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Interferon-gamma in the treatment of systemic sclerosis: a randomized controlled multicentre trial

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Summary We report the results of a randomized controlled multicentre study on interferon-gamma (IFN-γ) treatment of systemic sclerosis as determined by skin sclerosis, renal and other organ involvement, global assessment, subjective symptoms and quality of life. Forty-four patients were enrolled into the trial, 27 in the treatment group and 17 in the control group. All patients presented with type I or type II scleroderma. Twenty-nine patients (64%) finished the study. The mean duration of Raynaud's phenomenon and skin sclerosis was 15·3 and 10·8 years, respectively. The skin scores tended to improve in the treatment group ($P > 0{\cdot}05$). Mouth aperture increased significantly from 38·5 to 47·7 mm in the treatment group ($P < 0{\cdot}001$). Subanalysis of IFN-γ treated patients with normalized skin sclerosis scores ≥1 showed significant improvement in both skin involvement and subjective symptoms ($P < 0{\cdot}05$). Organ involvement improved in eight of 18 treatment patients and in three of 11 control patients. It worsened in three of 18 treatment patients and in four of 11 control patients. One control patient died due to cardiorespiratory failure during the study. No deterioration of renal function occurred during IFN-γ treatment. There was a significant improvement in quality of life parameters in the control group but not in the treatment group. Plasma levels of neopterin increased significantly during IFN-γ treatment but not in the control group, whereas N-terminal procollagen III peptide levels did not change in either group. There was a high frequency of mild to moderate influenza-like adverse events during IFN-γ treatment. Only four of nine drop-out patients, however, experienced symptoms most probably associated with IFN-γ treatment. We conclude that IFN-γ therapy has mild beneficial effects on skin sclerosis and disease-associated symptoms in type I and II scleroderma. IFN-γ treatment was associated with acceptable tolerability and did not induce major renal dysfunction in our patients.

Systemic sclerosis, or scleroderma, is a multisystem autoimmune connective tissue disease involving the skin and internal organs including the lungs, gastrointestinal tract, heart, kidneys and joints. It is widely accepted that vascular, immunological and connective tissue interactions are involved during the disease process but in-depth knowledge of the aetiology and pathogenesis is still lacking.

Two classifications have been established for the disease.[1,2] The German classification of scleroderma, as proposed by Barnett *et al.* in 1978, is preferred by us.[1,3] Type I scleroderma denotes acral involvement up to the wrists, type II has additional involvement of areas proximal to the wrists, and type III starts on the trunk and face with progression to the extremities. Each type

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is denoted non-inflammatory ('a') or inflammatory ('b').[1] In contrast, the classification of the American Rheumatism Association favours only two types, i.e. limited systemic sclerosis and diffuse progressive systemic sclerosis.[2]

Although many treatments have been studied in the past no unequivocally effective treatment for scleroderma has emerged.[4,5] Plasmapheresis with immunosuppression was reported to be of some benefit.[6] D-penicillamine, a potential candidate for long-term therapy, is associated with major adverse reactions.[7] Therefore, alternative and better tolerated therapy regimens, especially with lower risks for long-term usage, are urgently needed. In previous uncontrolled trials, interferon-gamma (IFN-γ) was shown to be effective for skin sclerosis[8–11] and lung involvement.[10]

As no controlled trials of IFN-γ treatment in systemic sclerosis have been performed until now we conducted a randomized controlled multicentre trial of IFN-γ in scleroderma to study effects on skin sclerosis, renal function and other visceral involvement, disease-associated subjective symptoms and quality of life. In addition, serum neopterin and N-terminal procollagen III peptide levels were studied in some of the patients.

Patients and methods

Patients

Recruitment of patients lasted for 2 years starting in 1992. Forty-four patients with systemic sclerosis were randomly assigned either to the treatment group (27 patients) receiving recombinant IFN-γ or to the control group (17 patients) after informed consent. Diagnosis of systemic sclerosis was based on the criteria of the *Arbeitsgemeinschaft für Dermatologische Forschung*.[1] A prerequisite for inclusion into the study was presence of scleroderma for at least 6 months followed up by a physician prior to study entry to preclude inclusion of patients with rapidly progressing disease, inclusion of whom was considered unethical.

