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ORIGINAL ARTICLE

Treatment of Primary Sjögren's Syndrome With Low-Dose Human Interferon Alfa Administered by the Oromucosal Route: Combined Phase III Results

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Objective. **This study tested the safety and efficacy of human interferon (IFN) alfa for treatment of salivary hypofunction and dry mouth symptoms in primary Sjögren's syndrome patients.**
Methods. **Combined results are reported from 2 phase III clinical trials in which a total of 497 subjects with primary Sjögren's syndrome received 150 international units of human IFN alfa or matching placebo 3 times per day for 24 weeks by the oromucosal route.**
Results. **Subjects given IFN alfa had a significantly ($P = 0.01$) greater mean increase in unstimulated whole saliva (UWS) flow, compared with subjects given placebo. In IFN alfa patients, increases in UWS correlated positively and significantly with improvements noted in 7 of 8 symptoms associated with oral and ocular dryness. The coprimary endpoints of stimulated whole saliva flow and oral dryness were not significantly improved in the IFN alfa group relative to placebo. No significant differences were found between the groups with respect to overall adverse event incidence or severity.**
Conclusion. **IFN alfa given at low dosage by the oromucosal route can significantly increase UWS flow in patients with primary Sjögren's syndrome, without causing significant adverse events.**

KEY WORDS. Interferon alfa; Sjögren's syndrome; Saliva; Xerostomia; Secretion.

INTRODUCTION

Sjögren's syndrome is a chronic autoimmune rheumatic disease characterized by salivary and lacrimal gland inflammation associated with symptoms of xerostomia (dry mouth) and xerophthalmia (dry eyes) (1). Sjögren's syndrome is a systemic disorder that can also affect the musculoskeletal, pulmonary, gastrointestinal, hematologic, vascular, dermatologic, renal, and nervous systems (2). Primary Sjögren's syndrome is defined by the presence of salivary and lacrimal gland involvement as a sole systemic disorder, whereas secondary Sjögren's syndrome includes involvement of 1 or both of these exocrine sites in association with another connective tissue disease, such as rheumatoid arthritis (3). More than 1 million people in the United States have primary Sjögren's syndrome, with 90% of these being women (3).

The characteristic histopathologic finding in the salivary glands of patients with Sjögren's syndrome is a focal, periductal monocellular cell infiltrate (4–6). As the inflammatory disease progresses, the lymphocytic infiltration increases, leading to acinar gland degeneration, necrosis, and atrophy and decreasing exocrine function (6).

Management of the xeroses associated with Sjögren's syndrome is problematic (7–9). Dry eyes are treated by protective measures, frequent ophthalmologic examination, and ocular wetting agents (10). Artificial saliva or frequent ingestion of nonsugared liquids may provide dry mouth relief for some; preventive measures such as supplemental fluoride, avoiding sugar, and avoiding medications known to cause a dry mouth are recommended to Sjögren's patients (8,9,11). Pilocarpine and cevimeline have both been shown to reduce symptomatic oral dryness and produce transient increases in salivary flow (12–14). However, neither drug addresses the underlying disease process or leads to increases in basal, unstimulated salivary flow.

Interferons are proteins derived from different cell types in response to many stimuli including bacteria, foreign cells, macromolecules, other chemical compounds, and

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viruses (15,16). In addition to their antiviral activities, interferons have potent immunomodulating effects (16). Interferon (IFN) has been shown to enhance phagocytic antigen processing and immune regulatory activity of macrophages (15), specific cytotoxicity of lymphocytes for target cells, and natural killer cell activity (17). The biologic activity of IFN alfa given in low doses via the oromucosal route has been examined in many species, including humans (18). Data from these studies suggest that IFN alfa can trigger a systemic biologic response when administered via the oral mucosa.

Shiozawa and colleagues first reported on the benefits of oromucosal IFN alfa in the treatment of Sjögren's syndrome (19–21). A consistent finding in these studies was an increase in stimulated whole saliva (SWS) flow in a proportion of patients given 150 international units (IU) of IFN alfa 3 times per day in the form of orally dissolved lozenges. Shiozawa et al performed minor salivary gland lip biopsies in 9 subjects who experienced a 2-fold or greater increase in saliva output in response to IFN alfa treatment. Compared with pretreatment, salivary tissue obtained posttreatment showed significant histopathologic improvement, including reduced mononuclear infiltration and increased histologically normal appearing epithelial tissue (21). Subsequently, Ship et al reported on the results of a double-blind, randomized, parallel phase II trial in which 109 patients with primary Sjögren's syndrome were given 1 of 4 daily doses of oromucosal IFN alfa or placebo for 12 weeks (22). Subjects given 150 IU IFN alfa 3 times per day had a significant increase in SWS at the end of treatment, compared with the placebo group.

The 2 present studies were intended to replicate the results reported by Ship et al and to demonstrate the safety and efficacy of 150 IU IFN alfa lozenges, compared with placebo, when administered 3 times per day for 24 weeks to subjects with primary Sjögren's syndrome. Because the 2 studies used identical protocols, the results were pooled for analysis.

