A phase II study of interferon-alpha for the treatment of refractory Churg-Strauss syndrome

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ABSTRACT

Objective. *Uncontrolled vasculitis is the major cause of early death in Churg-Strauss syndrome and standard therapy is not always effective. This study was carried out to examine the safety and efficacy of interferon-alpha for induction of remission in patients with refractory Churg-Strauss syndrome.*

Methods. *In a prospective open-label trial, seven patients with Churg-Strauss syndrome refractory to cyclophosphamide or methotrexate received interferon-alpha (3 million. I.U. 3 times weekly s.c.) for induction of remission. Primary end point was the successful induction of remission. Prednisolone was tapered according to the study protocol.*

Results. *All seven patients entered remission after 3 months of treatment. Five patients reached complete remission while in two patients, residual asthmatic complaints persisted. The mean Birmingham Vasculitis Activity Score (BVAS) decreased from 6.4 (±2.8) to 0 (±0) (p=0.017). Clinical improvement in response to interferon-alpha allowed to taper concomitant prednisolone according to the protocol from a mean dose of 20.4 mg/d (±13.3) to 6.9 mg/d (±1.9) (p=0.068). During a follow up of 6 months all patients remained in remission. In one patient, leukencephalopathy without clinical symptoms was seen on MRI after 61 months of treatment, as previously reported. In this cohort, no other cases of leukencephalopathy were observed during long-term follow-up. Constitutional symptoms related to the injection of interferon-alpha responded well to paracetamol. A transient leukopenia was found in two patients.*

Conclusion. *Interferon-alpha appears to be an effective and well-tolerated treatment for induction of remission in patients with refractory Churg-Strauss syndrome.*

Introduction

Churg-Strauss syndrome (CSS) is a primary systemic vasculitis occurring nearly exclusively in patients with severe asthma and hypereosinophilia. If not treated properly, many clinical manifestations of CSS such as mononeuritis multiplex or eosinophilic pneumonia are associated with impaired organ-function and/ damage while some manifestations like cardiac disease or severe gastrointestinal are potentially life-threatening (1-6). In patients with less severe disease course, CSS may respond well to glucocorticoids, but often high doses are required to control the disease (1, 7, 8). Therefore, in the majority of patients, administration of cyclophosphamide or other immunosuppressive agents in addition to glucocorticoids is required to induce remission and allow glucocorticoid taper (1, 8). In many patients unresponsive to glucocorticoids alone, remission can be induced by the addition of cyclophosphamide (3, 9). For high risk patients as defined by a score value ≥2 in the prognostic score of the French Vasculitis Study Group (FFS), CYC in addition to GC had a significant survival benefit over GC therapy alone in a retrospective analysis of 278 patients with CSS, polyarteritis nodosa or microscopic polyangiitis (10). Results from an open label trial suggest that in patients with less severe disease course, methotrexate appears to be an effective agent for induction of remission in CSS (11). In the aforementioned cohort from France and another series of 32 patients from Spain, up to 10% of cases did not sufficiently respond to cyclophosphamide plus prednisone and died as a result of active vasculitis (1, 2). In fact, uncontrolled vasculitis accounts for the majority of early deaths in patients with CSS who are treated with standard therapy (12). Intravenous immunoglobulins (13). tumor-necrosis-factor-alpha inhibitors (14). or rituximab (15). have

all successfully been used as an alternative or adjunct to cytotoxic therapies in small case series. Yet, there is still little published data on the treatment of refractory courses of CSS .

We earlier reported on the successful compassionate use of recombinant human interferon-α in four patients with active CSS (16). Based on this positive experience and anecdotal case reports from other centers (17-19), this prospective open-label trial was designed to confirm the hypothesis that interferon-α is effective and safe for the treatment of CSS refractory to conventional immunosuppressive therapy.

Methods

Eligibility criteria

This study was conducted as an investigator-initiated open label, prospective, single centre trial. The study protocol was approved by the institutional review board of the University of Lübeck. (Protocol Code 36-96 143). Patients with CSS and refractory disease course were eligible for participation in the trial after written informed consent was given. According to the EULAR recommendations for conducting clinical trials in systemic vasculitis (20), refractory disease was defined as a lack of response or incomplete response to standard therapy. Patients of both sexes aged from 18 to 70 years were eligible.

