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Reduction of Morning Stiffness and Improvement in Physical Function in Fibromyalgia Syndrome Patients Treated Sublingually with Low Doses of Human Interferon-α

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ABSTRACT

One hundred and twelve fibromyalgia syndrome (FMS) patients were randomized into one of four demographically similar groups (n = 28/group). Sequential primary FMS patient volunteers were to receive daily sublingual placebo or interferon-α (IFN-α) at 15, 50, or 150 IU. After a screening evaluation, analgesic or sedative hypnotic medications were withdrawn. Two weeks later, daily IFN-α or placebo was initiated with follow-up evaluations at 2-week intervals ending with week 6. One primary, three secondary, and seven tertiary variables were assessed. Study outcome was based on improvement in the tender point index (TPI). The TPI did not improve with any IFN-α dose. However, significant improvement was seen in morning stiffness and in physical function with the 50 IU IFN-α ($p < 0.01$). None of the other outcome means changed significantly and no adverse events were attributable to IFN-α therapy.

INTRODUCTION

FIBROMYALGIA SYNDROME (FMS) is a chronic, painful disorder commonly seen in rheumatology practice.[1–4] While it is often viewed as a musculoskeletal pain process, the most prominent biological abnormalities have been found in the levels of nociceptive neurotransmitters.[5–7] The etiology of FMS is not known although genetic,[8–10] traumatic,[11–13] affective,[14–16] and infectious[17,18] processes have been implicated. Clinicians typically employ combinations of education, medications, exercise, rest, and psychological support; the resulting benefits are often disappointing.[19]

In the past, there was a tendency to view FMS as a benign disorder that did not justify aggressive therapy or the risk of adverse side effects.[20] However, this approach can no longer be justified, considering the impact of this condition on the quality of life of affected individuals.[21] The annual cost ($12 billion in direct cost alone) of this disorder to the United States economy[22] mandates that innovative therapies for FMS be considered and rigorously tested.

Interferon- α (IFN-α) is a potent regulatory cytokine involved in immunologic responses.[23,24] Oral use of IFN-α has been reported to be beneficial in patents with Sjögren's syndrome.[25] Anecdotal information has been provided indicating that oral use of IFN-α has relieved the pain of some patients with chronic fatigue syndrome (CFS).

Since the pain component of CFS is believed[26,27] to be similar to that in FMS, it was hypothesized that IFN-α might prove to be beneficial for FMS. Additional support for that hypothesis has come from recent studies[28,29] showing that the concentration of kynurenine is elevated in the cerebrospinal fluid of patients with FMS. The enzyme involved in converting tryptophan to kynurenine (tryptophan, 2,3-dioxygenase) is augmented by IFN-γ, a proinflammatory cytokine sometimes physiologically antagonized by IFN-α.[30,31] The purpose of the clinical trial was to evaluate the efficacy of IFN-α in the treatment of deep palpation tenderness in FMS. A number of other standard outcome variables were included to more widely evaluate the clinical effects of IFN-α in FMS.

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MATERIALS AND METHODS

Patients

Primary FMS male and female patients (18–69 years) were offered inclusion if they met American College of Rheumatology (ACR) criteria[32] for that diagnosis. All patients were examined by one of us (IJR) to confirm the diagnosis of primary FMS and to exclude other diagnoses that might influence symptoms. Subjects were excluded for rheumatoid arthritis (RA),[33] systemic lupus erythematosus,[34] CFS,[35] untreated hypothyroidism,[36] or prior treatment with IFN-α. The study was approved by the Institutional Review Board for human studies at the University of Texas Health Science Center at San Antonio. Participants signed informed consent before receiving any study-related evaluations or treatment.

Study medication

With only minor exceptions, all analgesic and sedative hypnotic medications typically used for the treatment of FMS[37,38] were discontinued at the screening visit and proscribed for the entire duration of the study. Patients were permitted to take acetaminophen for severe headaches. In addition, low-dose (85 mg/day) aspirin was allowed if previously prescribed for its anticoagulation activity.