PATIENTS AND METHODS

Patients. Eligible patients were at least 18 years old, not pregnant, and had a diagnosis of primary Sjögren's syndrome according to the revised European Community (EC) proposed criteria (23,24). All had a SWS flow rate of at least 0.05 gm/minute and completed an institutional review board approved written consent form. Exclusionary criteria included current or anticipated use of a secretogogue (e.g., bromhexine, anetholetrithione, pilocarpine) or drugs known to be xerostomic, exposure to systemic steroids within 30 days of initiation of study treatment, and a history of antineoplastic chemotherapy or radiotherapy for treatment of head and neck tumors. A total of 705 subjects were screened for inclusion in the study. Of those, 497 from 51 clinical sites within the United States met eligibility criteria, chose to enter the study, and were randomized at baseline.

Experimental design. This was a randomized, parallel group, double-blind, placebo-controlled clinical trial. At screening, patients underwent complete physical and oral examinations, review of medical history, and pregnancy testing (if applicable). At baseline, subjects were randomized to 24 weeks of daily treatment with either 150 IU IFN alfa 3 times per day or placebo at a 3:2 ratio. Randomization was performed by a central coordinating center in blocks of 5. At the initial visit, subjects underwent an oral examination, measurement of vital signs, review of concomitant medications, collection of saliva, and completion of a series of 100-mm visual analog scales (VAS) concerning oral and ocular symptoms. Subjects returned for evaluation at 6, 12, 18, and 24 weeks of treatment. Sample size estimates were prepared for each study independently, and the trials had approximately 100% power to detect an effect on SWS equal to that seen in the phase II study (0.60) and approximately 93% power to detect an effect on oral dryness equal to that seen in the phase II study (0.44).

Saliva collection. Whole salivary flow rates were determined at each visit. Subjects were instructed not to eat, drink, smoke, chew gum, or perform oral hygiene for at least 60 minutes prior to saliva collection. To the extent possible, saliva collections were conducted for a particular patient within the same time period of the day (morning or afternoon) at each visit. Subjects were seated in a comfortable examination chair for at least 5 minutes before initiation of saliva collection.

First, unstimulated whole saliva (UWS) was collected for 5 minutes utilizing the spitting technique, according to established methods (25,26). Next, SWS was collected for a total of 5 minutes. The subject chewed a preweighed piece of unflavored chewing gum base 60 times/minute (timed with a metronome), and accumulated saliva was spit into a preweighed vial every minute, as previously described (25,26). All flow rates were determined gravimetrically, assuming a specific gravity of saliva of 1.0, and expressed as grams/5 minutes.

VAS for oral and ocular symptoms. At each visit, subjects were instructed to provide a rating for each of the following 8 items using a 100-mm VAS: oral dryness; oral comfort; difficulty swallowing dry food without any additional liquids; difficulty swallowing any food without any additional liquids; eye dryness; burning, stinging, and grittiness of the eyes (burning eyes); nasal dryness; and throat dryness.

Other patient questionnaires. At weeks 6, 12, 18, and 24, patients were asked to rate changes in their use of oral and ocular comfort agents as increased, decreased, or unchanged. At week 24, patients answered questionnaires related to overall incidence of adverse events; the frequency with which adverse events interfered with daily activities; and their desire to continue study medication.

Safety parameters and adverse events. Patients returned for oral (weeks 6, 12, 18, 24) and physical (week 24) examinations, measurements of vital signs (weeks 6, 12, 18, 24), reviews of medical history, concomitant medications and adverse events (weeks 6, 12, 18, 24), hematology

and blood chemistry tests (weeks 6, 24), and urinalysis (week 24). The safety variables assessed were divided into 7 main categories: 1) hematologic variables of red blood cells, hemoglobin, hematocrit, platelets, white blood cells, segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils; 2) body weight; 3) vital signs of temperature, heart rate, and blood pressure; 4) blood chemistry variables of glucose, sodium, potassium, chloride, blood urea nitrogen, creatinine, uric acid, phosphorus, calcium, cholesterol, triglycerides, protein, albumin, globulin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transaminase, total bilirubin, and lactate dehydrogenase; 5) adverse events as reported by each subject; 6) urinalysis variables of pH, specific gravity, ketones, protein, glucose, bilirubin, blood, leukocytes, red blood cell count, and microscopic examination of urine; and 7) oral pathoses including fungal infections and episodes of salivary gland enlargement.

Medication and placebo. All lozenges were identical in appearance, taste, and smell, and contained 200 mg pharmaceutical grade anhydrous crystalline maltose (carrier for the IFN alfa) and magnesium stearate (lubricant/excipient). Active drug lozenges also contained 150 IU IFN alfa. IFN alfa was produced by Hayashibara Biochemical Laboratories (HBL; Okayama, Japan) by in vitro induction of a human cell line (BALL-1) using hemagglutinating virus of Japan (also called Sendai virus) according to previously described criteria (27). HBL IFN alfa is greater than 98% pure and has a specific activity of approximately 2×10^8 IU/mg protein, which is comparable to Food and Drug Administration approved IFN alfa products. IFN alfa and identical-appearing placebo lozenges were individually strip-wrapped in plastic-lined foil, and subjects were asked to keep them refrigerated.

