaluating antithymocyte globulin (AG) and imatinib biologic in systemic sclerosis.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Matteson^30</th>
<th>Balaban^32</th>
<th>Stratton^31</th>
<th>van Daele^33</th>
<th>Sfikakis^34</th>
<th>Chung^35</th>
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<td>AG</td>
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<td>AG</td>
<td>Imatinib</td>
<td>Imatinib</td>
<td>Imatinib</td>
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<td>Observational</td>
<td>Observational</td>
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<td>Observational</td>
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<tr>
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<td>1</td>
<td>2</td>
</tr>
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<td>USA</td>
<td>UK</td>
<td>Netherlands</td>
<td>UK</td>
<td>USA</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin score</td>
<td>n = 2 improved*</td>
<td>Improved†</td>
<td>Improved‡</td>
<td>Improved‡‡</td>
<td>Improveda</td>
<td>Improvedb</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>n = 2 improved**</td>
<td>n = 3 stabilized**</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Joint count</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Adverse events (AE)</td>
<td>No serious AE</td>
<td>No serious AE</td>
<td>Serum sickness, n = 5</td>
<td>No serious AE</td>
<td>No serious AE</td>
<td>No serious AE</td>
</tr>
</tbody>
</table>

* Improvement defined as ≥ 25% decrease in skin score; stabilized defined as ± 25% baseline skin score. ** Improvement defined as ≥ 0.25-point decrease, stabilized defined as ± 0.25-point baseline. † Total skin score improved from 25 to 14 in Patient 1, and 22 to 7 in Patient 2. ‡‡ Mean Rodnan skin score (MRSS) improved from 28 to 17 after 12 months (p < 0.01). a MRSS improved from 18 to 13 at 3 months. b MRSS improved from 44 at baseline to 33 at 6 weeks and 28 at 6 months. c MRSS improved from 36 to 21 at 3 months in Patient 1; 36 to 20 at 6 months in Patient 2. NR: not reported; HAQ-DI: Health Assessment Questionnaire-Disability Index.

Table 3. Summary of studies evaluating rituximab in systemic sclerosis.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Caliri^42</th>
<th>McGonagle^43</th>
<th>Daoussis^46</th>
<th>Ketari^44</th>
<th>Smith^45</th>
<th>Lafyatis^47</th>
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<tbody>
<tr>
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<td>Observational</td>
<td>Observational</td>
<td>Observational</td>
<td>Observational</td>
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<td>Greece</td>
<td>Tunisia</td>
<td>Belgium</td>
<td>USA</td>
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<tr>
<td>Outcomes</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin score</td>
<td>Improved*</td>
<td>NR</td>
<td>No effect***</td>
<td>NR</td>
<td>Improveda</td>
<td>No effectb</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Joint count</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Adverse events (AE)</td>
<td>No serious AE</td>
<td>No serious AE</td>
<td>4 respiratory tract infections</td>
<td>No serious AE</td>
<td>No serious AE</td>
<td>46.7% infusion reactions</td>
</tr>
</tbody>
</table>

* Mean Rodnan skin score (MRSS) improved at 6 months. Baseline, 6-month followup Rodnan skin score, and p value not reported. ** Authors report arthropathy resolved completely. Joint count not reported. *** At 1 year, the rituximab group MRSS improved by 39.25% (mean 13.5 ± 6.84 at baseline vs 8.37 ± 4.65 at 1 yr). Control group improved by 20.80% (MRSS 11.50 ± 2.16 at baseline vs 9.66 ± 3.38 at 1 yr). Between-group differences were not statistically significant (p = 0.06). † Patient diagnosed with scleroderma-lupus overlap with catastrophic antiphospholipid antibody syndrome. a MRSS improved from mean 24.8 ± 3.4 at baseline to 14.3 ± 3.5 at 24 weeks (p < 0.001). b HAQ-DI mean 1.4 ± 0.6 at baseline to 1.3 ± 0.7 at 24 weeks (p > 0.05). c No significant change in MRSS between baseline and 6 months, mean change –0.37, 95% CI –3.8, 3.0 (p = 0.82). d HAQ-DI did not change significantly between baseline mean 0.67 ± 0.32 and 6 months 0.64 ± 0.36. HAQ-DI: Health Assessment Questionnaire-Disability Index; NR: not reported; RCC: randomized controlled trial.

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with MRSS increases of 3.5 (29.8%) and 3.5 (16.7%), respectively. There was no change in HAQ-DI (Table 4).