Exclusion criteria were: (i) localized scleroderma or clinical symptoms of overlap syndromes or other autoimmune diseases; (ii) immunosuppressive or immunomodulatory therapy including corticosteroids or apheresis, and pentoxifylline ≤ 3 months and D-penicillamine ≤ 6 months prior to the study; (iii) severe cardiovascular, pulmonary or neurological diseases; (iv) serum creatinine >2 mg%; (v) abnormal liver function with alkaline phosphatase >350 U/mL, aspartate aminotransferase >100 mU/mL and total bilirubin >2 mg%; (vi) haematological abnormalities with white blood cell count $< 2{\cdot}5 \times 10^9$/L, platelets $< 80 \times 10^9$/L; (vii) obvious neoplasm or infection; (viii) pregnancy or breast-feeding; (ix) lack of sufficient contraception; and (x) known hypersensitivity or intolerance to IFN-γ. Symptomatic therapies such as vasoactive treatment (prostaglandins, calcium channel blockers, angiotensin-converting enzyme inhibitors), analgesics and physiotherapy were allowed.

The study protocol was approved by the respective institutional review boards for treatment of human subjects at each centre and by the Ethical Committee of the University of Innsbruck, Austria. All aspects of the trial were carried out according to the recommendations of the Declaration of Helsinki.

Study design

The study was designed as a prospective, randomized controlled multicentre trial lasting for 18 months with a 12-month period of IFN-γ treatment and a 6-month follow-up period. Recruitment of patients lasted for 2 years. Additional participating centres and investigators are listed in the Acknowledgments. The aim was to study changes in skin sclerosis, renal function and other organ involvement, disease-associated symptoms noticed by the patients (termed 'subjective symptoms'), and patients' self-assessment of quality of life parameters. Laboratory parameters including N-terminal procollagen III peptide were determined at baseline and follow-up visits. Serum neopterin levels were determined to verify systemic effects of IFN-γ treatment. We considered skin involvement as a surrogate marker for organ involvement and survival, thus electing skin sclerosis as the primary outcome variable.[12,13] Secondary outcome variables were creatinine clearance, and scores of patients' symptoms and quality of life. In addition, we determined adverse reactions associated with IFN-γ treatment.

Patients randomized for treatment were to receive 100 μg recombinant IFN-γ (Imukin®, Bender, Vienna, Austria) subcutaneously three times a week for 12 months. To mitigate the well-known influenza-like adverse effects, patients were encouraged to take 0·5–1·5 g acetaminophen if needed on days of IFN-γ injection. The study protocol allowed reduction of dosage to 50–75 μg if toxicity grade 2 according to the WHO toxicity criteria was reached. Treatment had to be stopped at neurotoxicity grade 3 or other organ toxicity grade 4.

Two main reasons compelled us to avoid placebo treatment. First, frequent subcutaneous injections as a

sham treatment for 1 year were considered unethical because of the risk of skin trauma and secondary infections. Second, blinding of IFN-γ and placebo is hardly practicable as almost all patients receiving IFN-γ notice mild to moderate chills and/or fever (up to 38·5 °C).

Assessment of skin involvement, subjective symptoms and life quality

Data of skin scores for each group were pooled separately for calculating mean values of half-year periods. Evaluation of skin involvement was performed monthly and included a semiquantitative measurement of skin thickness, and indirect measures, as previously used by others, such as grip strength and mouth aperture.[14] Skin thickness rating was performed as described by Rodnan and coworkers with some modification.[7,15] Briefly, scores were calculated by measuring skin thickness in 15 body areas ($n = 15$), the rating being: 0, normal skin; 1, slight thickening of skin; 2, moderate thickening, hardly moveable skin; 3, severely thickened and/or hidebound and/or atrophic skin. The total scores thus could range from 0/15 to 45/15 (i.e. 0–3). This method is similar to the Rodnan scoring system as modified by Steen and coworkers.[7] This semiquantitative skin thickness method was previously shown to have better interobserver reliability than measurement of involved areas by the manikin method[16,17] and is now recommended for therapeutic trials.[18] Grip strength, as measured by compressing the balloon of a vigorimeter (in kPa) with the right and left hand, was calculated as a mean of both hands and of three trials each. As a third parameter of skin involvement, the mouth aperture was measured: greatest vertical and horizontal interlabial distance in millimetres.