Subjects were instructed to take the lozenges daily at approximately 8:00 AM, 2:00 PM, and 8:00 PM. Subjects were instructed to allow each lozenge to dissolve in the mouth and not to chew or swallow the lozenge while it was dissolving. They were further instructed to refrain from eating, drinking, using oral wetting agents, or brushing their teeth for 5 minutes before and 15 minutes after taking each lozenge. Lozenges were not used within 60 minutes of study visits.

Analysis. The coprimary efficacy endpoints were the VAS for oral dryness and the SWS flow. Thirteen secondary outcome measures were analyzed. These were 1 additional objective measure, UWS flow, 7 additional VAS items, and 5 other questionnaire items (see above).

Statistical assessments of efficacy and safety were directed at contrasts between the treated group (150 IU 3 times per day) and the placebo group. Exploratory analysis examined within-group changes from baseline to each of the followup visits. All statistical tests were 2-sided and conducted at the 5% level of significance. SAS (Cary, NC) software was used for all analyses.

For each of the 2 primary variables (SWS and the VAS for oral dryness) intent-to-treat analyses were carried out based on data arising from the week 24 visit using analysis of covariance on ranks. The independent variables were the baseline value, age, ethnicity, treatment arm, and center. Patients not evaluable at week 24 were assigned rank 0 regardless of treatment arm. Of secondary importance, assessment of changes in SWS and the VAS for oral dryness were carried out at weeks 6, 12, 18, and 24 on evaluable patients without any episodes of study medication noncompliance or other protocol violations using analysis of covariance. The independent variables were the baseline value, age, ethnicity, treatment arm, and center.

The secondary VAS variables and UWS flow were analyzed as continuously distributed variables with adjustment for center and center by treatment interaction. For the non-VAS questionnaires, patients were classified as positive responders based on the following criteria and as nonresponders otherwise: comfort agent use—report of decreased use; side effects severity—report of none or mild; side effects interference—report of never or rarely; desire to continue study medication—report of yes. Unadjusted analyses of the dichotomized variables were carried out with Fisher's exact test.

UWS flow was analyzed also using a last observation carried forward (LOCF) technique (28). Unlike the analysis of covariance on ranks, which assigned a rank of 0 to all patients who failed to complete the study, the LOCF analysis utilized a patient's final UWS measurement prior to leaving the study. Consequently, the LOCF analysis more closely reflected the true clinical picture because it related to changes in UWS flow in this study.

The correlation between changes in saliva flow (both SWS and UWS) and changes in each of the VAS variables was computed for each treatment group. The significance of the interaction between changes in saliva flow, changes in VAS variables, and treatment group were assessed.

The safety analysis included subjects who were enrolled to treatment, took at least 1 dose of study drug, and had evaluable data from at least 1 followup visit. Analysis of continuously distributed variables was performed using a 2-tailed *t*-test on changes from baseline. Secondarily, each variable was trichotomized to abnormally low, normal, or abnormally high, and changes from baseline (low to normal, normal to low; high to normal, normal to high; and low to high, high to low) were tabulated.

Oral pathoses were analyzed for incidence and severity. Because pathoses may be present at baseline and not after treatment, or not present at baseline and present after treatment, these analyses were carried out using a matched pair analysis in which only the subjects who experienced a change in pathology contributed. The significance of the association between adverse events and treatment group was assessed at each evaluation week using a Fisher's exact test.

RESULTS

The groups were similar with respect to age, sex, and race (Table 1). Most subjects were female (92.6%) and white (93.4%), and they ranged in age from 26 to 88 years with a mean age of 58.2 years. The groups were also similar at baseline with respect to clinical characteristics such as

Table 1. Study population at baseline and treatment schedule*

Group (n)	Age, years, mean ± SEM	Sex, F/M	Race, white/other
Placebo (197)	58.3 ± 0.9	187/10	182/15
150 IU IFN alfa 3 times daily (300)	58.0 ± 0.7	273/27	282/18

* IU = international units; IFN = interferon.

Table 3. Number of EC criteria used to qualify the study groups*

Group	<4 criteria	4 criteria	5 criteria	6 criteria
Placebo	1 (0.5)†	135 (68.5)	58 (29.4)	3 (1.5)
IFN alfa	1 (0.3)†	203 (67.7)	93 (31.0)	3 (1.0)

* Values represent number (%) of patients in each category. EC = European community; IFN = interferon.
† Patient met 3 criteria and was SS-A antibody positive.

salivary flow rates, Schirmer scores, percentage of patients who were positive for SS-A/SS-B antibodies, and percentage of patients with a positive minor salivary gland biopsy (Table 2). The groups were also similar in regard to the number of EC diagnostic criteria satisfied (Table 3). Most patients met 4 EC criteria and the majority were either lip biopsy or SS-A/SS-B antibody positive (placebo = 75.6%; IFN alfa = 71.3%). Loss to followup was not significantly associated with treatment group. The reasons for patient withdrawals in this study are detailed in Table 4. The groups did not differ significantly with respect to the number of patients who dropped out of the study for any particular cause.