Enrolled patients were randomized into one of four coded study mediations. Lozenges were prepared by Hayashibara Biochemical Laboratories, Inc. (Okayama, Japan) and contained IFN-α at 15, 50, or 150 IU. A placebo lozenge (0 IU) that matched the IFN-α lozenges in appearance and taste was used as the control for treatment.

Administration of study medication

Each participant was asked to dissolve one lozenge of placebo or IFN-α sublingually daily for 6 weeks.

Outcome assessment

The participants had four clinical outcome assessments at 2-week intervals over a 6-week period. These were conducted without knowledge of the randomization code of treatment. Questionnaires were used for self-assessment of symptoms and functional abilities. Tender point examinations were accomplished as previously reported[39,40] and systematically performed by a research nurse (Fane MacKillip) whose FMS examination skills had been previously validated to correspond with that of an experienced FMS investigator (IJR). The Fischer pressure pain threshold algometer was used for the dolorimetry measurements.[41,42]

Clinical measures

The primary outcome variable was the tender point index (TPI), the sum of individual tenderness severities at each of the 18 standard ACR tender points.[43] Three other variables were considered to be of secondary importance, including patient assessment of global pain (PAIN) on a 10-cm visual analog scale (VAS), subjective assessment of physical function by VAS (FUNCTION), and the average pain threshold (APT, mean value in kg derived from dolorimeter readings at each of the 18 ACR tender points).[44] Seven variables were considered to be of tertiary importance including: the patient's VAS for headache (HEADACHE),[45] the VAS for quality of sleep (SLEEP),[46] the VAS for global severity of morning stiffness (STIFFNESS),[47] the duration of morning stiffness,[39] the Standard Health Assessment Questionnaire (HAQ) assessment of physical function ability,[48] the Center for Epidemiology Studies Depression Questionnaire (CESD),[49] anxiety by the Hassles Scale (HASSLES),[50] and the concomitant use of proscribed analgesics (ANALGESIC).[39] In the intent-to-treat approach to assessing response in this study, the patient was defined as a responder (*i.e.*, the study intervention was clinically beneficial) if the patient experienced at least a 30% reduction in the TPI and no worsening with regard to PAIN, FUNCTION, or APT.

Adverse events

Adverse clinical events reported by the patients or noted by the investigational team were recorded at the assessment visits. Laboratory tests including complete blood count, serum chemistry profile, and urinalysis were performed at weeks 0 and 4 of treatment.

Sample size

Sample size needs were determined analytically. Assuming a 17% mean for nonspecific improvement in the TPI among the placebo-treatment subjects in a prior study conducted by the same investigative team,[39] it was determined that 23 evaluable patients in each group would support a 94% power for detecting a 52% average improvement (*i.e.*, about three-fold greater improvement than expected with placebo) in response to at least one of the IFN-α doses. Twenty-eight patients per group were enrolled to complete the study with at least 23 evaluable patients per group to accommodate an expected 20% loss-to-follow-up evaluation.

Statistical analysis

Assessments of treatment efficacy at evaluation visits were based on within-patient differences (changes in outcome from baseline, week 0, to the time of the evaluation visit, week 2, week 4, or week 6). For each outcome variable, three covariates were considered: age (dichotomized at the median of 47.9

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS WHO MET ELIGIBILITY CRITERIA AND WERE RANDOMIZED INTO THE STUDY

	IFN-α treatment group (IU)				
Variable	*Placebo*	*15*	*50*	*150*	*Total*
Number	28	28	28	28	112
Age (years)	49.5	47.0	43.7	43.7	46.9
Sex (F:M)	27:1	25:3	25:3	26:2	103:9
Ethnic	C:7	C:14	C:19	C:15	C:65
	H:10	H:13	H:8	H:13	H:44
	O:1	O:1	O:1	O:1	O:3

Age: mean, C = Caucasian; H = Hispanic; O = other ethnic.

years), race (Hispanic, non-Hispanic Caucasian, and other), and the week 0 value of the outcome variable (dichotomized on the median as low or high) to determine whether demographically definable subgroups existed which benefitted from the treatment.

