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A randomized, controlled trial of interferon-β-1a (Avonex®) in patients with rheumatoid arthritis: a pilot study [ISRCTN03626626]

Mark C Genovese[1], Eliza F Chakravarty[1], Eswar Krishnan[1] and Larry W Moreland[2]

[1]Division of Immunology and Rheumatology, Stanford University, Palo Alto, CA, USA
[2]Division of Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA

Corresponding author: Mark C Genovese (e-mail: Genovese@Stanford.edu)

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Abstract

The objective of this study was to evaluate the safety and possible efficacy of IFN-β-1a for the treatment of patients with rheumatoid arthritis (RA). Twenty-two patients with active RA were enrolled in a phase II randomized, double-blind, placebo-controlled trial of 30 μg IFN-β-1a by weekly self-injection for 24 weeks. The primary outcome of the study was safety. Secondary outcomes included the proportion of patients achieving an American College of Rheumatology (ACR) 20 response at 24 weeks. There were no significant differences in adverse events reported in the two groups. Fewer than 20% of patients in each arm of the study achieved an ACR 20 response at 24 weeks ($P = 0.71$). Sixty-nine percent of patients receiving IFN-β and 67% receiving placebo terminated the study early, most of them secondary to a perceived lack of efficacy. Overall, IFN-β-1a had a safety profile similar to that of placebo. There were no significant differences in the proportion of patients achieving an ACR 20 response between the two groups.

Keywords: clinical trials, cytokines, interferon-β, rheumatoid arthritis, therapy

Introduction

Advances in the treatment of rheumatoid arthritis (RA) in the past decade have resulted in significant improvements for many patients. The advent of biologic response modifiers has changed the paradigm of treatment options. However, despite the introduction of anti-cytokine therapy, there remains a significant unmet need for additional therapy in the treatment of RA that stems from several existing problems, namely that no one therapy or combination of therapies works for all patients, that patients who do respond rarely achieve remission, that therapy can lose efficacy over time, and that side effects can limit the utility of any therapy. These issues result in a demand for compounds that have minimal side effects while providing disease modification both by ameliorating signs and symptoms of RA and by retarding the erosion of joint tissue.

Recombinant human IFN-β is approved by the US Food and Drug Administration for the treatment of relapsing–remitting multiple sclerosis [1]. Although its mechanism of action is poorly understood, IFN-β is thought to antagonize the effects of IFN-γ and other proinflammatory cytokines, such as tumor necrosis factor and IL-1, and to down-regulate T-cell activity [2–5]. Since these proinflammatory cytokines and activated T cells are thought to mediate inflammation and destruction of joint tissue in RA, there has been optimism that IFN-β might be an efficacious therapy for human RA. Previously published reports have suggested a possible improvement in patients with RA treated with IFN-β [6,7]. Synovial biopsies in treated patients showed a modest reduction in expression of inflammatory cytokines and metalloproteinases [7].

ACR = American College of Rheumatology; ACR 20 (50, 70) = 20% (50%, 70%) improvement relative to baseline, according to ACR criteria; DMARD = disease-modifying antirheumatic drug; IFN = interferon; IL = interleukin; ITT = intention to treat; RA = rheumatoid arthritis.

We report a 24-week randomized, double-blind, placebo-controlled study of the use of IFN-β-1a (Avonex®) in patients with RA. The primary objective of the study was to evaluate the safety of its weekly administration. Secondary objectives included the evaluation of its potential efficacy in patients with RA who have active disease despite treatment with available disease-modifying antirheumatic drugs (DMARDs).

Materials and methods

This study was approved by the investigational review board at each participating institution. The study subjects were men or women at least 18 years of age with RA defined by the American College of Rheumatology (ACR) criteria [8]. All patients had failed at least one currently available DMARD or biologic response modifier and had active RA with more than six swollen and six tender joints at the time of enrollment. Patients were allowed to be receiving the following background DMARDS, if any, as long as the doses were stable for at least 2 months before enrollment: methotrexate, sulfasalazine, and hydroxychloroquine either as monotherapy or in combination. Patients taking up to 10 mg prednisone daily and/or nonsteroidal anti-inflammatory drugs were allowed to participate if the dose had been stable for 28 days before the screening visit. All patients gave their written, informed consent prior to participation. Exclusion criteria included a history of malignancy within the past 5 years, a history of seizure disorder, and a positive test for HIV, hepatitis B, or hepatitis C. Patients could be excluded for active psychiatric disease, major organ dysfunction, or serious local or systemic infection. Female patients were excluded if they were pregnant, breastfeeding, or unwilling to use an adequate method of contraception.