Intent-to-treat analysis of the coprimary endpoints failed to demonstrate a significant treatment effect based on analysis of covariance on ranks (data not shown). In evaluable patients (those who completed all study visits), mean SWS changes were greater in the IFN alfa group, albeit not significantly, compared with the placebo group at each visit (Figure 1A). A within-group analysis demonstrated a significant increase in mean SWS flow over the baseline level after 18 and 24 weeks of daily IFN alfa (data not shown). A similar increase was not seen in the placebo group. Mean changes in oral dryness VAS scores were nearly identical in both groups. Both groups experienced significant increases (improvement) in mean oral dryness VAS scores at all visits, compared with baseline (Figure 1B).

Mean UWS flow was significantly ($P = 0.01$) increased at week 24 in the evaluable IFN alfa group, compared with the placebo group (Figure 1C). The IFN alfa group had a significant increase ($P < 0.001$) in mean UWS flow at week 24, compared with baseline, whereas the placebo group was not significantly changed relative to baseline (Figure 1D). Intent-to-treat analyses were carried out on UWS (Table 5), although they had not been specified in the study design. Analysis of covariance on mean ranks did not find a significant difference between the groups. However, an LOCF technique applied to mean changes in UWS from baseline to week 24 found a significant mean increase in flow ($P = 0.05$) in the IFN alfa group.

For each of the treatment groups, the Pearson correlation is provided (Table 6) between changes from baseline to week 24 in UWS flow and each of the 8 VAS. In the IFN alfa group, a significant ($P \leq 0.05$) positive correlation was found between change in UWS and changes in 7 of the 8 VAS measures at week 24 (all but burning eyes). Although these r values are low, the pattern of positive correlations was consistent. In the placebo group, change in UWS was significantly and positively correlated with change in oral dryness, but not other symptoms. A similar pattern was noted for SWS (data not shown). In the IFN alfa group, change in SWS from baseline to week 24 correlated positively and significantly ($P \leq 0.05$) with changes in 5 of 8 symptomatic measures (all but eye dryness, burning eyes, and nasal dryness; data not shown). In the placebo group, changes in SWS did not correlate significantly with changes in any of the VAS questionnaires.

Among the remaining secondary variables, mean changes in the VAS scores for oral comfort, difficulty swallowing dry food, difficulty swallowing any food, and throat dryness were similar in both groups. Mean VAS values for oral comfort, difficulty swallowing dry food, and throat dryness were significantly increased (improved) over baseline levels in both groups at all followup visits (Figure 2). Mean changes in the VAS for nasal dryness were also similar between the groups. Mean followup scores were higher in both groups at all visits compared with baseline, but at week 24, neither group was significantly improved (data not shown). Mean changes in the VAS for eye dryness and burning eyes favored the placebo group. At weeks 6 and 18, the placebo group had borderline significantly greater mean increases (improvement) in

Table 2. Patient clinical characteristics at baseline*

Group (n)	SWS, gm/5 min	UWS, gm/5 min	Schirmer score, mm/5 min	SS-A/SS-B positive n (%)	Lip biopsy positive n (%)
Placebo (197)	2.16 ± 0.17	0.48 ± 0.05	2.1 ± 0.1†	130 (66.0)	26 (13.2)
IFN alfa (300)	2.05 ± 0.13	0.44 ± 0.03	2.1 ± 0.1‡	185 (61.7)	45 (15.0)

* Data reported as mean ± SEM unless otherwise noted. SWS = stimulated whole saliva; UWS = unstimulated whole saliva; IFN = interferon.
† n = 144.
‡ n = 229.

Table 4. Reasons for early study termination*

Reason	Group: IFN alfa, n = 300 no. (%)	Group: Placebo, n = 197 no. (%)
Adverse event	23 (7.7)	8 (4.1)
Lost to followup	9 (3.0)	3 (1.5)
Perceived lack of efficacy	4 (1.3)	4 (2.0)
Protocol violation	15 (5.0)	12 (6.1)
Withdrew consent	17 (5.7)	18 (9.1)
Total	68 (22.7)	45 (22.8)

* IFN = interferon.

eye dryness scores, compared with the IFN alfa group. Changes in mean eye dryness from baseline to week 24 were similar in both groups, however (Figure 3A). The placebo group had a significantly greater increase (improvement) in mean VAS score for burning eyes at week 6, compared with the IFN alfa group, and borderline significantly greater increases at weeks 12 and 18. Changes in the mean burning eyes VAS score from baseline to week 24 did not differ significantly between the groups (Figure 3B).