Separate linear models[51] were applied at each of the follow-up evaluations to assess the significance of differences in outcome variable changes with time among the treatment groups (15 IU, 50 IU, 150 IU of IFN-α) compared with 0 IU placebo (P). Possible adverse effects from IFN-α during the course of the study were assessed for statistical significance by Chi-square analysis. Pairwise comparisons with placebo (P vs. 50 IU, P vs. 100 IU, P vs. 150 IU) were examined.

RESULTS

Study subjects

One hundred twenty-four FMS patients were screened for eligibility; 112 patients qualified for study participation. Of those, 12 were not randomized because they proved not to have primary FMS ($n = 2$), were unable to tolerate the washout period ($n = 2$), or elected not to participate ($n = 8$). The randomized subjects exhibited a female:male ratio of 103:9, and a mean age of 46.9 years. The ethnic distribution (Hispanic 39.3%) was slightly different from that of the San Antonio general population (60% Hispanic). Twenty-eight subjects were randomly assigned to each of the four treatment groups. Table 1 summarizes the baseline values of the demographic variables at the time of study entry. Analysis of treatment groups disclosed no significant differences with regard to sex, age, or race at any visit.

Ninety-nine (88.4%) of the randomized subjects completed the week 2 assessment, 93 (83.0%) completed week 4, and 90 (80.4%, placebo $n = 20$, 15 IU $n = 25$, 50 IU $n = 23$, 150 IU $n = 22$) completed the week 6-evaluation. In all, 19.6% of the randomized patients were lost to follow-up before the end of the study. Chi-square analysis found no association between treatment group and the occurrence of protocol violations or loss to follow-up.

TABLE 2. OUTCOMES OF THE CODED-DRUG STUDY: NUMBERS OF SUBJECTS COMPLETING THE STUDY. CHANGE IN TREATMENT GROUP SIZES FROM WEEK 0 BASELINE TO WEEK 6

Variable		*Placebo*	*15 IU*	*50 IU*	*150 IU*
Number	@Wk0	28	28	28	28
	Chg	−8	−3	−5	−6
TPI	Wk0	31.50 ± 1.87	34.71 ± 1.56	32.32 ± 2.15	33.11 ± 1.93
	Chg	4.15 ± 2.85	1.32 ± 2.40	4.13 ± 1.27	3.82 ± 1.93
Pain	Wk0	7.08 ± 0.37	6.76 ± 0.32	6.53 ± 0.30	6.61 ± 0.30
	Chg	1.37 ± 0.41	0.21 ± 0.36	0.72 ± 0.52	1.09 ± 0.50
Funct	Wk0	7.68 ± 0.43	7.91 ± 0.38	7.93 ± 0.39	7.02 ± 0.51
	Chg	0.71 ± 0.49	0.73 ± 0.48	1.33 ± 0.63	0.23 ± 0.56
APT	Wk0	2.24 ± 0.15	1.91 ± 0.16	2.21 ± 0.21	2.13 ± 0.18
	Chg	−0.09 ± 0.21	0.06 ± 0.13	−0.16 ± 0.18	0.07 ± 0.09
Heada	Wk0	4.38 ± 0.59	4.08 ± 0.46	3.47 ± 0.45	3.86 ± 0.50
	Chg	1.39 ± 0.42	0.28 ± 0.60	0.23 ± 0.67	1.32 ± 0.54
Sleep	Wk0	3.36 ± 0.42	3.26 ± 0.38	3.46 ± 0.44	3.58 ± 0.40
	Chg	−0.90 ± 0.42	−0.39 ± 0.34	−0.90 ± 0.3	−0.79 ± 0.51
Stiff	Wk0	6.11 ± 0.52	7.39 ± 0.44	6.53 ± 0.50	7.13 ± 0.34
	Chg	−0.54 ± 0.74	0.31 ± 0.59	1.73 ± 0.58[a]	1.74 ± 0.55[a]
HAQ	Wk0	1.43 ± 0.11	1.52 ± 0.12	1.33 ± 0.14	1.33 ± 0.12
	Chg	−0.04 ± 0.09	0.08 ± 0.10	0.26 ± 0.08[a]	0.02 ± 0.08
HASSLE	Wk0	67.75 ± 11.89	70.46 ± 11.7	54.43 ± 8.85	57.86 ± 9.70
	Chg	9.05 ± 4.18	20.20 ± 10.18	9.04 ± 3.75	1.59 ± 6.42
CESD	Wk0	25.25 ± 2.48	27.82 ± 2.81	241.25 ± 2.88	26.32 ± 2.73
	Chg	1.75 ± 1.24	0.96 ± 1.76	4.74 ± 2.42	4.65 ± 2.06
Anal[%]	Wk0	4 [14.3]	2 [7.1]	3 [10.7]	1 [3.6]
	Chg	5 [25.0]	0 [0.0]	3 [13.0]	1 [4.5]

