Interferon-β-1a for the Treatment of Steroid-Refractory Ulcerative Colitis: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background & Aims: **We performed a randomized, double-blind, placebo-controlled, multicenter trial to investigate the efficacy and safety of recombinant interferon-β-1a (rIFN-β-1a) in outpatients with active steroid-refractory ulcerative colitis.** ***Methods:*** **Ninety-one randomized patients subcutaneously received 3 MIU rIFN-β-1a (group A, n = 32), 1 MIU rIFN-β-1a (group B, n = 30), or placebo (group C, n = 29) 3 times a week over a period of 8 weeks in addition to standard therapy. An intention-to-treat analysis was performed to evaluate the efficacy and safety of treatment.** ***Results:*** **In all 3 groups, the median prestudy clinical activity index (CAI) was 10. In 18 of 32 patients (56%) in group A, in 11 of 30 patients (36%) in group B, and in 10 of 29 patients (34%) in group C, a reduction of the CAI of 6 points or greater (response) was achieved (differences were not statistically significant). Complete response (reduction of CAI to ≤4) was achieved in 56%, 30%, and 38% of patients in groups A, B, and C, respectively. Compared with baseline, the median endoscopic index had been reduced by 5, 3, and 4 points in groups A, B, and C, respectively. Steroid reduction was 12 mg in group A, 6 mg in group B, and 10 mg in group C. Identical side effects occurred in all 3 groups. Seven serious adverse events were reported (1 in group A and 6 in group C). All were unrelated to therapy as judged by the investigating physicians.** ***Conclusions:*** **rIFN-β-1a was safe but not significant, at the dosage and/or duration of treatment used, in steroid-refractory ulcerative colitis. Further studies are indicated.**

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease of unknown cause. Standard treatment of UC includes 5-aminosalicylates such as sulfasalazine and mesalamine combined with corticosteroids if necessary. This therapy has proven to be effective in the acute phase of the disease in approximately 60%–90% of patients.[1,2] Steroid-refractory UC patients are treated with immunomodulators such as azathioprine, 6-mercaptopurine, or cyclosporine A.[3,4] However, there are many patients who fail to respond to immunosuppressive treatment or who cannot tolerate these treatment options. Therefore, other effective and safe compounds are needed.

The chronic mucosal inflammation in UC may be caused by an inappropriate secretion of proinflammatory cytokines in response to initial stimulatory events and/or an impaired down-regulation of cytokine secretion. Some of these disturbances, such as a disturbed production of interleukin-1 receptor antagonist, seem to be determined genetically.[5,6] Correcting these imbalances between pro- and anti-inflammatory cytokines has been shown to be of therapeutic benefit in Crohn's disease and UC.[7,8]

Interferon-β (IFN-β) has been used successfully in many experimental and therapeutic trials in patients with multiple sclerosis, which also is believed to be an immune-mediated disorder occurring in genetically susceptible people.[9] Several mechanisms of action of IFN-β in multiple sclerosis, such as the up-regulation of the anti-inflammatory cytokines interleukin-10 and interleukin-1 receptor antagonist, a down-regulation of the proinflammatory cytokines tumor necrosis factor and

Abbreviations used in this paper: CAI, clinical activity index; CR, complete response; IFN, interferon; rIFN-β-1a, recombinant interferon-β-1a.

1542-3565/05/$30.00
PII: 10.1053/S1542-3565(05)00208-9

interleukin-2, and of the costimulatory molecules B7-1 and CD40 in lymphocytes, have been described.[10–12]

Results of treatment with IFN in Crohn's disease have been rather inconsistent.[13,14] Several open-label, non–placebo-controlled series using IFN-alfa in patients with UC have delivered promising results[15,16] as well as our own noncontrolled pilot trial with IFN-β,[17] which was the basis for planning 2 dose levels of 1 MIU and 3 MIU recombinant interferon-β-1a (rIFN-β-1a) in our randomized, double-blind, placebo-controlled, multicenter trial. The decision to use IFN-β instead of IFN-alfa for treatment refers to in vitro studies in which IFN-β, in contrast to IFN-alfa, did not interfere with the arachidonic or the leukotriene B4 pathway.[18,19] Therefore, this type of interferon reduces the risk for promoting proinflammatory chemical mediators.