No significant differences were found between the groups in the responses to the non-VAS questionnaires utilized in the study (data not shown). An approximately equal percentage of subjects in each group expressed a desire to continue their treatment at the conclusion of the study (IFN alfa group = 72.2%, placebo group = 67.1%).

With respect to changes in clinical and laboratory safety variables, no detrimental effects of IFN alfa treatment were observed, and some beneficial effects on disease-associated markers were found with IFN alfa treatment. Of 173 patients in the IFN alfa group who started the study with elevated serum globulin, a common finding in primary Sjögren's syndrome patients, 31 (17.9%) decreased to within normal ranges during treatment, compared with 6 of 105 (5.7%) placebo patients ($P = 0.004$). Overall, no differences were found between the groups with regard to the percentage of patients experiencing adverse events by severity or relation to test article (all $P = 0.29$). A significantly higher percentage of IFN alfa patients (34.3%) experienced 1 or more adverse events related to the gastrointestinal (GI) body system, compared with patients in the placebo group (25.9%; $P = 0.05$). However, no particular GI adverse event was observed with a significantly greater incidence in the IFN alfa group. A significantly ($P < 0.001$) greater percentage of patients in the placebo group (40.1%) experienced 1 or more adverse events related to the musculoskeletal body system, compared with the IFN alfa group (25.0%). Within the musculoskeletal body system, adverse events seen more commonly in the placebo group, compared with the IFN alfa group, included chest pain

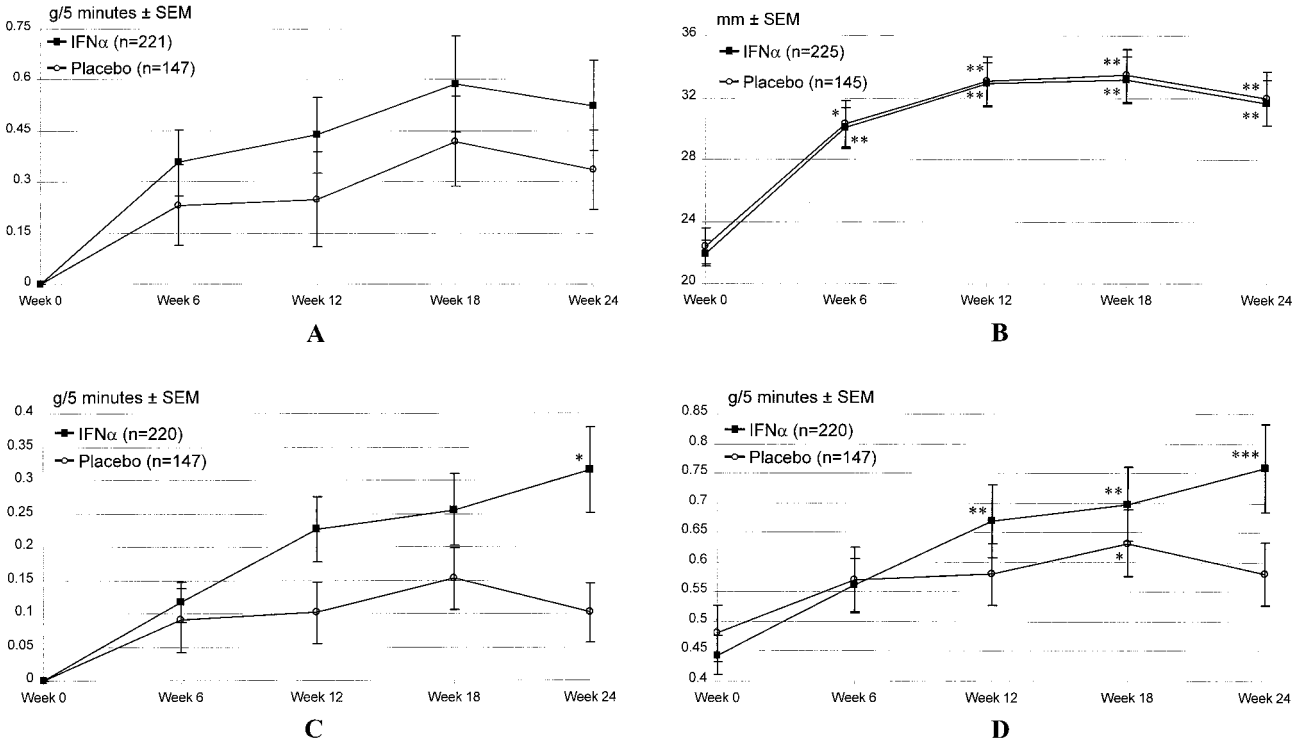

Figure 1. A, Mean changes in stimulated whole saliva (grams/5 minutes ± SEM) in evaluable patients. There were no significant differences between the groups. **B,** Mean oral dryness visual analog scale scores (mm ± SEM) in evaluable patients. Both groups had significantly increased scores (improvement) at all visits compared with baseline (*$P < 0.001$, **$P < 0.0001$). **C,** Mean changes in unstimulated whole saliva (grams/5 mm ± SEM) in evaluable patients. The interferon alfa (IFNα) group had a significant increase (*$P = 0.01$) in output at week 24 compared with placebo. **D.** Mean unstimulated whole saliva (grams/5 minutes ± SEM) in evaluable patients. The IFNα group had significantly greater flow at weeks 12, 18, and 24 compared with baseline. The placebo group was significantly increased at week 18 only (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Table 5. Results of intent-to-treat analyses on unstimulated whole saliva*

