Interferon-α for Induction and Maintenance of Remission in Eosinophilic Granulomatosis with Polyangiitis: A Single-center Retrospective Observational Cohort Study

Benjamin Seeliger, Martin Förster, Janett Happe, Thomas Forberg, Anne Moeser, Thomas Neumann, and Claus Kroegel

ABSTRACT. ***Objective.*** Eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by frequent relapses following induction therapy. Interferon-α (IFN-α) can reverse the underlying Th2-driven immune response and has successfully induced remission in previous reports. We undertook this study to investigate its efficacy and safety in patients with EGPA.

Methods. We conducted a retrospective monocentric cohort study including 30 patients (16 women) with active EGPA under IFN-α treatment. Primary endpoints were remission induction, occurrence of relapses, prednisolone (PSL) dosage at time of remission, and adverse events. Remission was defined by a Birmingham Vasculitis Activity Score (BVAS) of 0. Pulmonary function tests were recorded at baseline and at time of remission. Health-related quality of life was analyzed by questionnaire at baseline and following 12 months of treatment.

Results. At baseline, the median BVAS was 6 (interquartile range 4–13.5) and remission or partial response was achieved in 25/30 patients. After initiation of IFN-α treatment, the median PSL dosages could be reduced from 17.5 mg/day at baseline to 5.5 mg/day at time of remission. Following remission, 17 relapses (5 major) in 16 patients were observed. Pulmonary function tests improved and the time of hospitalization decreased. Adverse events at initiation of treatment were common, but mostly transient. Severe adverse events occurred during treatment in 4 patients (autoimmune hepatitis, n = 1; drug-induced neuropathy, n = 3).

Conclusion. IFN-α treatment results in high rate of remission and maintenance in EGPA with significant reduction in oral corticosteroids, although reversible adverse events may occur. IFN-α represents an alternative therapeutic option in cases of refractory to standard treatment. (First Release April 15 2017; J Rheumatol 2017;44:806–14; doi:10.3899/jrheum.160907)

Key Indexing Terms:
CHURG-STRAUSS SYNDROME VASCULITIS INTERFERONS

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Accepted for publication January 19, 2017.

Eosinophilic granulomatosis with polyangiitis (EGPA) is one of the antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides[1]. EGPA most frequently presents with involvement of the respiratory system, with asthma being present in 90% of cases, followed by neurologic, cutaneous, and ENT manifestations[2]. Initially described with high mortality, its prognosis has considerably improved following establishment of corticosteroid (CS) and cyclophosphamide (CYC) therapy[3,4,5,6,7]. Though induction of clinical remission is achieved in most patients, relapse rates are as high as 85% even without poor prognostic factors, and trials to guide therapy in patients who are refractory to first-line treatment are lacking[6,8].

Given the high relapse rates and toxicity associated with CYC and longterm CS treatment, novel targeted treatment strategies are desirable. Current recommendations endorse immunosuppressants such as azathioprine (AZA), metho-

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trexate, or leflunomide as potential CS-sparing agents, and brief reports have shown a CS-sparing effect with mepolizumab, omalizumab, and rituximab (RTX)[9,10].

Although the pathogenesis of EGPA is still incompletely understood, it is considered a Th2-mediated disease owing to its hypereosinophilic and asthmatic component. Additionally, the Th2-related cytokines interleukin (IL)-5, IL-4, and IL-13, as well the eosinophil-derived IL-25 are elevated in active EGPA, contributing to a shift toward the Th2-pathway and enhancing eosinopoiesis[11,12,13,14].

Interferon (IFN)-α was demonstrated to modulate the Th1/Th2 balance toward Th1 by increased IFN-γ production and inhibiting IL-5 and IL-13 production in Th2 cells[15,16,17]. This prompted its application in case series with asthma and EGPA and 1 prospective open-label trial by Metzler, *et al*[18,19,20,21,22,23,24]. Therein, IFN-α was shown to induce remission, but data regarding its efficacy in remission maintenance are inconsistent in patients with severe refractory EGPA[25]. IFN-α is considered as a second- or third-line therapy by the EGPA Task Force recommendations. Additionally, although IFN-α has been shown to be effective in severe persistent asthma, it is currently not mentioned as a treatment option in European asthma management guidelines[10,26]. However, because EGPA shares features with the hypereosinophilic syndrome in which IFN-α has been successful (especially in FIP1L1-PDGFR–negative cases), its therapeutic effect warrants further evaluation in EGPA[27]. The aim of our study was to report the monocentric experience of IFN-α in EGPA, including its efficacy for induction and maintenance of remission, adverse events, and its effect on pulmonary function tests (PFT) and quality of life.