Materials and Methods

Study Design

The study was a European, double-blind, placebo-controlled, multicenter trial of 3 parallel treatment groups of outpatients with steroid-refractory UC and was approved by the ethics committee of the Westphalian Wilhelms University, Münster, Germany, the Westphalian-Lippe General Medical Council, and by the respective ethics committees and General Medical Councils of all participating study centers. It was performed in accordance with the Second Helsinki Declaration and later amendments. Informed written consent was obtained from all participants. Supervision was performed by a steering committee of investigators who were blinded from the results throughout the trial. The steering committee reviewed the prospectively scheduled interim analysis of safety and efficacy performed after half of the patients had been enrolled.

Patients and Treatment

Patients eligible for randomization were at least 18 years of age and had an established diagnosis of active UC defined by clinical, histologic, and/or endoscopic findings. The extension had to be more than 15 cm from the anus with acute lesions to be identified by rectosigmoidoscopy. The clinical activity index (CAI) as published by Rachmilewitz[20] had to be at least 8 points. A steroid-refractory situation was assumed when the reduction of the CAI during a 4-week prestudy treatment phase with mesalamine of 3 g/day or greater (orally plus the optional topical administration) including a cumulative corticosteroid dose of 450 mg or greater was less than 5 points and did not decrease below the absolute limit of 8 points. From the beginning of the study, the dose as well as the mode of application of the conventional therapy had to remain constant. A tapering off of the steroid dose according to the procedure suggested by the European Cooperation Crohn's Disease Study (ECCDS) was not permitted until the patient's CAI had decreased below the limit of 4 points or less. Immunosuppressive or immunomodulatory treatment and putative treatments for UC were not permitted within the 4 weeks before entry and throughout the study. The use of nonsteroidal anti-inflammatory medication including ibuprofen was allowed.

Patients were assigned to either 3 or 1 MIU rIFN-β-1a (group A or B, respectively), or to placebo (group C) by a central randomization schedule. According to the study protocol, access to the code was limited strictly. The patients had to inject rIFN-β-1a or placebo subcutaneously 3 times a week over a period of 8 weeks. Regular visits were scheduled for days 1, 3, and 5 from weeks 2–8, during which patients underwent regular assessments unless they withdrew consent. Treatment had to be discontinued in case of intolerable adverse events, clinically relevant laboratory deviations, pregnancy, or progression of disease (ie, increase of ≥6 points at 2 consecutive visits).

Efficacy Parameters

The primary end point was the evaluation of the response rate at the end of treatment. Response was defined as reduction of 6 or more CAI points at week 8 compared with baseline. Secondary efficacy parameters were (1) number of patients with complete response (CR) = reduction of CAI to 4 score points or less after 8 weeks of treatment, (2) time until response, (3) reduction of CAI after 4 and 8 weeks, (4) reduction of the endoscopic index after 8 weeks, (5) number of patients receiving colectomy, and (6) reduction of steroid dose.

Statistical Analysis

Data management and statistical analyses were performed by an external institution (nQuery Advisor, by J. D. Elashoff, Los Angeles, CA; BZT GmbH, München, Germany). The sample size estimation was based on a comparison of response rates. Thirty-five percent was determined as the relevant clinical difference (effect size) between the placebo group and the active drug groups. To show a difference of 35% between the treatment groups with a significance level of $P = .05$ and a power of $1 - \beta = .80$, 35 patients were scheduled to be included in each treatment group. The scheduled total sample size was 105 patients, including a calculated drop-out rate of 10%.

Confirmatory analysis was performed in 3 steps by using the χ^2 and Fisher exact test (2-sided). Because a closed test procedure was applied, no adjustment of the significance level was required. Because 1 interim and 1 final analysis were performed, the significance level was adjusted according to group-sequential testing procedures of O'Brien/Fleming.[21] The α level was .05 for the interim analysis and .0482 for the final analysis.

Missing values in the CAI were imputed by a last-value-carried-forward procedure if at least 1 efficacy parameter was available and at least 1 application of the study medication was received by the patient. This missing value imputation procedure was performed for weeks 2–24. If a CAI value was available for any week during therapy but missing for baseline,