Disease-associated symptoms were assessed monthly. The following symptoms were specified: colour change of fingers or toes (Raynaud's phenomenon), arthralgia/myalgia, paraesthesia, sicca symptom of eyes or mouth, dysphagia, burning chest pain, vomiting, diarrhoea, constipation and dyspnoea at rest or during exercise ($n = 12$). These 'subjective symptoms' were rated as follows: 0, no symptoms; 1, slight symptoms; 2, moderate symptoms, 4, severe symptoms. Total scores could thus range from 0/12 to 48/12. Symptoms patients were unable to specify were excluded from evaluation ($n = 12 - x$).

Patients' global self-assessments reflecting aspects of their quality of life were determined every 3 months using a linear numerical scale from 1 to 5. Ten questions ($n = 10$) about everyday life were asked: general feelings, mood, physical activity, pain, dizziness/vomiting, appetite, body strength, social activity, anxiety and subjective evaluation of treatment efficiency (this question was omitted at the baseline evaluation, therefore $n = 9$ at the baseline visit). These questions were asked by the investigators at each centre. Our quality of life score including subjective assessment of treatment efficacy was not validated statistically before use. Questions were modified from standard psychosocial questionnaires.

Assessment of organ involvement

Organ involvement was assessed at baseline and at 6, 12 and 18 months thereafter. Lung involvement was assessed by X-ray of the thorax, high-resolution computed tomography of the thorax and/or pulmonary function test. Screening for pulmonary hypertension was performed by echocardiography. Screening for heart involvement was done by electrocardiography and echocardiography. Oesophageal involvement was evaluated by oesophageal X-ray or, if available, by manometry. Renal involvement was determined by urinalysis, serum creatinine levels and creatinine clearance. Semiquantitative evaluation was done as follows: 0, normal finding; 1, light to moderate pathology; 2, severe or most severe pathology; pathology was assessed by the respective specialists in the centres. Changes in pathology assessment were scored as follows: 0·5, better, if baseline was 1; 1·5, worse, if baseline was 1; better, if baseline was 2.

Laboratory assessment

Routine laboratory testing was performed at baseline and monthly thereafter in most of the patients. This included full blood count, erythrocyte sedimentation rate, electrolytes, serum creatinine, serum urea nitrogen and urinalysis. Determination of antinuclear antibodies (ANA) (Hep2 cells) with subsets (extractable nuclear antigens) and Scl70 antibodies (antibodies against topoisomerase I), creatinine clearance, serum neopterin and N-terminal procollagen III peptide was performed at baseline and 6, 12 and 18 months thereafter.

Statistical analysis

It was originally planned to enrol 65 patients in the study based on the skin sclerosis score to reach statistical significance at the 5% level with a power of 0·8, but

Table 1. Characteristics of all patients (intent-to-study)

	All patients	Control group	Treatment group
Number of patients	44	17	27
Female	36	16	20
Male	8	1	7
Mean age (years)	53·5	58·3	50·7
(Range)	(15·4–72·8)	(34·2–71·8)	(15·4–72·8)
Mean duration of Raynaud's phenomenon (years)	15·3	14·2	16·0
(Range)	(0·7–50·8)	(0·7–33·7)	(1·2–50·8)
Mean duration of skin sclerosis (years)	10·8	12·2	10·0
(Range)	(0·3–33·7)	(2·3–33·7)	(0·3–23·1)
Type of scleroderma			
Type I—non-inflammatory ('a')	18	10	8
Type I—inflammatory ('b')	1	0	1
Type II—non-inflammatory ('a')	21	7	14
Type II—inflammatory ('b')	4	0	4
Type II—non-inflammatory ('a') with morphoea	1	0	1
History of prior treatments			
Immunosuppressive including corticosteroids	17	6	11
D-penicillamine	4	2	2
Vasoactive only	5	2	3
None	15	8	7
Antinuclear antibody type			
Anticentromere	10	5	5
Non-anticentromere			
Antitopoisomerase I (Scl70)	16	4	12
Nucleolar	7	3	4
Speckled	8	1	7
Homogeneous	3	2	1
Negative	3	2	1
Drop-out patients	15 (34%)	6 (35%)	9 (33%)
Mean duration of Raynaud's phenomenon (years)	12·9	10·6	15·2
(Range)	(3–28)	(5–21)	(3–28)
Mean duration of skin sclerosis (years)	8·6	7·2	10
(Range)	(3–18)	(2–11)	(3–18)
Patients with anticentromeric antibodies	3	3	0
Patients with Scl70 or nucleolar antibodies	8	2	6
Timing of drop-out			
< 3 months	6	2	4
4–6 months	4	2	2
7–12 months	5	2	3
13–18 months	0	0	0