MATERIALS AND METHODS

Of 33 patients with EGPA who were treated with IFN-α between 1999 and 2015 at Jena University Hospital (Departments of Pulmonology and Rheumatology), 30 were evaluated for this retrospective observational cohort study (Supplementary Figure 1, available with the online version of this article). Three patients were excluded from the analysis because of loss of followup sooner than 2 months after entry (n = 2) and missing data (n = 1). All patients fulfilled the 1990 American College of Rheumatology classification criteria for Churg-Strauss syndrome[28]. Biopsy-proven vasculitis was not required for diagnosis, although 37% had biopsy-proven disease. Twenty of 30 patients (67%) had a new diagnosis of EGPA with prior asthma and 10 (33%) had relapsing or refractory disease. IFN-α was used as a first-line therapy [along with prednisolone (PSL)] in newly diagnosed patients only in absence of poor prognostic factors [as per the Five-Factor Score (FFS)] and life-threatening manifestations. Patients with poor prognostic factors had relapsing or refractory disease following treatment with other agents. Signed, informed consent was obtained from all patients.

Treatment protocols. Five patients (17%) received initial treatment with IFN-α2b (Yamanouchi) at a dose of 3 × 3 million units/week and 25 patients (83%) received pegylated IFN-α2a (Roche) at an initial dose of 135 μg/week, both administered subcutaneously. Four of the 5 IFN-α2b patients were later switched to pegylated IFN-α2a. Following initiation of IFN-α, PSL doses were gradually decreased according to symptom control, without application of a predefined reduction scheme.

Data collection. Data collection included baseline demographics and laboratory variables, PSL doses, pulmonary function tests, and disease activity assessment at initiation of treatment and at all followup visits (6- to 12-mo intervals). Times to remission and to first relapse, total treatment duration, triggers for discontinuation of therapy, and adverse events were recorded. Disease activity was measured using the Birmingham Vasculitis Activity Score v3 (BVAS)[4]. Disease extent at entry was measured by the Disease Extent Index[29]. PFT, performed using body spirometry including forced expiratory volume in 1 s (FEV1), FEV1/forced vital capacity ratio (FEV1/FVC), total airway resistance, and residual volume, were recorded prior to treatment and at time of remission, and were available for 27 patients. All PFT are stated as percentage of predicted value. At each visit, full blood count was obtained. Health-related quality of life was assessed prior to IFN-α treatment and after 12 months using a standard questionnaire for asthmatic control including frequency of nocturnal asthmatic symptoms that interfered with sleep, coughing fits per day, hospital admissions, and corresponding weeks spent in hospital during the past 12 months. Questionnaires were completed by 19 patients (63%). Data were collected until discontinuation of IFN-α because of relapse. If IFN-α was discontinued while in remission, data collection was extended until relapse or last followup visit.

Treatment outcome. Complete remission was defined as a BVAS of 0 and a PSL dose of ≤ 7.5 mg/day. Partial response was defined as a BVAS of 0 and a PSL dose of > 7.5 mg/day. Relapse was defined as the reoccurrence of symptoms of EGPA attributable to active disease with a corresponding increase in BVAS[30]. A major relapse was defined as potentially life- or organ-threatening disease. Isolated persistence of asthmatic symptoms without elevated eosinophil count or erythrocyte sedimentation rate was not considered as treatment failure, whereas asthmatic exacerbation or recurrent sinusitis accompanied by a rise in eosinophil count was considered as minor relapse.

Ethical approval. Approval for retrospective analysis of patient data was obtained from the ethics committee of Jena University Hospital (reference number: 4836-06/16).

Statistical analyses. Continuous variables were stated as median with interquartile range (IQR). Differences in relapse rates by clinical features were tested using the Kaplan-Meier method and log-rank test. Median time to relapse was estimated using the Kaplan-Meier-Median survival estimate. Group differences were analyzed using the chi-square test for categorical data and the Mann-Whitney U test for continuous data, as appropriate. A p value < 0.05 was considered significant. Analyses were performed with Stata 13.1 (StataCorp LP).