The diagnosis of CSS required the presence of systemic vasculitis documented by biopsy or surrogate parameters of vasculitis such mononeuritis multiplex, alveolar hemorrhage, presence of red cell casts in the urine or purpura. In addition, patients had to fulfil the Chapel Hill-definition (21) and American College of Rheumatology (ACR) (22) classification criteria for CSS.

Eosinophilic disorders other than CSS like idiopathic hypereosinophilic syndrome, chronic or acute eosinophilic pneumonia or eosinophilic leukemia were excluded. Refractory disease was defined as progressive disease unresponsiveness to standard treatment (glucocorticoids plus cyclophosphamide or methotrexate) for more than 6 weeks or progressive disease in patients intolerant to standard treatment (history of documented cytopenias or haemorrhagic cystitis). Patients with seizures or other severe disease of the central nervous system, severe impairment of liver, renal or cardiac function, viral or autoimmune hepatitis, thyroid diseases, coexistence of other autoimmune diseases, need for continued immunosuppression after transplantation, allergies to IFN-α 2b, leukocytopenia <2000/μL and thrombocytopenia <80 000/μL were not eligible for the trial. None of the patients had previously received recombinant interferon-α or had been included in the earlier reported cohort (7).

Treatment

1. *Interferon-α*

Recombinant human interferon-alpha 2b (Intron A, Essex Pharma, Munich, Germany) was administered at an initial dose of three million I.U. three times per week s.c. (corresponding to 9 million I.U. per week). All patients were hospitalized at the start of treatment and differential blood counts were analysed daily until discharge. Dosage of interferon-α was temporarily reduced by one million IU per injection in case of leukopenia or constitutional symptoms occurring after the s.c. injection that did not respond to 1 g of oral paracetamol. In case of progressive or persistent disease activity measured by an increase or persistence of the BVAS score and persistent eosinophil counts, dosage was elevated in increments of 3 million units per week until symptoms improved or a decline in blood eosinophil counts indicated efficacy. Increases of the interferon-α dosage were recorded, but were not considered to represent a treatment failure. After completing this study 6 months from remission, all patients continued interferon-α and were all switched to an observational long-term cohort study which was still ongoing at the time the present report was prepared. The simultaneous use of other immunosuppressants was not allowed. The previous immunosuppressive therapy except GC was discontinued immediately prior to study start without washout period as this was considered to be potentially unsafe given the severity of the disease.

2. *Glucocorticoid taper*

Patients entered the trial with different doses of prednisolone (Table I). Concomitant prednisolone was continued at unchanged dosage at study entry and subsequently tapered as follows: reduction by 10 mg every three days until 20 mg/d, then by 2.5 mg every week until 7.5 mg/d and, if clinically possible, thereafter by 1 mg/month. The inability to taper oral prednisolone to at least 10 mg per day while being treated with the maximally tolerated dose of interferon-α was considered a treatment failure. The 10 mg cut-off was chosen as it was acknowledged that, despite remission of vasculitis and eosinophilia, some patients require glucocorticoid doses of up to 10 mg per day for the treatment of asthma, which may persist despite aggressive immunosuppression. Experience from previous compassionate use of interferon-α in four patients with CSS, suggested that symptoms and eosinophil counts respond within a few days to dose elevations of the drug (16). Therefore, prednisolone taper was not delayed in case of persistent disease activity in minor BVAS items. Elevation of prednisolone was allowed in case of new or persistent organ- or life threatening manifestations occurring after treatment with interferon-α, but this was considered to represent a treatment failure. Additional inhalative glucocorticoids for local treatment of asthma were allowed.