this number could not be reached. Randomization was done by one centre (Innsbruck) according to standard statistical methods. Demographic and clinical data were recorded by individual centres and pooled for collective analysis. For every patient, baseline data were compared with the data obtained during the first, second and third 6-month periods of observation. Data from each 6-month period were pooled and averaged for the treatment and the control group, respectively. Mean values were compared by the (non-parametric) Wilcoxon–Mann–Whitney rank sum *W*-test between the control and treatment group, whereas within the two groups we used the Wilcoxon matched-pairs signed-rank test comparing mean values with baseline data.

Drop-outs were included in the intention-to-study analysis. If control visits in both groups were missed this was not considered a reason for drop-out.

Results

Patients

In a 2-year period, 44 patients with systemic sclerosis were enrolled into the study, 27 in the treatment group and 17 in the control group. All patients had type I or II

Table 2. (a) Skin involvement in all patients (intent-to-study); (b) Skin involvement in patients who completed the study

	Control		Treatment	
(a)	Mean	SD	Mean	SD
Skin sclerosis score (0, normal; 3, hidebound)				
baseline	0·34	0·31	0·67	0·46
months 1–6	0·48	0·48	0·55	0·34
months 7–12	0·47	0·54	0·55	0·30
months 13–18	0·34	0·35	0·50	0·30
Mouth aperture (mm)				
baseline	40·18	5·25	38·46	12·23
months 1–6	40·35	5·21	41·65*	10·09
months 7–12	41·08	6·75	43·22*	11·08
months 13–18	43·65	9·80	47·66**	10·83
Grip strength (mmHg)				
baseline	39·71	19·49	38·79	18·30
months 1–6	39·27	19·14	40·70	16·95
months 7–12	36·87	14·29	39·33	18·12
months 13–18	38·00	15·32	37·78	20·17

	Control		Treatment	
(b)	Mean	SD	Mean	SD
Skin sclerosis score (0, normal; 3, hidebound)				
baseline	0·33	0·31	0·66	0·47
months 1–6	0·47	0·48	0·56	0·35
months 7–12	0·50	0·62	0·51	0·26
months 13–18	0·35	0·39	0·52	0·31
Mouth aperture (mm)				
baseline	38·65	4·30	37·06	11·48
months 1–6	38·36	4·61	40·42	8·26
months 7–12	40·58	6·93	43·59*	9·43
months 13–18	43·28	9·26	46·3**	10·85
Grip strength (mmHg)				
baseline	34·25	11·84	37·68	19·67
months 1–6	34·74	11·19	41·42	15·30
months 7–12	35·00	10·83	38·86	15·99
months 13–18	33·90	12·26	36·23	19·12

Compared with baseline: *$P < 0·05$, **$P < 0·001$.

scleroderma (limited sclerosis) from a clinical aspect. Twenty-nine patients (64%) completed the 18-month study period. There was a female/male ratio of 4·5 : 1. The mean duration of Raynaud's phenomenon and of skin sclerosis was 15·3 years (range 0·7–50·8) and 10·8 years (range 0·3–33·7), respectively. Demographic and clinical data of the patients are listed in Table 1.