Treatments

Patients were randomized to receive IFN-β-1a (30 μg intramuscular weekly) or matched placebo in a 3:1 ratio at each of two sites (Stanford University and the University of Alabama at Birmingham). The standard dose of 30 μg was chosen based upon its known profile in the treatment of multiple sclerosis. All study personnel at both sites remained blinded to the randomization schedule. The study drug and matched placebo were provided in blinded fashion and were labeled with the patient's name and randomization number. Physician's visits were scheduled monthly. Patients who completed the study were seen again 4 weeks after the 24th injection (28 weeks) for a final visit.

Safety evaluation

Adverse events and safety issues pertaining to the use of IFN-β were carefully monitored during the study.

Evaluation of efficacy

The primary efficacy end point of the study was a 20% improvement in ACR criteria from baseline to week 24 [9]. The secondary end points were the proportion of patients achieving a 50% or 70% ACR response at week 24.

Statistical methods

The differences between the randomization groups were evaluated by Student's *t*-test (for differences in means) and chi-square test and Fisher's exact test (for differences in proportions). Analysis of safety end points included all patients who received at least one injection of placebo or study drug. Differences in adverse events between the placebo and interferon groups were analyzed using Fisher's exact test. The primary analysis of efficacy end points was based on an intention-to-treat (ITT) approach. All patients were analyzed according to their randomization category. Those whose ACR response status could not be ascertained because of a missing evaluation were considered nonresponders for the relevant time point. The primary analysis of the ACR response rates at week 24 was based on Fisher's exact test. A one-tailed α level of 0.05 was used for defining statistical significance.

Results

Although the target accrual for the study was 40 patients, the total number of patients screened was 25, with 22 patients enrolled (11 at each site) over a period of 12 months. The anticipated accrual numbers were not achieved because of difficulty recruiting. This difficulty stemmed from the availability of other therapies approved by the US Food and Drug Administration, the availability of other investigational therapies, and patients' reluctance to give themselves intramuscular injections.

The baseline demographics for this cohort were similar to those of other previously published clinical trials [10,11]. Patients in the IFN-β-1a treatment arm and the placebo arm were well matched for baseline characteristics (Table 1), with the exception of a statistically significant larger percentage of patients on background DMARDs in the IFN-β-1a treatment arm (81%) than in the placebo arm (33%). The majority (15/22; 68%) of patients in this study were on background DMARDs, with methotrexate most commonly used. The majority of patients were women. Disease activity was similar between the groups. The mean number of tender joints in the treatment and placebo groups was, respectively, 20 and 25; the mean number of swollen joints, 16 and 19; and the mean C-reactive protein, 2.4 and 1.6.

Of the 22 patients enrolled, only 7 completed the 24-week study. Sixty-nine percent (11/16) receiving IFN-β-1a and 67% (4/6) patients receiving placebo discontinued participation before 24 weeks. The median duration of time in the study for both groups was 63.1 days. Of those patients terminating the study before week 24, only two in the IFN-β-1a arm and one in the placebo arm left the study secondary to adverse events. The majority of patients

Table 1

Baseline characteristics of subjects in placebo and active-drug arms of a trial of interferon-β-1a in patients with rheumatoid arthritis

Characteristic	Placebo ($n = 6$)	Drug ($n = 16$)	P value[a]
Mean age (range)	53 (39–69)	54 (35–72)	0.80
Women (%)	6 (100)	13 (81)	0.53
Mean weight in pounds (range)	157 (109–211)	164 (117–289)	0.62
Mean number of tender joints (range)	25 (14–41)	20 (8–45)	0.40
Mean number of swollen joints (range)	19 (6–40)	16 (7–34)	0.68
Mean HAQ Disability Index (0–3) (SD)	1.45 (0.53)	1.36 (0.72)	0.76
Mean C-reactive protein (SD)	1.6(1.1)	2.4 (1.7)	0.31
Mean physician's global assessment (0–10) (SD)	5.8(2.2)	5.6 (2.0)	0.85
Mean patient's global self assessment (0–10) (SD)	5.6 (2.5)	5.9 (2.7)	0.87
Mean pain VAS (0–10) (SD)	5.8 (1.2)	5.8 (2.6)	0.97
Number of patients on DMARDS (%)	2 (33%)	13 (81%)	0.05
Number of patients on NSAIDs (%)	2 (33%)	12 (75%)	0.09
Mean number of DMARDS (range)	1.3 (0–3)	0.9 (0–2)	0.37
Number of patients on prednisone	4 (67%)	12 (75%)	0.54
Mean dose (mg) of prednisone (range)	4.7 (0–10)	5.2 (0–10)	0.82
Baseline disease duration (years) (range)	10.1 (0.2–29.4)	14.2 (0.4–33.8)	0.38