Disease assessments

During the initiation of interferon-α treatment all patients remained hospitalized until clinical symptoms started to improve and eosinophil counts decreased. After discharge patients were seen three months after study start and at further three-month intervals until remission was induced. From the time of remission, patients were followed up for additional 6 months at three-monthly intervals. All patients underwent a set of interdisciplinary clinical examinations by the same team of specialists in internal medicine, otorhinolaryngology, ophthalmology, neurology and radiology. In case of pulmonary infiltrations visible on chest x-ray or HR-CT, bronchoscopy with bronchoalveolar

lavage (BAL) and analysis of the BAL cell profile were performed like previously described (23). The presence of eosinophilia in BAL fluid of >5% was considered to represent eosinophilic alveolitis in patients with pulmonary infiltrations if other causes like infection were excluded (23-25), while eosinophil counts between 2 and 5% were considered to be of borderline significance. Iron-staining was performed to screen for iron-laden macrophages as indicators of alveolar hemorrhage. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver enzymes, creatinine, urine analysis and full blood cell count were determined at each visit. Antineutrophil cytoplasm antibodies (ANCA) were determined by indirect immunofluorescence and ELISA at three-month intervals.

To evaluation disease activity, the Disease Extent Index (DEI) (26) and the Birmingham Vasculitis Activity Score (BVAS) (27) were used. To stage disease severity at the start of the study, the Five Factor Score (FFS) (4) was calculated. Active disease was defined as clinical manifestations that can be clearly attributed to active vasculitis and/or tissue hypereosinophilia.

Endpoints

Primary end point was the successful induction of remission. Complete remission was defined as the absence of pathologic findings due to active disease (BVAS = 0) (20, 28). Remission was defined irrespective of the ANCA titer and blood eosinophil counts since there were no published data showing that either of these biomarkers can successfully predict clinical outcome in CSS. In addition, the inability to taper oral prednisolone to at least 10 mg per day while being treated with the maximally tolerated dose of interferon-α was considered a treatment failure. Residual asthmatic complaints not attributable to pulmonary vasculitis or eosinophilic alveolitis were not considered as activity of CSS, but were recorded separately.

Secondary endpoints were the time to remission, the scores for disease activity (BVAS and DEI), eosinophil counts, CRP serum levels, dosage of concomitant prednisolone and adverse events.

Statistical analysis

The Kolmogorov-Smirnov Z test was used to analyze the distribution of the samples. Normally distributed data are expressed as the mean ± SEM. For normally distributed data, statistical significance was tested using Student's *t*-test, Wilcoxon range test was performed if appropriate. Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS, Chicago, IL).

Results

Patient characteristics

Clinical characteristics and previous treatments of all seven patients are displayed in Table I. All, except one patient were either pANCA positive or had typical features of CSS on tissue biopsy such as eosinophil-rich granuloma or

Table I. Baseline characteristics of 7 patients with Churg-Strauss syndrome treated with interferon-α for induction of remission.

Pat. No.	Age (yr), Sex	Biopsy	ANCA	Immunosuppressive agents previously used				Predni-solone	DEI score (mg/d)	BVAS score	Clinical features at baseline
				drug	Duration (months)	Mean daily or weekly dose/cum. Dose*	Side effects				
1	43, F	P	negative	oCYC i.v.CYC	3 3	150 p.d/9 g /4 g	leucopenia	12.5	5	5	eosinophilic pleural effusion mononeuritis multiplex constitutional symptoms
2	48, F	*L*	negative	i.v.CYC MTX	11 12	1000 mg p.m./11 g (20mg/w)	nausea	40	2	6	eosinophilic alveolitis
3	59, F	GI	negative	oCYC	12	150mg/36 g	-	10	5	11	mononeuritis multiplex eosinophilic alveolitis constitutional symptoms
4	58, F	ND	pANCA/M PO-ANCA	oCYC	10	150 mg/30 g	leucopenia	12.5	4	6	peripheral neuropathy eosinophilc alveolitis
5	35, F	S	negative	MTX	9	25mg/w	-	40	5	3	arthritis subcutaneous eosinophilic granuloma constitutional symptoms
6	40, F	ND	negative	oCYC	28	150 mg/53 g	leucopenia	5	2	6	eosinophilic alveolitis
7	34, M	ND	pANCA± MPO-ANCA-	AZA MTX	2 4	150mg/d/ 25mg/w	vomiting diarrhoea	30	2	6	eosinophilic alveolitis