ANCOVA on mean ranks at week 24					LOCF on mean changes at week 24				
Group	n	Mean†	SEM	*P*	Group	n	Mean†	SEM	*P*
Placebo	197	244.2	10.0	—	Placebo	197	0.114	0.036	—
IFN alfa	300	252.2	8.4	0.54	IFN alfa	300	0.248	0.049	0.05

* ANCOVA = analysis of covariance; LOCF = last observation carried forward; IFN = interferon.
† Data in gm/5 minutes.

(4.1% versus 1.0%; $P = 0.03$) and arthropathy (2.5% versus 0.3%; $P = 0.009$). Other contrasts between the groups with respect to incidences of adverse events by body system were nonsignificant.

DISCUSSION

This 24-week study failed to confirm the finding of an earlier 12-week study in which 150 IU IFN alfa lozenges given 3 times per day led to significantly greater increases in SWS flow relative to matching placebo (22). The present study found instead a significant and beneficial effect of treatment on UWS flow. The failure of the current study with regard to SWS and oral dryness can be traced to a somewhat reduced beneficial response in the treated group and much greater response in the placebo group, compared with the prior study. In the current trial, the IFN alfa group had a mean ± SEM SWS increase of 0.525 ± 0.134 gm/5 minutes at the end of treatment, a 34% reduction from the increase found in the prior study (0.79 ± 0.46) (22). Conversely, the placebo group experienced a 462% increase in mean SWS in the current study (0.337 ± 0.117 versus 0.06 ± 0.11) at the end of treatment compared with the earlier 12-week study. Although the IFN alfa group still had a greater mean increase in SWS than the placebo group, the study was not powered sufficiently to overcome such a dramatic placebo effect.

The other coprimary endpoint, oral dryness VAS, failed to achieve significance for the same reason. At the end of treatment in the current study, the IFN alfa group demonstrated a mean ± SEM increase (improvement) in oral dryness score of 9.75 ± 1.25 mm, a 29% reduction from the previous study (13.79 ± 6.61 mm). In contrast, the placebo group exhibited a 109% increase in effect, having a mean ± SEM oral dryness score increase of 9.55 ± 1.64 mm in the current study versus 4.56 ± 4.66 mm in the prior trial (Michalek JE, Cummins MJ, unpublished observations). Again, this study had insufficient power to allow for such a vigorous placebo response.

Table 6. Correlation between changes in UWS and 8 VAS questionnaires in evaluable patients at week 24*

	Placebo group		IFN alfa group	
VAS	Correlation coefficient	*P*	Correlation coefficient	*P*
Oral dryness	0.176	0.03	0.224	0.0008
Oral discomfort	0.134	0.11	0.131	0.05
Swallow dry food	0.030	0.70	0.173	0.01
Swallow any food	0.125	0.14	0.170	0.01
Eye dryness	0.113	0.18	0.130	0.05
Eye burning	0.141	0.09	0.081	0.23
Nasal dryness	0.035	0.68	0.196	0.004
Throat dryness	0.071	0.40	0.177	0.009

* UWS = unstimulated whole saliva; VAS = visual analog scale; IFN = interferon.

The robust improvements in VAS scores observed in the placebo group in this study were unprecedented. Previous controlled studies of IFN alfa treatment in this patient population have shown consistently lower placebo responses (21,22). The significance of the findings in the placebo group in this study is punctuated by the fact that two-thirds of the patients receiving placebo expressed a desire to continue treatment at the end of the trial. That two-thirds of primary Sjögren's syndrome patients with documented dry mouth who received no other treatment except 200-mg maltose lozenges 3 times per day for 6 months would express satisfaction with that therapy was completely unexpected. The only explanation the authors can provide for this finding is that the maltose lozenges, being held in the oral cavity and allowed to slowly dissolve 3 times per day, did provide some benefit to the patients. The fact that placebo patients reported such benefits at study visits that were at least 1 hour removed from treatment is particularly striking.

It is accepted that saliva can be stimulated nonspecifically by lozenges or other objects placed in the mouth. Both sweet and sour tastes are known to increase salivary flow, as well. To avoid this expected stimulation having an effect on the results, patients were instructed not to take their study medications or use anything by mouth for at least an hour prior to examination and measurement of salivary output during study visits. However, it is likely that patients did experience some salivary response to the placebo lozenges. The use of lozenges for symptomatic relief in Sjögren's syndrome is well recognized. Dietary analysis of Sjögren's patients, as well as other xerostomic patients, has shown that consumption of sugar, especially in the form of slowly dissolving candies, is significantly increased (29–31). The patients use these candies to soothe their dry erythematous mucosa. Thus, it is not surprising that a lozenge with maltose would be soothing and stimulate saliva. It would not be expected, however, that the effect would last much beyond the time that the lozenge was being used. This raises the issue as to whether the maltose was inducing other, more long-lasting changes in the oral cavity or whether the data collection instruments failed to capture the acute versus chronic nature of the treatment response with sufficient sensitivity.

