CONCISE REPORT

Intravenous immunoglobulins improve the function and ameliorate joint involvement in systemic sclerosis: a pilot study

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Background: In systemic sclerosis (SSc), joint involvement may reduce the functional capacity of the hands. Intravenous immunoglobulins have previously been shown to benefit patients with SSc.

Aim: To verify the efficacy of intravenous immunoglobulins on joint involvement and function in SSc.

Patients and methods: 7 women with SSc, 5 with limited and 2 with diffuse SSc, with a severe and refractory joint involvement were enrolled in the study. Methotrexate and cyclophosphamide pulse therapy did not ameliorate joint symptoms. Hence, intravenous immunoglobulins therapy was prescribed at a dosage of 2 g/kg body weight during 4 days/month for six consecutive courses. The presence of joint tenderness and swelling, and articular deformities (due to primary joint involvement and not due to skin and subcutaneous changes) were evaluated. Before and after 6 months of treatment, patients were subjected to (1) Ritchie Index (RI) evaluation of joint involvement; (2) Dreiser Algo-Functional Index (IAFD) evaluation of hand joint function; (3) pain visual analogue scale (VAS) to measure joint pain; (4) Health Assessment Questionnaire (HAQ) to evaluate the limitations in everyday living and physical disability; and (5) modified Rodnan Skin Score for skin involvement.

Results: After 6 months of intravenous immunoglobulins therapy, joint pain and tenderness, measured with the VAS, decreased significantly ($p < 0.03$), and hand function (IAFD) improved significantly ($p < 0.02$), together with the quality of life (HAQ; $p < 0.03$). All patients significantly improved, except for one. The skin score after 6 months of intravenous immunoglobulins therapy was significantly reduced ($p < 0.003$).

Conclusion: This pilot study suggests that intravenous immunoglobulins may reduce joint pain and tenderness, with a significant recovery of joint function in patients with SSc with severe and refractory joint involvement. The cost of intravenous immunoglobulins might limit their use only to patients who failed disease-modifying antirheumatic drugs.

Systemic sclerosis (SSc) induces skin and internal organ fibrosis, causing a wide spectrum of functional impairments. Articular and periarticular involvement and painful fingertip ulcers progressively reduce the functional capacity of the hands, leading to a severe limitation of patients' self-sufficiency.

In SSc, joint involvement is usually referred to as joint "pain",^{1,2} at the onset³ and during disease progression.^{4,5} Arthralgias are more frequent than arthritis.¹

Various radiological joint abnormalities have been described in SSc,² such as periarticular osteoporosis, intra-articular calcification, loss of joint space, erosion and, rarely, aseptic necrosis.^{1–5} Intravenous immunoglobulins have been shown to

be efficacious in immunomediated rheumatic disease⁶ and in Kawasaki disease.⁷ In systemic lupus erythematosus, intravenous immunoglobulins control thrombocytopenia;⁸ in myositis, they induce a complete remission of muscle and skin involvement;⁹ and in rheumatoid arthritis (RA), they successfully control joint pain and swelling.¹⁰ In SSc, intravenous immunoglobulins significantly decreased skin score (18–20) and improved patients' quality of life.¹¹ The aim of this pilot study was to verify the efficacy of intravenous immunoglobulins on joint involvement and functionality in patients with SSc.