(p)ANCA: (perinuclear) Antineutrophil Cytoplasmatic Antibodies; MPO-ANCA: ANCA against Myeloperoxidase; AZA: azathioprine; BVAS: Birmingham Vascultis Activity Score; DEI: Disease Extent Index; i.v. CYC: intravenous pulse Cyclophosphamide; L: lung; oCYC: daily oral Cyclophosphamide; MTX: methotrexate; ND: not done; P: Peripheral nerve; PRD: Prednisolone; S: Skin; Gi: Gastrointestinal tract; *cumulative doses are displayed for CYC only.

necrotizing vasculitis with eosinophil tissue infiltration. All seven patients with Churg-Strauss syndrome included had active disease in up to three organ systems despite treatment with prednisolone and conventional immunosuppressive agents (Table 1). Among these seven patients, four had active disease despite treatment with oral cyclophosphamide and prednisolone. Eosinophilic alveolitis (n=4) and new onset of mononeuritis multiplex (n=2) were the most severe manifestations requiring an escalation of therapy. Two patients showed increased disease activity (arthritis, constitutional symptoms, subcutaneous eosinophilic granuloma in one, worsening of asthma, eosinophilia and sinusitis in the other) after treatment with methotrexate and high doses of prednisolone of 30-40 mg and were included as the lack of life-threatening disease and their young age were considered to represent relative contraindications against a use of cyclophosphamide. Another patient suffered from a relapse with eosinophilic alveolitis while being treated with methotrexate and prednisolone following previous extended exposure to cyclophosphamide.

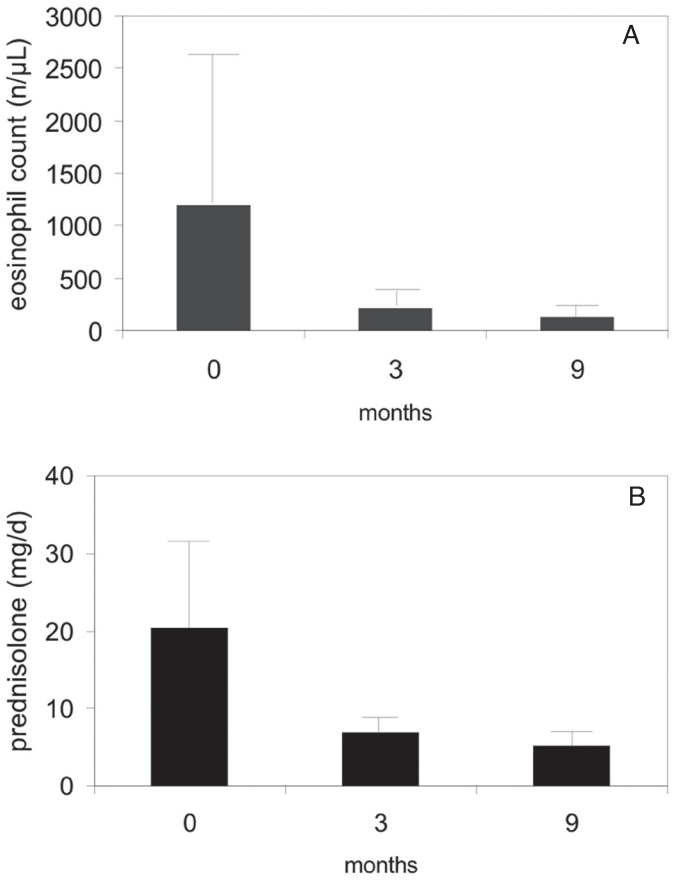

Fig. 1. Blood eosinophil counts (panel **A)** and daily prednisolone dosage (panel **B)** at study entry, at 3 months and at 9 months. Black bars represent mean values ± standard deviation.