One patient of the control group (patient 20) died in the thirteenth month of the study due to respiratory failure. She had a type II involvement with skin sclerosis known for 11 years and Raynaud's phenomenon for 12 years. At baseline this patient had oesophageal, lung and heart involvement. Baseline creatinine clearance was 108 mL/min and decreased slightly to 85 mL/min at month 12, which is at the lower normal limit.

Skin involvement

Measurement of skin involvement included skin thickness score, mouth aperture and grip strength (Table 2a,b). Table 2a shows the data obtained in the intention-to-study analysis. Skin involvement at baseline was more severe in the treatment group than in the control group with a baseline skin sclerosis score of 0·67 and 0·34, respectively ($P = 0·017$). In the treatment group the skin score tended to decrease after 12 months of IFN-γ treatment. Grip strength did not change significantly. In contrast, mouth aperture improved significantly after 12 months of treatment ($P < 0·0001$). Analysis of patients who completed the trial revealed very similar trends (Table 2b).

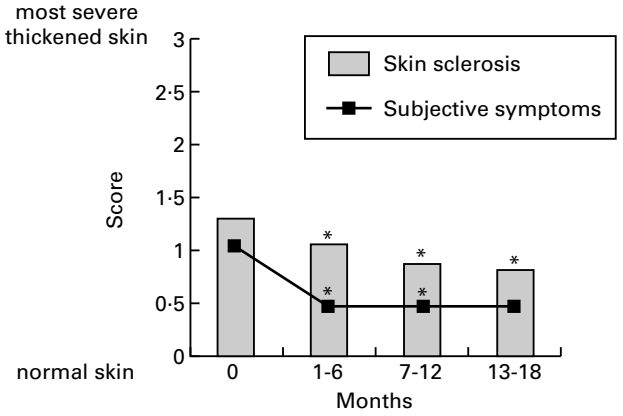

Fig. 1. Skin sclerosis and subjective symptoms: subanalysis of patients ($n = 7$) with baseline skin sclerosis scores ≥1. A significant improvement in sclerosis is paralleled with improvement in subjective symptom scores (*$P < 0{\cdot}05$ compared with baseline).

Subanalysis of patients

Subanalysis of IFN-γ treated patients ($n = 7$) with sclerosis scores ≥1 (or absolute score ≥15 according to Rodnan) showed significant improvement in skin sclerosis of 13–22% and of disease-associated 'subjective' symptoms ($P < 0{\cdot}05$), as shown in Fig. 1. These patients had a significantly shorter duration of Raynaud's phenomenon when compared with the remaining treatment patients (7·7 vs. 16 years, $P < 0{\cdot}05$), but did not differ in mean age and duration of skin sclerosis.

Subanalysis according to signs of inflammation in our patients showed significant improvement in subjective symptom scores and a trend of improvement for skin sclerosis in the treated inflammatory type 'b' patients (data not shown).

Subanalysis of patients according to ANA patterns (anticentromere type vs. non-anticentromere type) did not yield significant changes within or between groups (data not shown).

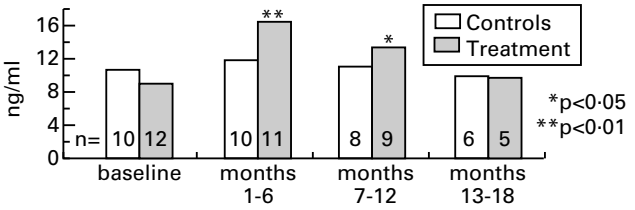

Fig. 2. Neopterin levels increased significantly in the treatment group (compared with baseline).

Laboratory parameters

Neopterin and N-terminal procollagen III peptide were measured in sera of several patients. The results for neopterin levels are shown in Fig. 2. N-terminal procollagen III peptide levels did not change significantly in either group (not shown).

Organ involvement

Lung, gastric, renal and cardiac involvement were assessed routinely at baseline and 6, 12 and 18 months in most of the patients. The incidence of changes in organ involvement are shown in Table 3.