[a]*P* values are for one-tailed *t*-tests and Fisher's exact test, as appropriate. DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; VAS, Visual Analog Scale.

leaving the study early did so secondary to a perceived lack of efficacy: 8/11 (73%) of patients enrolled in the IFN-β-1a group and 3/4 (75%) in the placebo group.

Safety

In general, IFN-β-1a was well tolerated in this RA population. There were no serious adverse events during the study: no deaths, malignancies, hospitalizations, or infections requiring intravenous antibiotics occurred. No autoimmune events were reported. Three patients left the study secondary to adverse events. One patient in each treatment arm withdrew from the study secondary to symptoms of depression. The third patient, who was in the IFN-β-1a group, withdrew secondary to flu-like symptoms associated with the injection. No statistically significant differences were seen in any of the adverse events between the two treatment arms (Table 2). The most common adverse events reported were flu-like symptoms associated with the administration of the study drug; these included arthralgias, myalgias, headache, fatigue, chills, and subjective fever.

Efficacy

The primary efficacy end point of the study was the ACR 20 response at the completion of the 24-week study (Table 3). In the intention-to-treat (ITT) responder-at-end-point analysis, 19% of patients in the IFN-β-1a arm and 17% of patients in the placebo arm achieved an ACR 20 response at 24 weeks, with only seven of 22 patients completing the 24-week study. When using a more liberal, ITT last-observation-carried-forward analysis, the ACR responder rates were higher, with the ACR 20 response of 44% with IFN-β-1a and 33% with placebo ($P = 0.52$) (Table 3). In this analysis, the last efficacy variables were used irrespective of study completion status.

Discussion

The goal of this study was to assess the effects of IFN-β-1a in the treatment of RA. The decision to consider the use of this therapy in RA was predicated on the well-known safety profile of the agent when used in the treatment of multiple sclerosis [1] and on work that has suggested a potentially beneficial role in the treatment of inflammatory arthritis.

Prior studies utilizing IFN-β (Rebif®) for the treatment of collagen-induced arthritis in rhesus monkeys suggested clinical improvement in 75% of the animals treated and a notable decrease in the C-reactive protein [6]. The same authors also demonstrated possible benefits during a 12-week study in patients with active RA using fibroblast IFN-β (Frone®). Of the 10 patients who completed this

Table 2

Comparison of adverse events between placebo and active-drug arms of a trial of interferon-β-1a in patients with rheumatoid arthritis[a]

Adverse event	Drug ($n = 16$) No. (%)	Placebo ($n = 6$) No. (%)
Flu-like symptoms		
Arthralgias/myalgias	6 (38)	2 (33)
Headache	8 (50)	1(17)
Fatigue/weakness	2 (13)	1(17)
Subjective fevers	3 (19)	0
Chills	6 (38)	0
Hypertension	3 (19)	0
Oral ulcers	3 (19)	0
Pain at injection site	1 (6)	0
Insomnia	0	1(17)
Depression/anxiety	1 (6)	1(17)
Menstrual irregularities	1 (6)	1(17)
Rash	3 (19)	1(17)
Wheeze	2 (13)	0
Gastrointestinal distress		
Nausea	2 (13)	0
Abdominal pain	2 (13)	0
Diarrhea	0	1 (17)
Infections		
Upper respiratory infection	2 (13)	3 (50)
Sinus infection	0	1(17)
Infection on right arm	1 (6)	0
Perineal fungal rash	1 (6)	0
Varicella-zoster rash	1 (6)	0
Other (single reports only)	9 (56) *	5 (83) **

[a]All the differences in occurrences were tested by Fisher's exact test (one-tailed) and were statistically not significant. *Hypoglycemia, paresthesia on left side of face, contact dermatitis, photosensitivity, flare of arthritis, cramping in toes, dysphagia, nasal lesion, blurred vision. **Hematuria, burn on arm, tachycardia, paresthesia on left leg, lymphadenopathy.