Values of clinical outcome variables at week 0 baseline. Changes from week 0 to week 6 in the values of all outcome variables [week 0 minus week 6].

Notes: The first row of each variable indicates the actual value from the week zero [wk0] assessment. The second row for each variable indicates the change [Chg] in variable value after 6 weeks of treatment. Plus means decreased and minus means increased. A higher positive value means improvement for all variables except APT and SLEEP where lower values indicate improvement. All values are expressed as mean ± SEM of the mean.

[a]Significant, $p < 0.05$.

Abbreviations: TPI, tender point index; Pain, pain by visual analog scale [VAS]; Funct, physical function; APT, average pain threshold measured by algometry; Heada, severity of headache by VAS; Sleep, quality of sleep by VAS; Stiff, morning stiffness severity by VAS; HAQ, Stanford Health Assessment Questionnaire disability score; HASSLE, Anxiety as evidenced by the Hassles scale score; CESD, Center for Epidemiologic Studies Depression scale; Anal, the use of analgesics [acetaminophen]; Wk0, week zero baseline assessment value; Chg, change in outcome variable value from week 0 to week 6 assessment.

Response to treatment

The treatment responses for each of the outcome measures are shown in Table 2. According to the intent-to-treat analysis, the primary variable (TPI) failed to exhibit a significant mean change from 0 to week 6 among all of groups receiving IFN-α when compared with the placebo group. The same was true for the APT and subjective PAIN by VAS.

A significant improvement for global severity of morning STIFFNESS by VAS was detected for FMS subjects in the 50 IU/day ($p = 0.01$) and the 150 IU/day ($p = 0.01$) IFN-α treatment groups when compared with the placebo groups (Fig. 1). Pairwise treatment groups contrasts for each visit showed that this change was evident at weeks 2 and 4. Improvement in this variable at week 6 for subjects receiving 50 IU of IFN-α per day was more apparent in non-Hispanic Caucasians (mean = 3.0, 95% CI = 1.0, 5.1) than in Hispanics (mean = 0.2, 95% CI = −3.6, 4.0) and in subjects older than the median 47.9 years (mean = 3.0, 95% CI = 0.5, 5.5) compared with the younger subgroups (mean = 0.6, 95% CI = −1.8, 3.1).

Non-Hispanic Caucasians ($n = 68$) with an average baseline STIFFNESS level (mean = SEM) of 6.65 ± 0.29, median = 6.69 (range 0.0–9.9) exhibited an average improvement of 3.0 units, a 45% improvement over baseline. This was not a finding isolated to non-Hispanic Caucasians with the 50 IU dosage of IFN-α, but was most dramatic with this demographic and dose combination.