Denton, et al40 report a trial of recombinant human anti-TGF-ß1 in 45 patients with diffuse SSc. Patients were randomized to placebo or 10 mg/kg, 5 mg/kg, or 0.5 mg/kg anti-TGF-ß1. There was no difference in the 6-month MRSS change score or HAQ-DI scores across the groups (Table 4).

Postlethwaite, et al41 report a study of 168 patients with SSc randomized to oral bovine type I collagen 500 µg daily or placebo. There was no difference in the mean change in MRSS at 12 months (–2.4 ± 7.3 vs –1.8 ± 7.4; p = 0.563; Table 4).

DISCUSSION
There has been much recent interest in the use of biologic therapies in the treatment of SSC. In our systematic review, we have synthesized the 23 published studies that have evaluated the effect of these agents. Five studies have evaluated the use of anti-TNF-α therapies in SSc26,27,28,29,48. The remaining 18 studies evaluate a variety of other biologic agents. Review of these studies gives us insight into the clinical utility of these agents, and potential future directions for research.

Anti-TNF therapy appears to confer benefits on inflammatory arthritis and disability. This finding has particular clinical relevance because inflammatory arthritis confers a significant burden of disease. Patients with SSc who have arthritis experience more severe pain than patients with RA, and more disability than patients with PsA49. The first-line therapy for inflammatory arthritis is usually MTX. However, in the setting of pulmonary fibrosis commonly seen in SSc, many clinicians may not feel comfortable initiating MTX. The use of TNF inhibitors may provide an alternative treatment option. The ability of anti-TNF agents to improve joint symptoms and disability is promising. However, the small sample sizes and observational study designs make these study findings subject to a number of biases. Further, these studies did not report joint counts, a commonly used outcome measure in RA studies. Therefore a comparison of the magnitude of the treatment effect in SSc cannot be compared to RA studies. It is worth noting that the utility of tender and swollen joint counts in SSc may be limited by overlying tight and thickened skin that can prohibit accurate assessment. Because of the potential difficulties associated with joint count assessment in SSc, investigators should consider additional measures of joint involvement (e.g., HAQ-DI, MRI). The studies in our review do indicate a potential beneficial treatment effect. The lack of statistical significance likely reflects the small sample sizes and insufficient power. These studies provide the necessary justification to proceed with larger, adequately powered studies to further evaluate this effect. In the future, the efficacy and safety of combination therapy (anti-TNF and MTX) in SSc-associated inflammatory arthritis should be evaluated because combination therapy has been found to be superior to TNF monotherapy in RA50.

Some of the studies report improvement in skin scores with the use of anti-TNF agents. The generalizability of this finding is uncertain for a number of reasons. First, it is uncertain whether the observed skin softening reflected that which can occur as part of the natural history of the diseases, or reflects true treatment effect. Second, the more severe

Table 4. Summary of studies evaluating other biologic agents in systemic sclerosis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grasseygger16</th>
<th>Black37</th>
<th>Seibold38</th>
<th>Genovese39</th>
<th>Denton40</th>
<th>Postlethwaite41</th>
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<td>Agent</td>
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<td>Relaxin</td>
<td>PVAC</td>
<td>Anti-TGF-ß1</td>
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</tr>
<tr>
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<td>Improved*</td>
<td>No effect**</td>
<td>Improved***</td>
<td>Improved 15 mg arm</td>
<td>No effectb</td>
<td>No effectd</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Joint count</td>
<td>NR</td>
<td>NR</td>
<td>Menorrhagia</td>
<td>Injection site reaction</td>
<td>4 deaths related to disease</td>
<td>No serious AE</td>
</tr>
<tr>
<td>Adverse events (SE)</td>
<td>85% headache, 81% fever, 70% arthralgia/myalgia</td>
<td>19–35%</td>
<td>67–100%</td>
<td>29.8%</td>
<td>16.7%</td>
<td></td>
</tr>
</tbody>
</table>