RESULTS

Thirty patients (16 women) were included in our study. Clinical and demographic data are shown in Table 1. Twelve patients (40%) had cardiac involvement (Supplementary Table 1, available with the online version of this article). Twenty-two patients (73%) had either biopsy-proven vasculitis or a clinical surrogate for polyangiitis (Supplementary Table 2 and Supplementary Table 3, available with the online version of this article). Median duration of treatment was 25.5 months (IQR 10–45); IFN-α was discontinued in 23/30 patients (77%) after a median of 24 months (IQR 10–55), and 7 patients were still receiving treatment for a median duration of 22 months (IQR 7–47) at the time of data collection. Twelve patients (52%) discontinued IFN-α therapy because of adverse events, and 5 patients (21%) because of lack of efficacy, with individual triggers for discontinuation summarized in Supplementary Table 4 (available with the online version of this article). Doses for

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Table 1. Baseline characteristics of 30 patients with EGPA treated with IFN-α. Values are n (%) unless otherwise specified.

Characteristics	All, n = 30
Female	16 (53)
Age at first IFN-α, yrs, median (IQR)	51 (44–58)
Prior disease duration, mos, median (IQR)	72 (30.8–108)
ANCA	1 (3)
Peripheral eosinophil count, × 10^9/l, median (IQR)	
At diagnosis	2 (0.8–3.4)
At initiation of IFN therapy	0.5 (0.11–0.9)
Biopsy performed	24 (80)
Biopsy-proven vasculitis	11 (37)
BVAS at first IFN-α, median (IQR)	6 (4–13.5)
Five-factor score	
0	22 (73)
1	7 (23)
2	1 (4)
DEI, median (IQR)	6 (4–8)
Organ involvement at entry according to DEI	
Lung	30 (100)
ENT	26 (87)
Cardiac	12 (40)
Peripheral nervous system	10 (33)
Central nervous system	1 (3)
Skin	8 (27)
Eyes	2 (7)
Arthralgia, arthritis	2 (7)
Gastrointestinal tract	1 (3)
Evidence of polyangiitis*	22 (73)
Immunosuppressive drugs prior to IFN-α	
Prednisolone	30 (100)
Dose at entry, mg/day, median (IQR)	17.5 (10–20)
Cyclophosphamide	4 (13)
Azathioprine	3 (10)
Omalizumab	6 (20)
Methotrexate	2 (7)
Mycophenolate mofetil	1 (3)
Rituximab	1 (3)

* Defined as presence of vasculitis on biopsy or presence of strong clinical surrogate for polyangiitis (i.e., myocardial ischemia because of coronaritis, palpable purpura, alveolar hemorrhage, scleritis, mononeuritis multiplex). EGPA: eosinophilic granulomatosis with polyangiitis; IFN-α: interferon-α; ANCA: antineutrophil cytoplasmic antibodies; BVAS: Birmingham Vasculitis Activity Score; DEI: Disease Extent Index; IQR: interquartile range.

pegylated IFN-α2a and IFN-α2b ranged from 67.5–180 μg per week and 6 million to 10.5 million units per week, respectively; IFN-α dose was adjusted in 7 patients because of side effects or lack of response.

Eleven out of 30 patients (37%) had received at least 1 immunosuppressive or immunomodulatory drug other than PSL prior to IFN-α treatment. These drugs were discontinued before initiation of IFN-α treatment, except for 1 patient who received omalizumab during the first 3 months of IFN-α.

Remission induction. The median BVAS at initiation of IFN-α treatment was 6 (IQR 4–13.5). Of the 30 patients treated with IFN-α for remission induction, 16 (53%) achieved complete remission and 9/30 patients (30%) had a partial response after a median time of 6 months (IQR 3–6). Among the patients showing partial response, 2/9 received a PSL dose of < 10 mg/day. Four of the remaining 5 patients had an FFS of ≥ 1. Among these, 1 patient had a decrease in BVAS from 18 to 4 after 7 months. The other 3 showed no decline in disease activity and discontinued treatment after 2 and 3 months because of depression (n = 2) and worsening of cardiac involvement of EGPA (n = 1). The fifth patient had an FFS of 0 and also discontinued therapy because of depression after 4 months. An FFS of 0 was associated with higher rates of remission or partial response (p = 0.003; Supplementary Table 5, available with the online version of this article).

Remission maintenance and relapses. Twenty-five patients who achieved remission or partial response continued maintenance treatment with IFN-α. Nine patients (36%) sustained their response without relapse until the end of followup for a median time of 31 months (IQR 10–39). The remaining 16 patients had a total of 17 relapses (5 major, 12 minor) after a median time of 11.5 months (IQR 6–33). Using the Kaplan-Meier method, median time to relapse was 30 months (95% CI 8–42). Major relapses consisted of new-onset neuropathy (n = 3), decompensation of heart failure in the setting of cardiac involvement (n = 1), and new ventricular arrhythmia (n = 1). Minor relapses occurred mostly as sinusitis (n = 7) or asthma exacerbation (n = 3), with a rise in eosinophil count. Other minor relapses were progression of neuropathy and granulomatous external otitis (n = 1 each). Patients without evidence of polyangiitis on biopsy or clinical surrogates had fewer relapses and a longer relapse-free survival compared with patients with evidence of polyangiitis (38% vs 72%, 45 mos vs 14 mos, log-rank p = 0.118), without achieving statistical significance. Additionally, patients with relapsing or refractory disease had a statistically nonsignificant shorter time to first relapse compared with newly diagnosed patients (30 mos vs 38 mos, log-rank p = 0.367). Early relapses were associated with rapid PSL withdrawal. Notably, 5 patients had discontinued IFN-α at a mean of 5 months (range 1–10) prior to relapse.