The same analytic approach detected significant ($p = 0.06$) overall improvement in physical function ability averaged over time, as assessed by the HAQ, in subjects taking 50 IU/day of IFN-α compared with placebo. A progressive trend in the direction of improvement with time was evident and achieved significance (mean = 0.3, 95% CI = 0.0, 0.6) at week 6. Significant improvement in the HAQ was seen in younger patients (age <47.9 years) (mean = 0.5, 95% CI = 0.0, 0.9) at week 4 and non-Hispanic Caucasian patients (mean = 0.40, 95% CI = 0.1, 0.7) at week 6. Non-Hispanic Caucasians ($n = 68$) with an average baseline HAQ level (±SEM) of 1.28 ± 0.07, median = 1.38 (range 0.0–2.63) exhibited an average improvement of 0.15 HAQ units, an 11.7% improvement over baseline. None of the other secondary, and tertiary outcome variables (*e.g.*, VAS FUNCTION, PAIN, HEADACHE, SLEEP, CESD, HASSLES, ANALGESIC) showed significant improvement with any IFN-α dosage.

Adverse events

Adverse events present during more than one evaluation were considered as a single event. There were 105 events reported among 65 patients; none were considered serious, nor were any of the events judged by the physician to be "related," or even "probably related" to IFN-α administration. Adverse events were quantitatively documented to determine improvement or decline over time. While the total numbers of individuals experiencing adverse gastrointestinal symptoms was small, patients taking the 15 IU/day IFN-α were more likely to experience nausea and diarrhea than those on placebo. A borderline significant ($p = 0.07$) change in the occurrence of diarrhea was