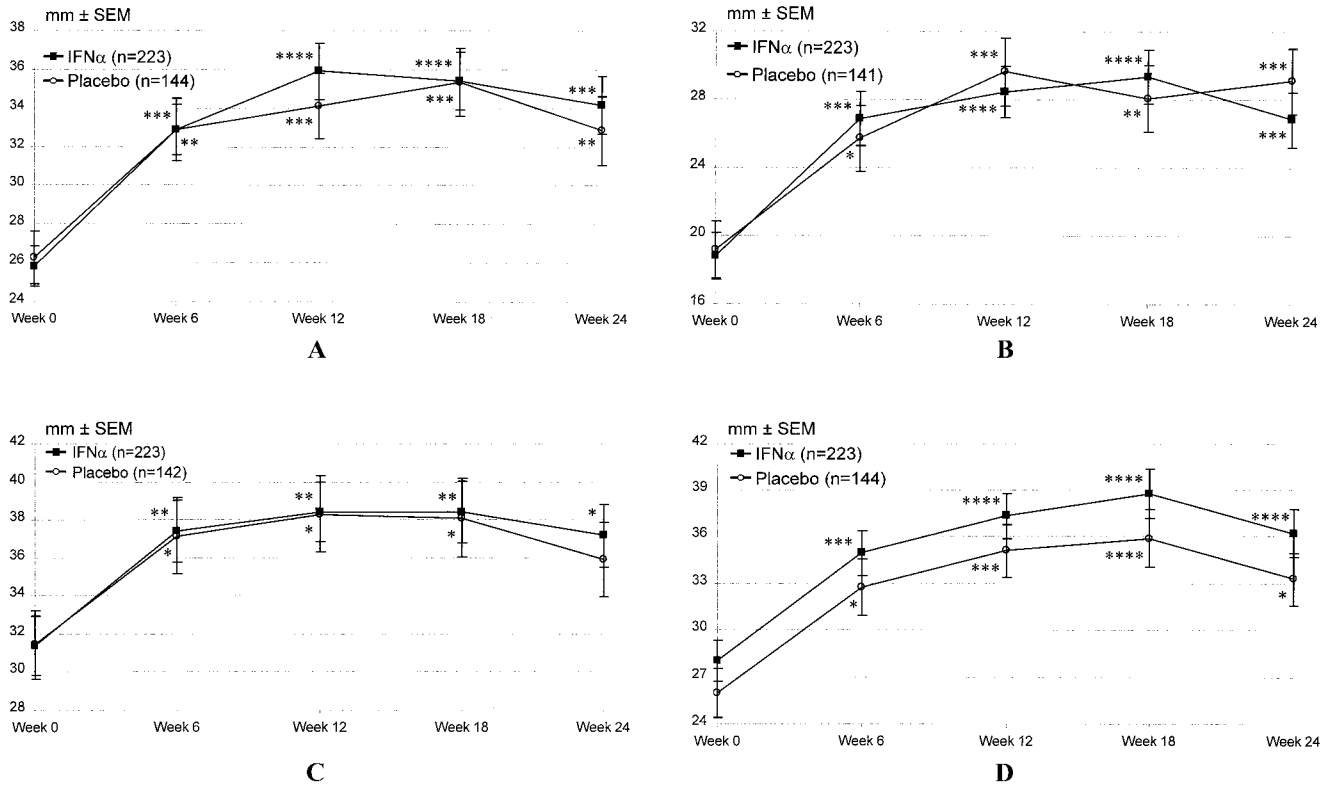

Figure 2. Mean visual analog scale scores (mm ± SEM) in evaluable patients. **A,** Oral comfort. **B,** Difficulty swallowing dry food. **C,** Difficulty swallowing any food. **D,** Throat dryness. Significantly greater than baseline at $*P < 0.05$, $**P < 0.01$; $***P < 0.001$; $**** P < 0.0001$.) An increased score denotes improvement in the symptom. INFα = interferon alfa.

The ability of IFN alfa lozenges to significantly increase UWS flow as demonstrated in this study is an important observation. UWS flow represents the basal salivary output patients generate more than 90% of the day. Adequate unstimulated saliva flow is important for the preservation and maintenance of oral health (32,33). Importantly, UWS increases in patients given IFN alfa correlated significantly and positively with improvement in 7 of 8 symptom measures, suggesting that patients were able to perceive a clinical benefit related to this treatment.