PSL dose. Prior to IFN-α administration, all 30 patients received PSL at a median dose of 17.5 mg/day (IQR 10–20), which was tapered to a median dose of 5.5 mg/day (IQR 3–10) at time of remission (p < 0.001; Figure 1). All patients were receiving longterm PSL treatment before IFN-α, and PSL doses were not increased when IFN-α was started, except for 2 patients who had previously received on-demand PSL pulses before referral to our center and were then started on a daily oral regimen.

At the time of IFN-α discontinuation or end of followup, the median dose was 5 mg/day (IQR 0–12.5). At entry, only 4/30 patients (13.3%) were receiving a daily dose < 10 mg/day. Following IFN-α treatment, the proportion of patients receiving < 10 mg/day increased to 19/25 (71%) at time of remission or partial response and 21/30 (70%) at the

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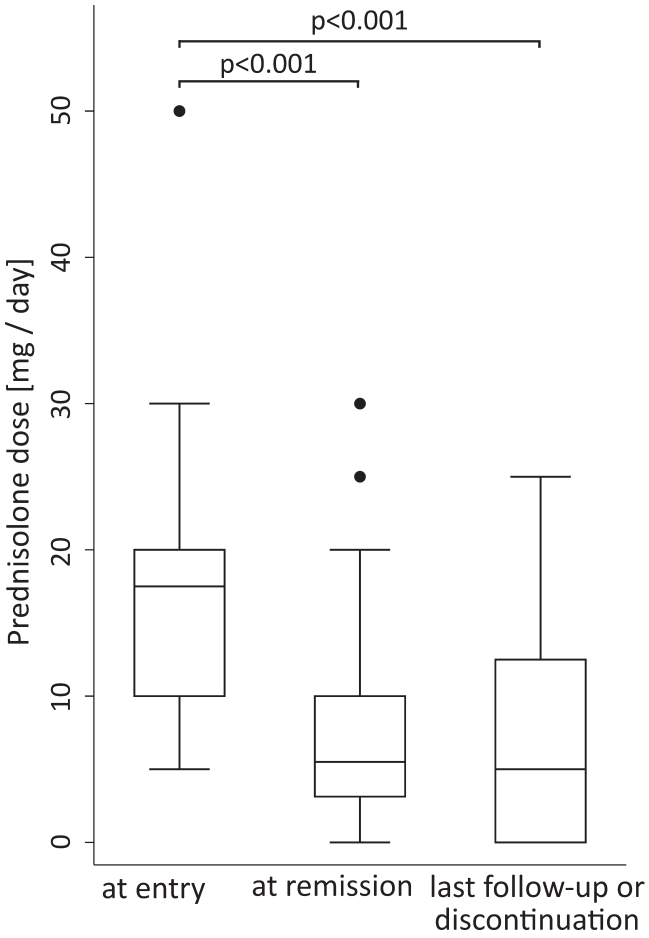

Figure 1. Prednisolone doses of patients with eosinophilic granulomatosis with polyangiitis treated with IFN-α at time of study entry (n = 30), remission or partial response (n = 25), and at the time of last followup or discontinuation of IFN-α therapy (n = 30). IFN-α: interferon-α.

end of followup or discontinuation of IFN-α ($p < 0.001$). Six out of 25 patients (24%) were without PSL at time of remission and 11 (44%) had discontinued PSL at the end of followup.

Pulmonary function tests. PFT were available at initiation of IFN-α treatment and at time of remission or partial response for 27/30 patients (Figure 2). For 2 patients who did not achieve remission, data for the 6-month followup was available. Prior to treatment with IFN-α, the median FEV1 was 71% (IQR 56.1–87.6) and increased to 85.7% (IQR 64.2–99) at time of remission ($p < 0.001$). The corresponding median FEV1/FCV ratio was 75.7% (IQR 59.5–87.4) and 78.8% (IQR 65.7–92.7; $p < 0.001$), respectively.