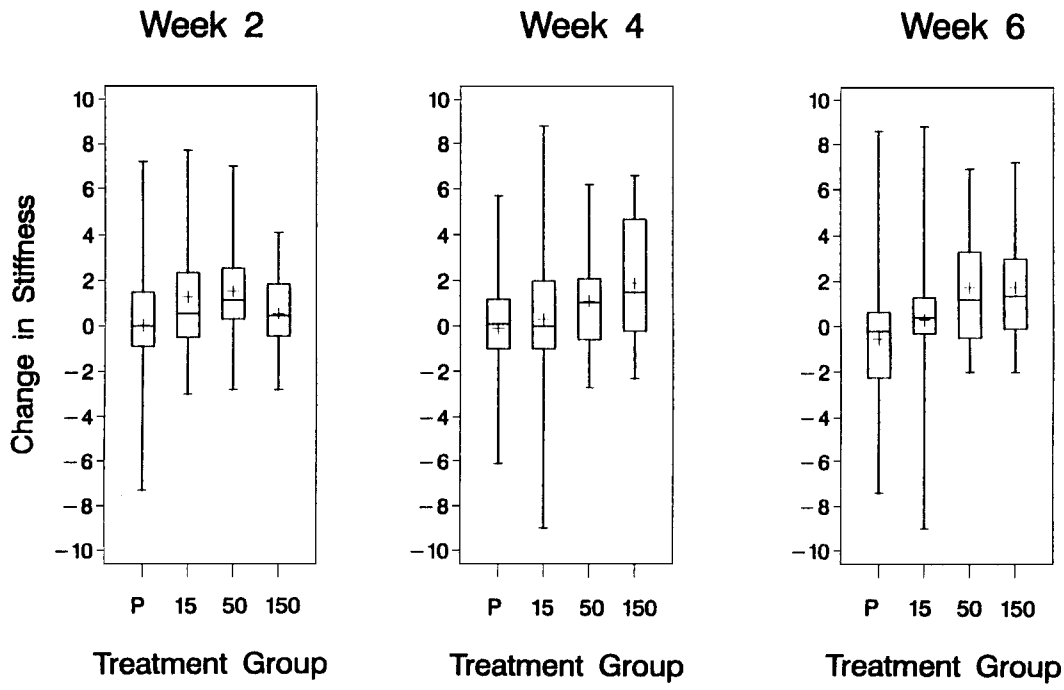

FIG. 1. Mean change (*y*-axis) from week 0 (baseline) to week 6. Changes in morning stiffness with time [week 0 minus week 2, 4, or 6] by groups (P, Placebo; 15 IU, 15 IU/day; 50 IU, 50 IU/day; 150 IU, 150 IU/day) during coded drug treatment. Positive changes indicate improvement. Decreases in the perceived morning stiffness among the 50 IU/day and the 150 IU/day groups are statistically significant ($p < 0.05$). Notice that this change at week 6 was anticipated at both the week 2 and the week 4 assessments.

found between the placebo-treated group (improved $n = 4$, worsened $n = 0$) and subjects in the 15 IU IFNα-treated group (improved $n = 3$, worsened $n = 6$) between baseline and week 6. Similarly, the change in the prevalence of nausea was more favorable ($p = 0.05$) in the placebo-treated group (improved $n = 5$, worsened $n = 1$) than in the 15 IU IFN-α-treated group (improved $n = 1$, worsened $n = 5$) between baseline and week 6.

The effects of treatment on clinical laboratory test values were assessed using changes in each variable from baseline to week 4 (*i.e.*, changed from normal at week zero to abnormal at week 4). Matched pair analysis failed to disclose any significant change in laboratory values with treatment or by treatment group.

DISCUSSION

IFN-α

IFN-α was the first cytokine to be produced by recombinant DNA technology specifically for human administration. It has emerged as an important regulator of growth and differentiation, affecting cellular communication, signal transduction and immunological regulation.[52] In addition, Ho *et al.*[53] proposed an opioid-mediated dopaminergic mechanism for some of the effects of IFN-α.

CFS

A study by Brook, Bannister, and Weir[54] suggested that a proportion of patients with CFS may benefit from 3 weekly doses (3 million IU) of IFN-α therapy. Although the numbers of patients involved in that study were too small to draw a firm conclusion, the temporal relationship of recovery with therapy and a significant association with IgM anti-coxsackievirus B antibody in the same subjects provides a basis for a treatment-mediated positive responses. Two explanations for the results of their trial were suggested.[54] First, if the IgM antibodies to coxsackievirus B reflected chronic enterovirus infection, then IFN-α might suppress enterovirus replication. Alternatively, if the IgM antibodies represented an aberrant immune response, the observed improvement may have been due to the immunoregulatory properties of IFN-α.[55]

Some believe that the pain component of CFS results from a clinical overlap with FMS.[26,27] We hypothesized that IFN-α might also reduce the severity of the widespread discomfort associated with FMS. Here FMS was studied instead of CFS because the former is substantially more prevalent than the latter.[56,57]

FMS

All of the patients in this study met the published ACR criteria for primary FMS.[32] Sample size calculations had predicted that if IFN-α were clinically beneficial in FMS, 23 patients should be adequate to demonstrate a significant improvement in TPI with IFN-α treatment relative to placebo. This number of subjects completed the week 6 evaluation. The finding of no statistically significant or clinically relevant relief from deep pressure tenderness with IFN-α treatment in this study suggests that physiological doses of IFN-α are not effective for pain relief in FMS over the short treatment interval tested.

In a companion analysis of the data in this study,[58] the APT was found to be a more reliable outcome measure than the TPI, so the APT might have been a better choice as the primary outcome variable. Indeed, a trend (nonsignificant) toward clinical benefit in the APT was observed with the 50 IU. However, those findings were not sufficient to change the major conclusions of the study with regard to IFN-α monotherapy for FMS pain.

The unanticipated improvement in both the global severity of morning stiffness and in the ability of the subjects to be physically active, as measured by the HAQ, must be carefully considered. Therapeutic options for the treatment of FMS are limited and most of those in current use appear to have quite similar mechanisms of action. Further exploration of the findings of this study with IFN-α has the potential to disclose a novel model of adjunctive therapy and to bring into focus new information about the pathogenesis of FMS.