PATIENTS AND METHODS

Of a cohort of 292 patients with SSc who visited our department, seven Caucasian women with SSc with severe and refractory joint involvement (mean age 51.8 (range 34–68) years) were enrolled in the study. They were classified as having limited SSc ($n = 5$) and diffuse SSc (dSSc; $n = 2$; mean (SD) disease duration 3.6 (2.5) years, since onset of Raynaud's phenomenon).¹² All patients were treated with calcium channel blockers, proton pump inhibitors, prokinetics and intravenous prostanoids. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors and oral steroids were ineffective in controlling joint pain. Methotrexate (starting from 7.5 mg and reaching the dose of 15 mg intramuscularly/weekly) was administered to four patients, and cyclophosphamide pulse therapy (1 g/m²/month intravenously for 6 months, for lung involvement) in the other three patients were ineffective on joint symptoms. For this reason, intravenous immunoglobulin therapy was started at a dosage of 2 g/Kg/4 days/month for six consecutive courses. Patients signed an informed consent form. As no validated clinical and radiological criteria exist today for the evaluation of articular involvement in SSc, the presence or absence of articular involvement was decided on the basis of the clinical assessment, ultrasound and radiological characteristics. Patients presented various grades of involvement, such as periarticular osteoporosis, intra-articular calcification, loss of joint space, erosion and, rarely, aseptic necrosis. Two skilled rheumatologists separately established the articular involvement on 28 joints: joint tenderness, joint swelling (due to joint effusion or synovitis; interobserver variability was kept to $\kappa > 0.6$) and articular deformities (due to primary joint involvement and not due to skin change) were evaluated.¹² Other parameters, used to exclude patients with RA overlap, were onset of arthritis before Raynaud's phenomenon, positivity of RA test and cyclic citrullinated peptide, increased C reactive protein level, prolonged morning stiffness and no distal interphalangeal joint involvement.¹² All patients

Abbreviations: dSSc, diffuse systemic sclerosis; HAQ, Health Assessment Questionnaire; IAFD, Dreiser Algo-Functional Index; RA, rheumatoid arthritis; RI, Ritchie Index; SSc, systemic sclerosis; VAS, visual analogue scale

underwent x rays of the hands and wrists. Additional articular location was imaged (x ray and ultrasound) if suspected to be involved on the basis of clinical symptoms. Patients were considered positive for articular involvement if ultrasound/radiological signs and/or symptoms of arthritis were detected. When it was not possible to differentiate the primary joint involvement from the modification due to skin changes, patients were excluded from the study. In all, 15 patients of our cohort failed to be enrolled in the study because of these exclusion criteria.

Before and after 6 months of treatment, the patients were assessed using: (1) Ritchie Index (RI) to evaluate joint involvement (0–78); (2) Dreiser Algo-Functional Index (IAFD) to evaluate hand joint function; (3) pain visual analogue scale (VAS) to measure joint pain (0–100); (4) Health Assessment Questionnaire (HAQ) to determine the limitations in everyday living and physical disability (0–3); and (5) modified Rodnan Skin Score for skin involvement.

Different scales and Rodnan Skin Score were analysed by Wilcoxon's test for non-parametric data. Parametric data were compared by paired Student's t test (significant at $p \leq 0.05$).

RESULTS

In all patients with a severe and refractory joint involvement, x rays showed joint space reduction, erosions and juxta-articular osteoporosis.

Before treatment, all patients presented joint pain and swelling and a significant number of swollen and painful joints: the wrists, metacarpophalangeal, proximal interphalangeal joints and knees were mainly involved. RI, as well as the functional joint assessment of patients, was increased in all patients (table 1). All parametric data were analysed by Wilcoxon's test and were compared by paired Student's t test. After 6 months of intravenous immunoglobulin therapy, the number of swollen ($p < 0.001$) and tender joints ($p < 0.001$) was significantly reduced: joint pain, measured with the VAS scale ($p < 0.05$), and RI ($p < 0.005$) decreased significantly. Hand function, measured with IAFD ($p < 0.05$), and general functionality, measured with HAQ ($p < 0.05$), also improved significantly (table 1). Functionality improved in all patients except in one: this patient presented with an erosive arthritis that did not show any amelioration of RI, IAFD, VAS and HAQ.

After 6 months, the modified Rodnan Skin Score was also significantly reduced ($p < 0.005$; table 1).

Intravenous immunoglobulin infusion was well tolerated, and no adverse reactions were observed during and after the treatments.

DISCUSSION

This pilot open-label study, on a limited number of patients with SSc with a severe and refractory joint involvement,

suggests that intravenous immunoglobulins are effective in controlling joint pain and tenderness, leading to a significant improvement of joint functionality.

In autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome, myasthenia gravis and vasculitides), intravenous immunoglobulin therapy still remains an empirical treatment, whereas in other diseases, such as polymyositis,⁹ it represents a new treatment, and in Kawasaki disease and in Guillain-Barré syndrome it is a mandatory therapeutic choice.

After intravenous immunoglobulins therapy, about 70% of patients with chronic, refractory polymyositis have a significant clinical improvement that allows a 50% reduction of prednisone.⁹

In systemic lupus erythematosus refractory to conventional treatment, intravenous immunoglobulins reduced the Systemic Lupus Activity Measure score with a beneficial clinical response to arthritis, fever, thrombocytopenia, neuropsychiatric symptoms and psychosis, as well as decreased significantly the daily steroid dosage.⁸

In SSc, clinical evidence of synovitis was observed in 88% of patients and joint inflammation was detected in 91% of patients: a distinctive subset of patients with deforming arthritis was identified, and 70% of whom fulfilled the criteria for both RA and SSc.¹³ These patients, when compared with the others with SSc, showed limited skin involvement and were positive for rheumatoid factor and anticitromere antibodies.¹³ In 120 patients with SSc, Avouac *et al*² studied joint radiological modifications causing functional disability. Their findings were articular erosion (21%), joint-space narrowing (28%), arthritis (defined by concomitant erosion and joint-space narrowing; 18%), radiological demineralisation (23%), acro-osteolysis (22%), flexion contracture (27%) and calcinosis (23%). In dSSc, flexion contractures were found in association with disability, indicating a tendency towards fibrosis and functional impairment in this subset of patients.² These characteristics were also found by La Montagna *et al*,⁴ who confirmed the higher prevalence of finger flexion in dSSc. In our patients, intravenous immunoglobulins reduced significantly the number of swollen and tender joints, thus ameliorating joint functionality. Indeed, intravenous immunoglobulins confirmed their efficacy in reducing cutaneous involvement reducing, as reported previously,¹¹ the Skin Score. These data clearly show that SSc an arthropathy is common in patients with SSc and is a major determinant of disability.

The mechanism of action of intravenous immunoglobulins in autoimmune diseases is still a matter of debate.¹⁴ The interaction with the Fc receptor, the activation of idiotype—anti-idiotype reaction, neutralising or reducing autoantibody synthesis, and reduction of chemokines and complement have been suggested.¹⁵ Induction of production of the interleukin (IL) 1 receptor antagonist and suppression of production of tumour necrosis factor α , IL1 and IL6 by intravenous immunoglobulins might explain the possible beneficial effect in the treatment of arthritis, even in a fibrosing disease such as SSc.¹¹

In conclusion, this pilot study suggests that intravenous immunoglobulins may be useful for SSc with a severe and refractory joint involvement. Because of the costs of intravenous immunoglobulins, their use may be restricted to patients who have failed disease-modifying antirheumatic drugs. Tumour necrosis factor α blockade should be used with caution because this treatment may accelerate pulmonary involvement.¹⁴ Further studies are needed to confirm these preliminary results.

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Table 1 Mean (SD) value at baseline and after 6 months of intravenous immunoglobulins therapy of systemic sclerosis

Scale	At baseline	After 6 months	p Value
HAQ	2.3 (0.9)	1 (0.8)	<0.05
VAS	4.7 (1.9)	0.7 (1.7)	<0.05
RI	25.6 (6.7)	13.6 (5.6)	<0.001
IAFD	14.4 (3.9)	8.7 (3.4)	<0.05
Skin Score	29.2 (8.3)	21.1 (4.6)	<0.005
Swollen joints	10 (1.7)	7 (1)	<0.001
Tender joints	18.8 (1.3)	10.2 (2.3)	<0.001

HAQ, Health Assessment Questionnaire; IAFD, Dreiser Algo-Functional Index; RI, Ritchie Index; VAS, visual analogue scale.

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