The median residual volume dropped from 131.1% at entry (IQR 116.1–155.8) to 121.6% at time of remission (IQR 103.3–147.6, $p = 0.061$), and airway resistance dropped from 143.7% at entry (IQR 91.2–187.5) to 111.7% at time of remission (IQR 84.8–150.7, $p = 0.005$). At 6 months, 8/27 patients (30%) still showed an impaired FEV1 of < 70% at a median of 55.5% (range 47.5–68.6), but improved from initial 51.4% (range 25.4–71, $p = 0.674$).

Health-related quality of life. Questionnaires were obtained from 19 patients at entry and following 12 months of therapy (Figure 3). Prior to initiation of IFN-α, patients experienced nocturnal asthmatic symptoms a median of 3 nights per week (IQR 0–7), which decreased to 0 nights per week (IQR 0–1) within the first year of IFN-α ($p < 0.001$). Median coughing fits per day decreased from 6 (IQR 3–10) before entry to 1 (IQR 0–3) within the first year of IFN-α ($p < 0.001$). In the year prior to entry, patients were admitted 1 time (IQR 1–3) and 0 times (IQR 0–1) within the first year of IFN-α ($p = 0.001$). The corresponding weeks in hospital decreased from 3.5 (IQR 0.8–7) to < 1 (IQR 0–1, $p < 0.001$).

Laboratory findings. In the 29 patients with complete laboratory data, total eosinophil count decreased from a median at entry of 0.5×10^9/l (IQR 0.11–0.9) to 0.19×10^9/l at time of response (IQR 0.04–0.37, $p = 0.008$). Following 12 months of therapy, the median eosinophil count was at 0.26×10^9/l (IQR 0.05–0.34) in 21 patients still receiving IFN-α ($p = 0.003$ vs entry value; Figure 4).

Adverse events. During a median time of treatment of 25.5 months (range 2–131), a total of 78 adverse events occurred in 30 patients (Table 2). The most common were constitutional symptoms, which occurred in 23 patients (77%) following IFN-α injections. These symptoms were transient in all patients following 4 weeks of treatment, except for 2 patients who discontinued treatment because of nausea or hot flashes. Hematologic events such as leukopenia and thrombocytopenia were frequent but mild, and neither required discontinuation of IFN-α or specific therapeutic measures. Thirteen adverse events led to the discontinuation of treatment, with depression (n = 4) and IFN-induced neuropathy (n = 3) as leading causes (Table 2). All events of depression occurred within the first 3 months, whereas neuropathy occurred at 9 and 3 years and following 6 months, resolving after discontinuation of IFN-α. One patient developed a reversible IFN-α–associated anemia after 5 years of treatment. New-onset autoimmune events were observed in 3 patients. Two developed autoimmune thyroiditis that was managed with antithyroid drugs while IFN-α was continued. In addition, 1 subject developed autoimmune hepatitis after 5 years, prompting discontinuation of IFN-α and re-initiation of PSL to control hepatitis. Other adverse events leading to discontinuation of IFN-α were increased hair loss in 1 patient, skin pruritus (n = 1), and increase in transaminases because of suspected IFN-induced liver injury after 5 years (n = 1), all of which resolved following discontinuation of IFN-α.

DISCUSSION

In our retrospective study, IFN-α induced complete remission or partial response in 53% and 30% of 30 patients, which is the largest cohort of IFN-α–treated patients with

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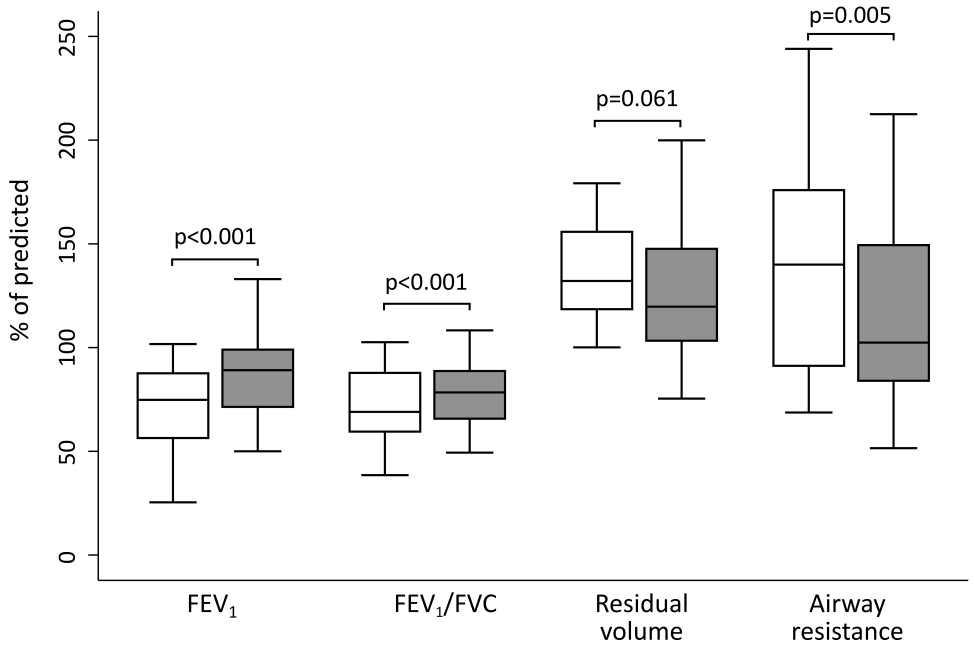