Outcome

All of the seven patients were in complete remission of Churg-Strauss syndrome at the three months visit, except persisting asthmatic complaints in two patients. Pulmonary infiltrations resolved and dyspoena improved in all patients with eosinophilic alveolitis. Peripheral neuropathy resolved in one patient and remained stable in two patients and was considered to represent damage rather than persistent activity on follow-up. The mean Disease Extent Index decreased significantly from 3.1 (±1.1) to 0 (±0) points (p=0.017) and the mean Birmingham Vasculitis Activity Score also decreased from 6.4 (±2.8) to 0 (±0) (p=0.018). The eosinophil count in peripheral blood fell from 1194/µl (±1587) to 214/µl (±168) (p=0.080) (Fig. 1). ESR and CRP normalized at the time of remission (ESR 21.8 mm1st/h (±21.8) to 16.3 (±10.6), CRP 3.1 mg/dl (±6.9) to 0 (±0); p=NS). Two patients wo had positive MPO-/P-ANCA at study entry became ANCA-negative at remission.

The dose-range needed to control eosinophil counts was broad. In two patients, it was necessary to progressively increase the dosage of interferon-α to 15 and 21 million I.U./week s.c, respectively, in order to normalize eosinophil counts. In two patients, the dosage of interferon-α was decreased to 2 million I.U./week s.c because of leukopenia. At the time of remission, the mean dosage of interferon-α was 9 (±2.8). million I.U./week s.c.. In all patients, clinical improvement allowed taper of prednisolone according to protocol to at least 10 mg or lower. This resulted in a drop from a mean 20.4 mg/d (±13.3) to 6.9 mg/d (±1.9) in the entire cohort (p=0.068) at the 3 months visit with all patients reaching a dose of 10 mg per day or less and three patients reaching 7.5 mg per day or less.

During a further follow up period of six months after successful induction of remission, all patients remained in complete remission and the eosinophil count (126/µl ±124) and prednisolone dosage (5.1 mg/d ±3.5mg/d) decreased modestly (p=NS) (Fig. 1).

Safety

Overall, interferon-α was well tolerated. Constitutional symptoms related to the injection of interferon-α- were reported frequently, but responded well to paracetamol. In two patients, a transient leukopenia was seen which resolved after a temporary dose reduction to 2 x 3 million units/week. Further routine laboratory analyses and clinical assessments did not indicate toxicity. No infections requiring antibiotic treatment were recorded.

Beyond the 6-months follow-up of this study, leukencephalopathy without clinical symptoms was seen in one patient on MRI after 61 months of treatment, as previously reported (29). In the present cohort, no other cases of leukencephalopathy were observed during long-term follow-up.

Discussion

In this pilot trial of interferon-α for treatment of Churg-Strauss syndrome refractory to previous treatment with prednisolone and cyclophosphamide or methotrexate remission was induced

in all patients. The clinical response was linked to a substantial decrease in blood eosinophil counts. This favourable outcome was not attributable to the concomitant prednisolone treatment, because the prednisolone dose was reduced during the interferon-α treatment rather than augmented.

The results of the present study in patients with refractory Churg-Strauss syndrome extend earlier observations on the compassionate use of interferon-alpha in four other patients with Churg-Strauss syndrome (16). While the efficacy of interferon-alpha in *non*-refractory Churg-Strauss syndrome was subsequently confirmed in single case reports (17-19) this is the first controlled prospective study on this novel form of therapy in Churg-Strauss Syndrome. Although the data presented herein are promising, we acknowledge that the open label-design and the small size are important limitations of this study. However, since Churg-Strauss syndrome is a are disease with an annual incidence of only one per million per year (30) and because most patients respond sufficiently to prednisolone and conventional immunosuppressive agents, larger randomized controlled trials confirming our data will only be possible in a multicenter design which we considered premature at this stage. Finally, the definition of refractory disease in this trial was not very restrictive as the two patients who were unresponsive to methotrexate may have been treated with cyclophosphamide instead of interferon-α. However, in view of their young age and the lack of organ- or life-threatening manifestation the use of interferon-α was felt to be fraught with lesser risks compared with cyclophosphamide (16).