Changes in creatinine clearance, a surrogate marker for renal function, are shown in Fig. 3. Mean values increased from 95 to 99 mL/min in the treatment group (not significant). Two of nine patients of the control group showed a decrease in clearance to 18 and 29 mL/min at months 15–18. They did not present clinically with renal crisis. In 24 patients tested there

Table 3. Interferon-gamma treated systemic sclerosis patients with baseline skin scores ≥1. Characteristics of seven patients. Organ involvement was assessed as described in Patients and methods

			Duration of (years)		Antinuclear antibodies		Organ involvement		
Patient no.	Sex	Type	Raynaud's	Sclerosis	Titre	Subtype	Baseline	During study	Change
10	M	IIa	8	5	2560	ACA	O	O	Stable
12	M	IIb	2	2	640	Scl70	L,O	L,O	Stable
16	F	IIa	4	4	160	Speckled	O,H	O,H	Stable
19	M	IIa	13	10	1280	Speckled	L,O,H	L,O,H, npl vesicae	Heart worsened
25	F	IIa	6	3	1280	Scl70, Ro, La	None	L,O	Stable
38	F	IIa	10	8	800	Scl70	L,O,H	L,O,H	Heart improved
39	F	IIa	11	8	1280	Scl70	L	O,H	Lung improved

ACA, anticentromeric antibodies; O, oesophagus; L, lung; H, heart; npl, neoplasm.

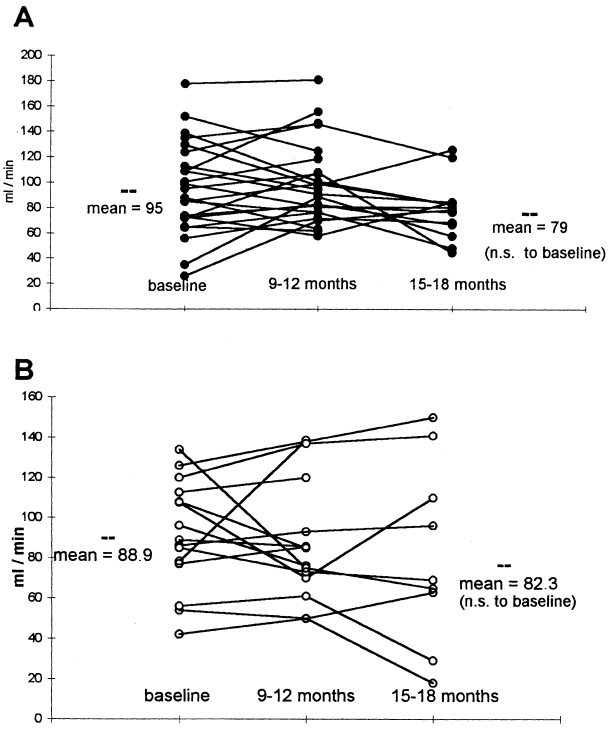

Fig. 3. (A) The creatinine clearance in interferon-gamma (IFN-γ) treated patients ($n = 24$) is shown at baseline, after 9–12 months of IFN-γ treatment, and at the end of the study period. Apparently low baseline levels were increased during the treatment period in two patients. (B) The creatinine clearance in the control group ($n = 14$) shows a decrease in two control patients at the end of the study period. n.s., not significant.

was no clinically relevant decrease in creatinine clearance during the 12-month IFN-γ treatment.

Global assessment by investigative physicians and patients

In the first 3 months beneficial global assessment by physicians was found in both the treatment and the control patients, whereas later beneficial effects were attributed only to the treatment group (Fig. 4). Quality of life (patients' global assessment) improved significantly in the control group but not in the treatment group (Fig. 5).