* Baseline mean 0.34 (SD 0.31) to 0.34 (SD 0.35) in control group; 0.67 (0.46) to 0.50 (0.30) in treatment group (p > 0.05). ** Mean change in IFN-α group was –4.7 (SEM 9.5) vs –7.5 (SEM 7.2) in placebo group (p = 0.36). *** Mean change from baseline in relaxin group was –3.6 at 4 wks (p = 0.021); –7.5 at 12 wks (p < 0.001); and –8.7 at 24 wks (p = 0.040). † Mean change from baseline in the relaxin 25 µg/kg group was –0.125 ± 0.10 (p = 0.154); 100 µg/kg group 0.036 ± 0.06 (p > 0.2). †† Mean change from baseline in the relaxin 25 µg/kg group was –0.9 ± 0.06 (p = 0.133); 100 µg/kg group 0.2 ± 0.5 (p > 0.2). a Mean change from baseline in placebo group 3.5, PV AC 15 µg group –4.3, and PV AC 50 µg group 3.5. b No difference in skin score across groups (p = 0.49). c No statistically significant differences in HAQ-DI scores across 4 treatment groups ranging from 0.80 ± 0.60 in 0.5 mg/kg group to 1.40 ± 0.90 in 5 mg/kg group. d No significant difference in mean change in MRSS at 12 months: –2.4 ± 7.3 versus –1.8 ± 7.4 (p = 0.563). IFN: interferon; RCT: randomized controlled trial; PVAC: delipidated deglycolipidated M. vaccae; TGF: tumor growth factor; HAQ-DI: Health Assessment Questionnaire-Disability Index; NR: not reported.
skin scores in the treatment arm could reflect random variation. When the measurement is repeated, the skin score is lower as a result of “regression to the mean,” rather than true treatment effect. Third, the small observed treatment effects may be within the margin of measurement error. Clements, et al have reported an interrater variability of ± 4.6 units with the Rodnan skin score. Fourth, the use of different measures of skin score across studies precludes comparisons. Although the majority of studies report the 17-site MRSS, others report the Rodnan total skin score, or the 15-site and 18-site MRSS. Fifth, timing of inclusion into the study may affect the outcome. Patients who are recruited early in their disease or who have active skin involvement are more likely to derive benefit. Some studies explicitly state that patients were recruited early in their disease course or were mandated to have active disease as inclusion criteria, while other studies do not. Given these differences, we are unable to definitively conclude whether anti-TNF agents confer a beneficial effect on skin in SSc. The reported findings do provide a potential signal of benefit, and provide the necessary data required for justification of a larger, adequately powered study.

Anti-TNF agents were generally tolerated in patients with SSc. There was a high frequency of infusion reactions in patients with SSc treated with infliximab, which may be related to the development of anti-infliximab antibodies, and could be minimized with concurrent use of other immunosuppression. There was only 1 report of a lupus-like reaction, and 1 report of a decline in lung function in patients treated with etanercept. In this study, 2 patients were concomitantly treated with minocycline. Although unclear from the report, if the patient who developed the lupus-like reaction was also treated with minocycline, the lupus-like reaction could also have been attributable to the minocycline. All the published studies are limited in their sample size and duration of followup. Therefore we are unable to draw any conclusions about infrequent adverse effects or longterm safety. Large, longitudinal cohort studies (such as biologic registries) are needed to properly evaluate longterm safety.

Review of other non-TNF biologics in SSc was less promising. Patients treated with IFN-γ showed stabilization of skin scores while those on placebo had progression. In that study, baseline skin scores between treatment and control groups were not comparable, and IFN-γ treatment was poorly tolerated. The use of relaxin and PVAC showed a trend toward improved skin scores at low doses but worsening at high doses. The observed improvement in skin score may reflect that natural softening of skin observed in many patients with SSc over time. IFN-α, TGF-B1, and oral type I collagen did not show promise for the treatment of SSc skin disease or disability. Initial small observational studies suggested improvements in skin score with rituximab, but this effect was not statistically greater than that observed in the control arm of the randomized trial. Case reports of imatinib demonstrated evidence of skin improvement, and larger studies are currently evaluating this effect.

The heterogeneity across studies precluded our ability to aggregate or conduct a metaanalysis of the data. The studies differed in sample selection (inclusion and exclusion criteria), intervention, outcomes assessed (e.g., different skin scores), and study duration. Therefore it would be inappropriate to aggregate data from such variable sources. Future investigators should consider using recommended outcome measures that have demonstrable validity and reliability. This would facilitate quantifiable comparisons across studies.

Despite the limitations of this systematic review, qualitative synthesis of the existing literature and presentation of the individual study findings is useful, especially when considering one of these agents for an individual patient. The results of this systematic review suggest that etanercept and infliximab may be safe (in the short term) and effective for the management of inflammatory arthritis. The utility of anti-TNF agents for skin involvement is less certain. ATG and imatinib may be effective for skin involvement but the longterm safety is unknown. None of the other biologic agent studies were able to demonstrate a significant change in inflammatory arthritis, disability, or skin score. Well designed, adequately powered clinical trials are needed to further evaluate the efficacy, and large, longitudinal studies are needed to evaluate the longterm safety of these agents in SSc.

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