Morning stiffness

The symptom of morning stiffness is not unique to FMS. Indeed, it is best known as a clinical feature of RA.[59] It is clearly important in RA because it is the first of the listed criteria in the ACR revised classification of RA.[59] A substantial reduction in its duration is a key element in the criteria for remission of RA disease activity.[60] As a result, every routine clinical evaluation of RA patients should include questioning about morning stiffness. Despite the importance of morning stiffness to the assessment of disease activity status in RA, it is not well understood. Although morning stiffness is generally believed to parallel the severity of RA,[61] it does not correlate directly with the erythrocyte sedimentation rate or the severity of synovitis.[62–64] Morning stiffness is generally believed to be less severe and of shorter duration among patients with osteoarthritis (OA) than in RA.[65] The severity of morning stiffness and especially of its long duration in FMS is more similar to RA than OA. That observation may partially explain why FMS was initially considered to be an inflammatory condition and why it was originally referred to as "fibrositis."

There has been very little research specifically focused on the phenomenon of morning stiffness in either RA or OA.[61,66,67] Morning stiffness may have different meanings among care givers and patients with inflammatory conditions such as RA, polymyalgia rheumatica, systemic infections, OA, stiff-man syndrome, and hypothyroidism. It should also be noted that morning stiffness can be viewed as a worst case outcome for the "gelling phenomenon," which occurs in affected individuals any time during the day or night when they are sedentary for at least 30 minutes. Gelling may also be influenced by several other clinical symptoms such as pain and limited movement.[66,68]

Morning stiffness is an important component of FMS.[47,68,69] It was encouraging to observe clinical improvement in morning stiffness and in physical function ability with IFN-α. Considering this, it seems surprising that there was not more influence of IFN-α in the standard pain measures, especially if IFN-α exhibits analgesic properties.[53] In a companion analysis[58] of the data from this study, it was shown that

the subjective outcome variable (PAIN) correlated ($r = 0.66$) with morning stiffness, suggesting that pain was an important contributor to the severity of the morning stiffness variable.

This study showed that the severity of morning stiffness was significantly reduced with the 50 IU/day when compared to the placebo group. An average 45% reduction in the average severity of the morning stiffness observed among non-Hispanic Caucasians was not trivial, especially since some subjects had much greater relief than the mean. In fact, the change in morning stiffness severity meets the 30% criteria for clinically relevant improvement. By contrast, cyclobenzaprine treatment of FMS resulted in a trend toward improvement in fatigue but morning stiffness was not affected.[70] Although improvement in physical function (HAQ) seen with IFN-α was statistically significant, it did not meet the 30% standard for clinical relevance. With further study, IFN-α may prove to be additively or even synergistically beneficial with regard to morning stiffness when combined as adjunctive treatment with concomitant analgesic or sedative hypnotic agent therapy.

The slightly increased frequency of nausea and diarrhea seen with the lowest dose of IFN-α may not be due to IFN-α because these side effects were not seen with the higher doses.

Hepatitis C

It is of interest that Middleton *et al.*[24] studied 13 patients with chronic hepatitis C infection being treated systematically with supraphysiological, pharmacological dosages (3 million IU, 3 times per week) of IFN-α. Large doses of IFN-α caused a generalized reduction in pain thresholds in most patients and may have actually induced fibromyalgia in some hepatitis C-infected patients.[24] If high levels of IFN-α are capable of lowering pain thresholds and inducing FMS, one could speculate that increased cytokine production resulting from inflammation may contribute to the increase in the prevalence of FMS among patients with autoimmune or inflammatory diseases like RA[71] and lupus.[72,73]

Summary

The findings of this study suggest that there may be a role for low-dosage IFN-α as an adjunct to a comprehensive therapy program of education, exercise, and analgesic/sedative hypnotic therapy for FMS. The results of such combination therapy may be overall improvement in sleep, pain, morning stiffness, and physical function.

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