Withdrawals and adverse reactions

In two patients IFN-γ dosage had to be reduced from 100 μg to 75 μg three times weekly due to arthralgia or severe fatigue after 2 months (patient 2) and after 3 months (patient 8). Arthralgia and fatigue were absent or minimal with 75 μg IFN-γ. However, patient 2 refused treatment after 9 months of therapy. Although

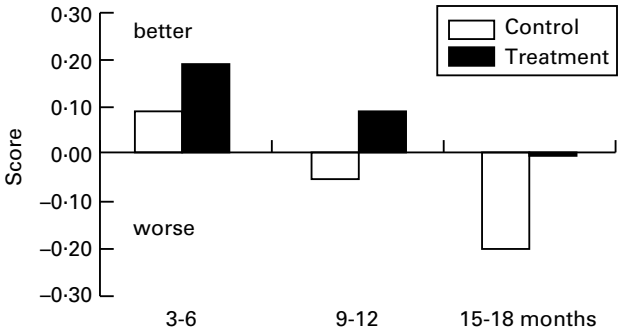

Fig. 4. Global impression by physicians compared with baseline. Note that the control group appeared to improve according to the physician's assessment at the beginning of the study. However, this impression vanished after 9–12 months of study duration.

arthralgia was mild to moderate in subjective ranking by the patient, we considered this a treatment-associated reason for discontinuation of IFN-γ. We did not evaluate dosage effects on skin sclerosis or disease-associated parameters for these two patients. Most of the patients used acetaminophen concomitantly. Headache was reported by 23 of 27 patients (85%), fever and fatigue by 81%, and arthralgia/myalgia by 70% of patients. Fever and arthralgia were reported by all seven patients with a skin sclerosis score ≥1 (i.e. Rodnan score ≥15) and by all five patients with the 'inflammatory' type of scleroderma. Adverse events or patient refusal leading to discontinuation of treatment were seen in four of 27 patients (15%). These symptoms included arthralgia (patient 2), cardiac pain (patients 21 and 29), atrioventricular block I (patient 29), reversible loss of hearing (patient 19) and impotence (patient 19).

Discussion

In systemic sclerosis several therapeutic approaches have been tried targeting modulation of the vascular system, the immune system and/or connective tissue metabolism.[5] No unequivocally effective treatment has been established. Based on *in vitro* studies showing

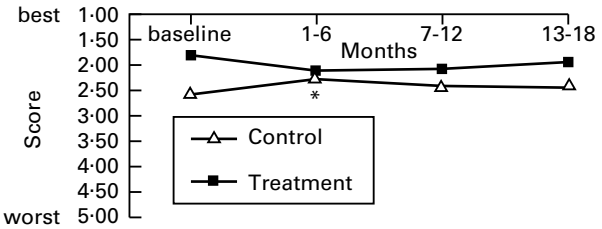

Fig. 5. Quality of life improved significantly in the control patients (*$P < 0{\cdot}05$ compared with baseline).

potent inhibition of IFN-γ on collagen synthesis in normal human and scleroderma-derived fibroblasts,[16,19] treatment of systemic sclerosis with IFN-γ has been studied previously.[8–11,20,21] Although small numbers of patients were included in these trials, beneficial effects, especially on skin sclerosis, could be demonstrated. All of these trials, however, were non-randomized and uncontrolled.

In our randomized controlled multicentre study of IFN-γ on systemic sclerosis we found mild beneficial effects on skin sclerosis parameters and disease-associated 'subjective' symptoms. In addition, organ involvement remained stable or even improved in most of our treatment patients. It should be mentioned, however, that asymmetrical randomization, by-chance confinement to type I and II scleroderma, and some heterogeneity of the patients might be shortcomings of the study. As fewer patients were enrolled into the study than had originally been planned, this might explain the asymmetrical distribution concerning both the number of patients and degree of sclerosis in the treatment and control group. Moreover, there were no patients with skin involvement suggesting type III scleroderma fulfilling study inclusion criteria. Patients with rapid progressive disease were excluded as we agreed the best treatment for these patients to be immunosuppression with or without plasmapheresis.[6]