The finding of increased UWS flow in the IFN alfa group was not an artifact of pooling the data from the 2 studies, since the same effect was noted in both of the trials independently. In 1 of the individual studies, the mean UWS increase observed at week 24 was significantly greater ($P < 0.05$) in the IFN alfa group, compared with placebo; and in the other study a similar trend ($P < 0.10$) was observed.

An increase in UWS flow after 24 weeks of 150 IU IFN alfa treatment 3 times per day suggests an effect at the level of the affected salivary glands. It is well recognized in Sjögren's syndrome that loss of secretory capacity is the result of chronic inflammatory infiltrate and a loss of fluid-producing acinar cells. The mechanism by which low doses of IFN alfa administered into the oral cavity bring about increases in UWS flow is unknown. In a previous study, 9 Sjögren's patients given 150 IU lozenges 3 times per day for 6 months had an increase in the amount of histologically normal saliva gland tissue observed upon biopsy (21). Thus, IFN alfa may be reducing salivary inflammation in an immunomodulatory manner, thereby resulting in greater salivary output. An immunomodulatory activity of the IFN alfa lozenges is consistent with the finding that a significantly greater number of patients had normalization of their elevated serum globulin concentration following IFN alfa than placebo.

In another study, human parotid gland tissue cultured in the presence of low doses of IFN alfa expressed augmented aquaporin-5 (AQP5) transcription and protein production (34). Consequently, the increased UWS flow seen following IFN alfa treatment may be due to an upregulation of AQP5, with highly selective water channel proteins reported to be abnormally distributed in lacrimal and salivary glands of Sjögren's syndrome patients (35,36).

The secondary endpoint questionnaires related to severity of side effects and the interference of side effects in daily activities showed no differences between the groups. Along with the absence of deleterious effects on laboratory variables and physical findings, and the finding of no differences between the groups in overall adverse event rate or severity, these results demonstrate the excellent safety of 150 IU IFN alfa lozenges in Sjögren's syndrome patients. In fact, the observation that significantly more patients in the IFN alfa group experienced normalization of serum globulin levels, compared with placebo patients, suggests an immunologic benefit of IFN alfa lozenge therapy.

In summary, this study failed to demonstrate a significant effect on the a priori primary endpoints. However, 150 IU IFN alfa lozenges given 3 times per day for 24 weeks did lead to a statistically significant increase in

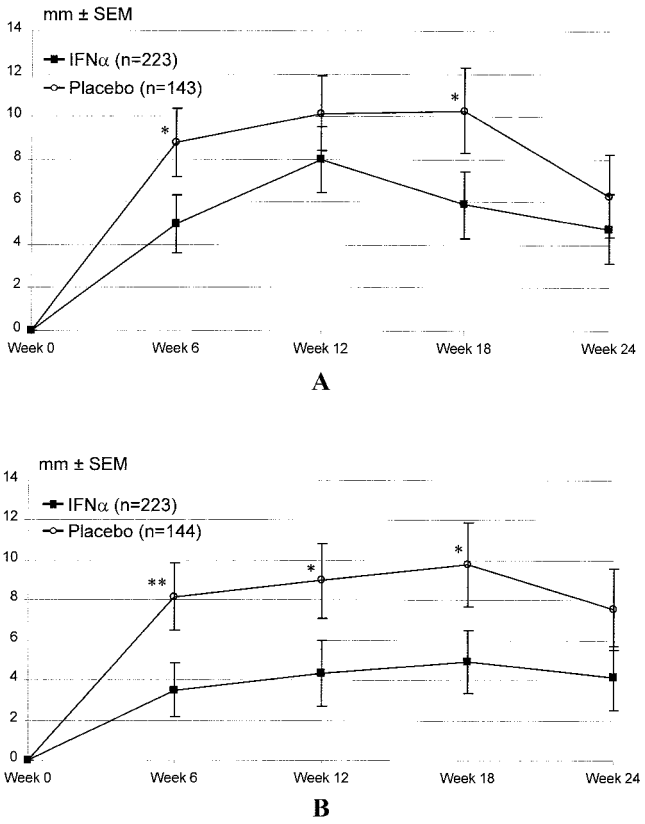

Figure 3. Mean visual analog scale changes (mm ± SEM) in evaluable patients. **A,** Eye dryness. **B,** Eye burning. The placebo group had significantly or borderline significantly greater mean increases (improvement) at labeled time points (*$P < 0.10$; **$P < 0.05$). IFNα = interferon alfa.

mean UWS flow in patients with primary Sjögren's syndrome. In IFN alfa-treated patients, increased UWS flow correlated with improvements in 7 of 8 common sicca symptoms of Sjögren's syndrome. IFN alfa treatment was safe and free from significant side effects.

Further research into the use of low-dose IFN alfa as a treatment for Sjögren's syndrome is clearly warranted. No other treatment has shown the ability to increase basal salivary flow, as IFN alfa lozenges did in this trial. A study aimed at replicating the histologic improvements demonstrated by Shiozawa et al (21) would further define the benefit of IFN alfa lozenges in treating Sjögren's syndrome.

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