Figure 2. Pulmonary function tests of 27 patients with eosinophilic granulomatosis treated with interferon-α at study entry and following treatment (median of 6 mos). Graph shows changes in FEV1, FEV1/FVC ratio, residual volume, and airway resistance, each stated as percentage of predicted value. FEV1: forced expiratory volume in 1 s**;** FVC: forced vital capacity.

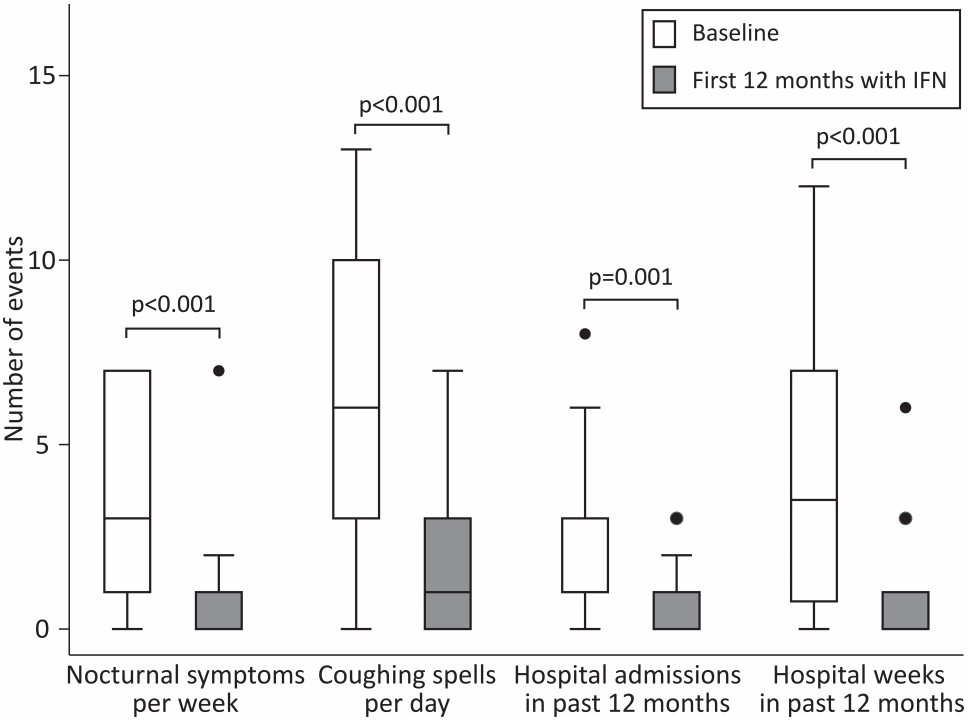

Figure 3. Quality of life in 19 patients with eosinophilic granulomatosis with polyangiitis treated with IFN-α measured by questionnaire. Patients were asked to rate their symptoms and give the average number of hospital admissions with corresponding weeks spent in hospital within the year before IFN-α therapy and during the first year of therapy. IFN: interferon.