Considering skin sclerosis as a surrogate marker for severity of organ involvement and survival, this parameter was considered the primary outcome variable.[12,13] Skin thickness score (modified Rodnan score) did not improve significantly in overall analysis of the treatment or control group. However, when patients with relatively higher baseline skin sclerosis scores ≥ 1 (available only in the treatment group) were subanalysed, a significant improvement in skin sclerosis compared with baseline scores was found. We consider a 20% reduction in skin sclerosis score a mild to moderate improvement which is clinically relevant in limited systemic sclerosis. An improvement of $\geq 30\%$ is considered clinically relevant in diffuse progressive (type III) scleroderma.[22] As our subanalysis was performed retrospectively and no control patients were available for this subgroup, cautious interpretation is necessary. These seven patients who tended to improve most in skin sclerosis had a shorter duration of Raynaud's phenomenon when compared with mean values of all patients. The duration of skin sclerosis, however, did not differ significantly. Measuring skin involvement by a modified Rodnan thickness skin score was previously shown to give good interobserver reliability.[18] Some observation bias, however, cannot be ruled out in our study. In our scoring method, division of absolute scores by '*n*' was introduced to be independent of the number of body areas studied. This might facilitate comparison of other skin scoring methods in the future, e.g. when fewer body areas are measured, as was proposed recently by Silman and coworkers.[23]

The mechanism underlying reduction in skin sclerosis in treatment patients remains unclear, as baseline levels of N-terminal procollagen III peptide did not decrease in our patients. These findings are in accordance with others.[8] In addition, these authors found no significant decrease in type I collagen gene expression in the skin.[8] The bioavailability of IFN-γ has been demonstrated, as there was a rise in serum neopterin levels. This IFN-γ effect was also shown in previous trials.[8,11]

We decided to treat systemic sclerosis patients with relatively stable disease to minimize the risk of renal side-effects. IFN-γ might be deleterious for renal function, especially when early stages of systemic sclerosis are treated.[9,24,25] In a study using IFN-α, however, renal crisis was also seen in one of 19 patients with early disease, suggesting that this adverse potential might not be confined to type II interferons.[26] As renal crisis is less likely to occur spontaneously in limited scleroderma (and possibly in later stages of diffuse progressive sclerosis) this might explain the absence of major renal impairment in our patients. Consequently, timing of or patient selection for IFN-γ treatment could be crucial.

As a TH2-type immune response seems to predominate in systemic sclerosis,[22] IFN-γ as a typical TH1 cytokine, above its inhibitory effects on collagen synthesis, might be considered immunomodulatory in scleroderma, especially in early stages of the disease. A potential disadvantage, however, might be IFN-γ-induced major histocompatibility complex class II or intercellular adhesion molecule-1 expression on endothelial cells and fibroblasts,[27,28] or induction of interleukin-2 receptor genes.[29] However, the exact role of upregulation of such accessory molecules and possible impairment of renal function in scleroderma remain to be determined.

Recent guidelines for clinical scleroderma trials recommended the study of primarily early stages of diffuse systemic sclerosis.[30,31] This might not be advisable for the treatment with IFN-γ as our findings suggest at least mild beneficial effects of IFN-γ treatment in relatively stable and long-lasting scleroderma with a considerable chance of avoiding renal impairment. Although our results suggest improvement in skin

sclerosis in type I–II scleroderma with a higher sclerosis score, we do not recommend IFN-γ treatment for early progressive type III scleroderma.

There was a trend to reduction in patients' assessment of quality of life in the treatment group, whereas significant improvement could be detected in our control patients. Control patients might benefit from the psychological support provided by systematic follow-up, whereas frequent, although mild to moderate, side-effects of IFN-γ such as fever, fatigue, headache and arthralgia (consistent with the influenza-like symptoms) are likely to reduce quality of life. Several findings, however, argue against poor acceptance of IFN-γ treatment in our patients. First, reduction in dosage was necessary in only two patients. Second, the drop-out rate was almost the same in both the treatment and the control group and third, only four of nine drop-out patients in the treatment group needed discontinuation of therapy as a consequence of adverse effects.

In conclusion, improvement in skin sclerosis and subjective symptoms, stabilizing organ involvement, lack of renal crisis and only occasional withdrawals due to side-effects indicate mild beneficial effects and acceptable tolerability of IFN-γ in our patients. Thus, IFN-γ might be considered an alternative low-risk treatment modality to immunosuppressive therapy in type I and type II systemic sclerosis, especially when considerable skin sclerosis is present. However, minimizing even mild to moderate adverse events of IFN-γ treatment is particularly important to reach substantial benefits in the well-being of those patients.

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