Table 3

Response, according to ACR criteria, of subjects in a trial of interferon-β-1a in patients with rheumatoid arthritis

Efficacy end point	Response to placebo ($n = 6$) No. (%)	Response to interferon ($n = 16$) No. (%)	*P* value[a]
ITT responder-at-end-point analysis			
ACR 20, week 12	1 (17)	3 (19)	0.71
ACR 20, week 24	1 (17)	3 (19)	0.71
ACR 50, week 24	0 (0)	2 (12.5)	0.51
ACR70, week 24	0	0	0
ITT last-observation-carried-forward analysis			
ACR 20, week 24	2 (33)	7 (44)	0.52

[a]Fisher's exact test; ACR 20 (50, 70), 20% (50%, 70%) improvement relative to baseline, according to ACR criteria.

open-label study, 4 achieved an ACR 20 response and the agent was reportedly well tolerated. Additional work done with this same cohort looking at the effects of IFN-β on synovial tissue showed interesting results. Based on serial synovial biopsies before and during therapy, there appeared to be a reduction of $CD3^+$ T cells, reduced expression of matrix metalloproteinase-1 and IL-1β at 1 month after therapy, as well as a reduction of expression of IL-6 and IL-1β at 3 months [7]. This study provided support for the hypothesis that IFN-β could result in immunomodulation of RA and potentially lead to a reduction in symptoms and increase in function in patients with RA.

The present study was designed to assess the effects of the use of IFN-β-1a for the treatment of RA in a double-blind, placebo-controlled fashion. The investigators initially planned to enroll 40 patients. This number was based on the maximum number thought possible to enroll as well as an appropriate number by which to assess safety parameters of this agent for this indication. However, the investigators were unable to meet this initial goal because of an inability to recruit patients to participate. Several factors affected recruitment, including the commercial availability of other biologic response modifiers, patients' concerns regarding self-administration of an intramuscular injection, and perception on the part of patients and referring physicians that patients would develop side effects in the peri-injection period.

It is important to recognize that this study was not well powered to address issues of efficacy. Although we did not achieved the desired number of patients for this study, we did obtain important safety and efficacy information.

The primary outcome of the study was safety. IFN-β-1a was generally well tolerated by these RA patients. We did not see any serious safety problems with the study drug and no serious adverse events were reported as part of this study. There have been rare reports of autoimmune phenomena developing in patients treated with IFN-β for multiple sclerosis [12]. Although autoantibodies were not examined in this study, no overt autoimmune events were reported. There were, however, adverse events seen in this population (many of which were expected on the

basis of the known side effects of the study agent), including flu-like symptoms occurring after the injections. The adverse events occurred with similar frequency in patients receiving IFN-β-1a and those receiving placebo. It is still possible that rare or uncommon adverse events, including serious adverse events, are associated with the use of IFN-β but were not detected in this small study.

The critical observation in this study was the degree of attrition, with only 7 of 22 patients (32%) completing the study. The majority of patients who did not complete the 24-week study terminated because of perceived lack of efficacy rather than because of adverse events. Irrespective of the study's power, the efficacy end point of a 20% response defined by the ACR response criteria [9] with an ITT responder-at-end-point analysis was quite low and was without a clinically meaningful difference from that seen in the placebo group. Using a more liberal ITT last-observation-carried-forward analysis, it appears that 44% of patients were responding at the time of their last visit but chose to leave the study anyway. The patients' decision to terminate the study reflects either their perceptions of lack of efficacy despite having achieved a 20% improvement in some cases or a lack of improvement substantial enough to warrant continuing in the study in the face of mild adverse events.

Conclusion

The results of this small pilot study suggest that IFN-β-1a, while generally safe, may not be a significantly efficacious agent for the treatment of RA. However, in order to definitively answer the question as to whether IFN-β-1a has efficacy beyond that seen in placebo for the treatment of RA, a larger and more appropriately powered study would be required.

Competing interests

The authors received grant support and free drug and placebo from Biogen, Cambridge, MA, USA.

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Correspondence

Mark C Genovese, MD, Division of Immunology and Rheumatology, Stanford University, 1000 Welch Road #203, Palo Alto, CA 94304, USA. Tel: +1 650 498 4528; fax +1 650 723 9656; e-mail: Genovese@Stanford.edu