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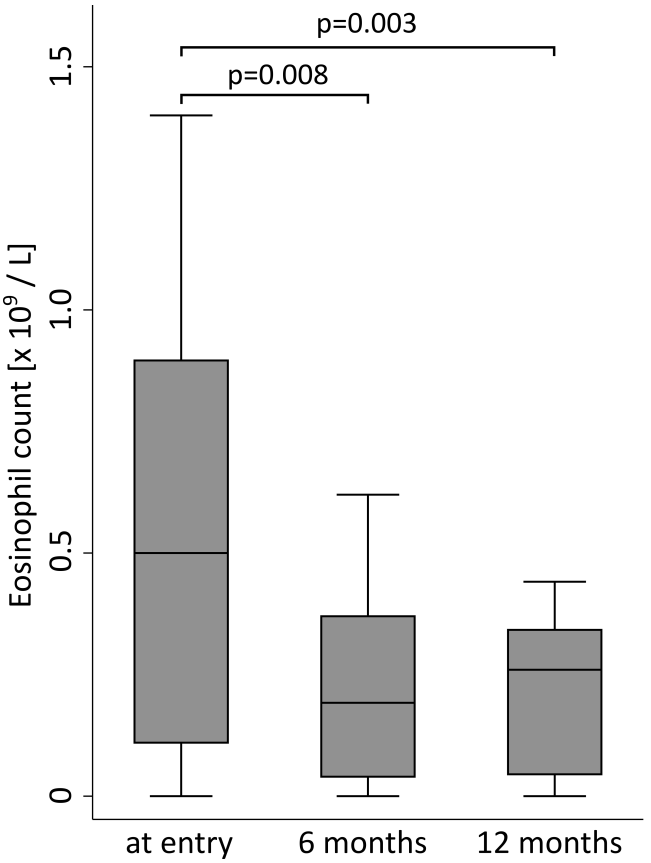

Figure 4. Peripheral blood eosinophil counts of patients with eosinophilic granulomatosis with polyangiitis treated with interferon-α at time of study entry (n = 30), following 6 months (n = 29), and 12 months of therapy (n = 21).

EGPA, to our knowledge. Treatment was accompanied by a significant decrease in eosinophil counts, symptoms, and hospital admissions.

According to recommendations by the European Vasculitis Study Group/European League Against Rheumatism, complete remission should be defined as a BVAS of 0 along with a PSL dose of ≤ 7.5 mg/day. This definition was not applied in all studies, making comparison of remission rates difficult. In a previous study with IFN-α in EGPA, the remission rate was 100%[22]. Mohammad, *et al* reported complete remission (BVAS of 0) in 34% and 49%, and partial response (reduction of BVAS of ≥ 50%) in 49% and 39% following 6 and 12 months of RTX; however, the PSL dosages at time of remission were not indicated[31]. Jachiet, *et al*[32] reported complete remission in 35% and partial response in 30% of the patients treated with omalizumab, and Moosig, *et al* reported a complete and partial remission rate of 70% and 10%, respectively, in 10 patients receiving mepolizumab using definitions equal to our present study[33]. Despite different definitions, the data presented herein suggest that IFN-α shows a remission rate comparable with other biologic agents.

Table 2. Adverse events in 30 patients with EGPA treated with IFN-α. There were 78 events in 30 patients recorded over a median time of treatment of 25.5 months. In 11 patients, adverse events resulted in discontinuation of IFN-α.

Adverse Events	No. Events	
	Major*	Minor
All adverse events	13	65
Hematologic reactions		
Anemia	1	1
Leukocytopenia, < 4.0 × 10^9/l		13
Thrombocytopenia, < 150 × 10^9/l		10
Allergic reactions		
Pruritus	1	4
Exanthema		5
Autoimmune reactions		
Autoimmune thyroiditis		2
Autoimmune hepatitis	1	
Metabolic-toxic reactions		
Neuropathy	3	
Liver damage†	1	
Others		
Constitutional symptoms‡	1	22
Depressive disorder*	4	2
Hair loss	1	3
Weight gain, > 2 kg		2

* Allocation to "major" if prompted a discontinuation of IFN-α. † Asymptomatic rise in transaminases. ‡ Nausea, malaise, fever, arthralgia, and fatigue after administration of IFN-α. EGPA: eosinophilic granulomatosis with polyangiitis; IFN-α: interferon-α.

The most significant limitations to remission induction in our study were side effects, most notably early-onset depression in 3 patients. Depressive symptoms are common with IFN-α therapy, occurring in up to 60% of patients, with 20%–30% developing major depression, but symptoms are usually self-limiting after discontinuation[34,35,36,37].

Regarding remission maintenance, 64% of patients experienced a relapse after a median time of 11.5 months, which is similar to the results of the followup study by Metzler, *et al,* which reported a relapse rate of 69%[25]. The relapse rates of prospective trials vary between 39% and 86%, but their comparison is arbitrary because different definitions of relapse have been applied[5,6,25]. A study evaluating PSL for patients without poor prognostic factors did not explicitly consider exacerbations of asthma or sinusitis with a rise of eosinophilia as relapse[5]. Thus, the relapse rate of 64% observed herein might be an overestimation. Retrospective studies that included exacerbating sinusitis or asthma in the definition of relapse include studies with RTX, mepolizumab, and omalizumab, indicating a relapse rate of 12%, 87%, and 57% after a followup of 12 months, 40 weeks, and 22 months, respectively[31,32,38]. Given the short followup in the RTX trial, the high relapse rate of our study seems similar to other treatment regimens evaluated in retrospective trials and data from 2 large pooled retrospective cohorts[39,40].