The efficacy of interferon-α in refractory Churg-Strauss syndrome is of note for several reasons. First, given the high mortality of Churg-Strauss syndrome in patients who do not respond to cyclophosphamide and glucocorticoids, interferon-alpha represents a novel and effective form of therapy for otherwise difficult to treat patients. In a series of 96 patients with Churg-Strauss syndrome observed by the French Vasculitis Study Group, 8 patients died of uncontrolled vasculitis despite treatment with cyclophosphamide and corticosteroids (1) and uncontrolled vasculitis accounts for the majority of early deaths in patients with CSS (12). Solans and coworkers reported a fatal outcome due to active vasculitis refractory to cyclophosphamide in three of 32 patients (6). Second, interferon-alpha may represent an alternative to existing therapies also for *non*-refractory Churg-Strauss syndrome, but this needs to be confirmed in randomized controlled clinical trial, as outlined above. Although the number of patients in this study was small, the rate of successful induction of remission in our patients treated with interferon-α and prednisolone was somewhat higher than that reported in three other cohorts (72%, (11), 81% (31) and 91.5% (1) treated with a variety of treatment regimens including azathioprine, cyclophosphamide, methotrexate or plasmapheresis. Third, due to its distinct mode of action and favourable toxicity profile interferon-α can be used in patients who do not tolerate or have contraindications against conventional immunosuppressives like cyclophosphamide or methotrexate.

In agreement with data from a randomized controlled clinical trial of interferon-α 2a in hepatitis C-associated cryoglobulinemia (32), the observed number of adverse events during this study was low and the drug was well tolerated. Previously, we reported the occurrence leukencephalopathy in two patients who were treated with interferon-alpha for an extended period of time (29), of which one patient had been included in the present study. No other cases of leukencephalopathy were seen during long-term follow-up of the seven patients described inhere. Although leukencephalopathy in our two patients was detected by chance on an MRI performed for ENT-disease, was not associated with clinical symptoms and had a benign course, it is a major concern of a long-term treatment with interferon-alpha, not only in CSS, but also in other diseases such as hepatitis C or hematologic malignancies (29). As the short duration of this trial and the small number of subjects preclude definite conclusions on safety of this novel treatment for patients with Churg-Strauss syndrome, the tolerability of interferon-alpha and its potential to prevent disease flares is currently being evaluated in a long-term observational study involving 13 patients. In addition to the above-mentioned second case of leukenecephalopathy (29), an interims analysis of that cohort revealed the development of autoimmune thyreoditis in one patient and several infectious complications (33).

Although, data on the mode of action of interferon-alpha in Churg-Strauss syndrome *in vivo* are lacking, several lines of evidence suggest that interferon-α modulates the over-production of eosinophil-activating cytokines in Churg-Strauss syndrome. Interleukin-5 (IL-5) is the most potent eosinophil-activating cytokine and not only stimulates eosinophil production, but also prolongs the survival of mature eosinophils in culture (34). We recently demonstrated that peripheral blood mononuclear cells from patients with Churg-Strauss syndrome release significantly more IL-5 compared to healthy controls (35). Furthermore we found that T cells from patients with CSS are characterized by a Th2-biased cytokine profile with overproduction of other eosinophil-activating Th2 cytokines like IL-13 (36). Finally, 30 % of patients with Churg-Strauss syndrome, especially those with active disease, had elevated plasma levels of interleukin-5 (37, 38). In vitro, interferon-α reduces expression of both IL-5 and IL-13 by differentiated Th2 cells (39, 40). Thus, given the overproduction of interleukin-5 in Churg-Strauss syndrome, downregulation of IL-5-released by activated T-cells is a potential explanation for the therapeutic effect of interferon-alpha in Churg-Strauss syndrome, which is associated with a decrease in peripheral blood eosinophils, the central effector cells in Churg-Strauss syndrome. Further studies are needed to address this hypothesis.

In conclusion, data from the present trial suggest that interferon-α appears to be an effective treatment for induction of remission in patients with Churg-Strauss syndrome who failed to respond to standard treatment.

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