Following 6 months of therapy, FEV1, FEV1/FVC, and

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airway resistance improved significantly while PSL doses could be reduced, which is comparable to previous studies with IFN-α in severe asthma[23,41]. Likewise, symptomatic burden could also be significantly reduced. Although asthma is a feature of almost all patients with EGPA, little attention has been paid to PFT[2,8]. One study reported an improvement of FEV1 from 68.8% to 92.7% following induction of remission[42]. Similar results were demonstrated in another recent report (from 68.5% to 93%) following omalizumab treatment in 5 patients with EGPA[43]. However, in up to 50% of patients in clinical remission, irreversible impairment of lung function is present with a post-bronchodilator FEV1 < 70% predicted. Similarly, 30% of patients included in our present study showed persistent FEV1 impairment[42,44].

Following IFN-α therapy, PSL doses could be reduced from 17.5 mg/day to 5.5 mg/day at time of treatment response, with 6 patients having completely discontinued steroid at the end of followup, rendering IFN-α an effective steroid-sparing agent. Reduction and withdrawal of PSL in EGPA remains a challenge because reduction regularly results in recurrent asthmatic symptoms and relapse, often necessitating unaccountably high maintenance doses. Other expert centers have therefore established the routine use of additional immunosuppressive drugs and steroid-sparing agents[39]. Notably, in our present study, neither a predefined steroid tapering protocol nor additional immunosuppressive drugs were used, resulting in some early relapses after presumably early PSL withdrawal. PSL discontinuation in EGPA is a subject of debate and is associated with increased risk of relapse, highlighting the need for steroid-sparing drugs[45].

Adverse events of IFN-α treatment are frequent. However, the most common adverse events were constitutional symptoms, such as headaches and arthralgia, and usually cease within 1 month of treatment. However, major adverse events can occur and may require discontinuation of IFN-α. Still, all side effects were transient and resolved following discontinuation of treatment except for 3 cases of autoimmune thyroiditis or autoimmune hepatitis necessitating further treatment with antithyroid agents or PSL, respectively. Consequently, regular monitoring of patients receiving IFN-α with particular attention to thyroid and liver function is recommended.

Traditionally, systemic vasculitides have been treated with a combination of CYC and CS during the induction phase, followed by AZA for maintenance therapy. Treatment-associated adverse events including infection, osteoporosis, malignancy, cardiovascular disease, infertility, and death remain a major challenge[46]. New biologic treatments such as RTX were expected to cause fewer side effects, but this was only proven for some of them, reviewed elsewhere[47]. Similarly, the data shown herein suggest that although the spectrum of adverse effects may differ from established immunosuppressants, IFN-α may also cause serious adverse effects.

Our study has some limitations from its retrospective design, including missing PFT and questionnaire data for some patients. BVAS scores rely on accurate documentation of all items and were calculated retrospectively. Some adverse events, such as infections, could not be reliably determined because patients were seen by several outpatient clinics. The unexpectedly low number of ANCA recorded in only 1 patient may be because of recruitment through the pneumology outpatient clinic. Patients with renal or neurologic manifestation, who are more likely to be ANCA-positive, were preferentially treated in other departments. Thus, the beneficial effects of IFN-α described herein may be restricted to ANCA-negative patients only. Of note, despite being statistically nonsignificant, IFN-α seemed to be more effective in maintenance of remission in patients without evidence of polyangiitis. The efficacy of IFN-α therapy in ANCA-positive patients with EGPA needs to be further evaluated. Last, 6/12 of our patients had potentially life-threatening cardiac involvement, 3 of which had received CYC as per recommendations prior to IFN-α and 3 had solely received high-dose CS because of significant comorbidities. Because of its potential cardiac toxicity, IFN-α should be used with caution in these patients.

The data demonstrate that IFN-α is an effective agent for remission induction and steroid tapering in EGPA, although serious adverse effects may occur. Given its beneficial effect on PFT and symptoms, it provides an alternative for standard therapy, especially for patients with persistent asthmatic symptoms and without poor prognostic factors. The optimal duration of treatment to avoid side effects needs to be addressed in future studies.

ACKNOWLEDGMENT

The authors acknowledge Christine Michaelis and Monika Möbius for their assistance with acquiring patient records.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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