Interferon-alpha for maintenance of remission in Churg-Strauss syndrome: a long-term observational study

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ABSTRACT

Background. *Interferon-α has been successfully used for induction of remission in patients with Churg-Strauss syndrome, but data on its ability to prevent relapses and its safety during long-term use are lacking.*

Objective. *To examine the safety and efficacy of interferon-α for maintenance of remission in Churg-Strauss syndrome.*

Patients and methods. *In a prospective open-label long-term observational study, 13 patients with CSS in stable remission received interferon-α (3 x 3 Mio. I.U/week s.c.) for maintenance of remission. Primary end point was the incidence of relapses. Secondary end points were the doses of concomitant prednisolone and the frequency adverse events.*

Results. *After a median follow up of 64 month three patients were still on treatment with interferon-α all with a dose of 9 million units/week. In nine patients, interferon-α was discontinued for lack of efficacy (n=5), due to adverse events (n=2), or both (n=2) after median of 63 months (15–153) of therapy. A total of 3 major and 18 minor relapses occurred in 10 of the 13 patients with a median time to first relapse of 17 months (range 5–46). Sera of relapsing patients did not contain antibodies against interferon-α. In 6 relapsing patients treatment was switched to cyclophosphamide (n=4) or methotrexate (n=2). Four episodes of worsened asthmatic symptoms associated with a mild rise of blood eosinophils occurred in 3 patients and resolved following a transient increase of the oral prednisolone dosage. After 49 months one patient died probably due to a relapse. IFN-α was ceased prematurely, because of autoimmune-thyreoiditis in one, depression in another and cerebral leukoencephalopathy in two patients. Overall, 18 infectious episodes with need of antimicrobial treatment were observed.*

Conclusion. *Recombinant interferon-α appears to be partially effective in the prevention of major relapses in patients with Churg-Strauss syndrome. Due to numerous side effects and infections during long-term administration its use should be restricted to patients with contraindications against conventional immunosuppressive therapies.*

Introduction

Churg-Strauss-Syndrome (CSS) is a primary systemic vasculitis, characterized by a history of asthma and hypereosinophilia. Its clinical appearance includes migratory pulmonary infiltrates, granuloma and vasculitis of the skin, polyposis nasi, neuropathy, heart and gastrointestinal involvement, constitutional symptoms and arthralgias. Antineutrophil cytoplasmatic antibodies with perinuclear staining (p-ANCA) directed against myeloperoxidase (MPO) are found in around 40% of all patients with CCS and active disease (1-4).

Clinical symptoms and eosinophila often respond well to treatment with glucocorticoids (GC), but often high doses are needed to accomplish disease control (5, 6). Although a large meta-analysis reveals a better outcome than in other small vessel vasculitides with 5 year survival rates from 68 to 100% (7-10) uncontrolled vasculitis accounts for the majority of early deaths in patients with CSS (9). In case of major organ involvement (*e.g.* heart or severe neuropathy) and bad prognosis the additional use of immunosupressive agents was shown to improve outcome (6, 11, 7). The administration of cyclophosphamide (CYC) in combination with GC is the treatment of choice for severe disease courses, but long-term side effects (myelodysplasia, bladder cancer and opportunistic infections) (12, 13) limit the use of CYC. In patients without life-threatening manifestations both cyclophosphamide and methotrexate turned out to be effective

(14, 15). At present there is little data on whether if and how long imunosuppression needs to be continued beyond the time of remission. However, in a cohort of 28 patients with CSS treated with MTX for maintenance of remission relapse rates were still considerably high (15), indicating a need for a treatment for maintenance of remission similar to other forms of ANCA-associated vasculitis.

Reports from case series and data from a prospective clinical trial suggest that interferon-α (IFN-α) can effectively induce remission in patients with CSS (14-20). Although the results of the latter trial were encouraging, the period of observation of 6 months from remission was too short to reliably assess safety and the potential of IFN-α to prevent relapses. Therefore, this observational long-term study was designed to assess the efficacy and safety of IFN-α for the maintenance of remission of CSS in a larger cohort of patients.

Methods

Eligibility criteria

Patients fulfilling the following eligibility criteria were eligible to participate in this trial: 1. a diagnosis of CSS based on the presence of asthma, blood eosinophilia of >10% and 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; 2. presence of four of the seven classification criteria of the American College of Rheumatology (ACR) (21) for CSS; 3. remission, defined as the absence of active disease as listed in the Birmingham Vasculitis Activity Score (BVAS) (22), 4. previous treatment for induction of remission with a) IFN-α, or b) conventional immunosuppressive agents (CYC, MTX or azathioprine), but intolerability or contraindications against extended use of these drugs; and c) oral prednisolone at a dose of ≤10 mg/day. Seven patients who had been treated with IFN-α for induction of remission within a previously published trial (20) were included in the present trial after the 6 months follow-up within the first trial was completed.

Eosinophilic disorders other than CSS like idiopathic hypereosinophilic syndrome, chronic or acute eosinophilic pneumonia or eosinophilic leukemia were excluded. Patients with any kinds of severe psychiatric disease, viral or autoimmune hepatitis, thyroid diseases, pre-existing malignancies or active infections were not eligible for the trial. The study protocol was approved by the local institutional review board. All patients were seen at the primary centre for vasculitidis in the department of rheumatology and immunology at the university hospital of Schleswig-Holstein in Luebeck and Bad Bramstedt.

Treatment

Recombinant human IFN-α 2b (Intron A, Essex Pharma) was administered at nine million units per week (three times three million I.U.) s.c. in all patients, who started for maintainance of remission, except two who received IFN-α 2a (Roferon, Roche). Six patients received IFN-α 2b already for induction of remission (20). Three of them received 9 million I.U. /week, two patients, were on 15 million I.U./week, one at 7.5 million I.U./week. Dosage 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 1g of oral paracetamol. In case of a disease flare, 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 IFN-α dosage were recorded, but were not considered to represent a treatment failure. In case of disease flares unresponsive to a maximally tolerated dose of IFN-α, treatment was terminated and switched to conventional immunosuppressive agents like cyclophosphamide or methotrexate.

At study entry, all patients were on oral prednisolone at doses from 5 to 10 mg/day. During the study prednisolone doses were reduced in 2.5 mg steps every week until 5 mg/d and thereafter by 1 mg/month. Prednislone taper was halted at a dosage required to control asthmatic complaints and thus complete taper was not required. Locally applied GC for asthmatic symptoms or nasal obstruction was allowed. In case of disease flares unresponsive to a dose escalation of IFN-α alone, prednisolone dosage was elevated as needed. The simultaneous use of other immunosuppressants was not allowed.

Disease assessments

Patients were followed up at three-monthly intervals from the time of remission. 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 an analysis of the BAL cell profile were performed like previously described by our group. Blood samples including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver enzymes, creatinine, urine analysis and full blood cell count were determined at each visit. ANCA were determined by indirect immunofluorescence (IFT) and ELISA at study entry and by IFT at three-month intervals during follow-up. The Birmingham Vasculitis Activity Score (BVAS) (22) and the Disease Extent Index (DEI) score (23) were determined for evaluation of disease activity and extent. To stage the disease severity, the Five Factor Score (FFS) (7) was calculated.

The primary outcome measures were the frequency and severity of relapses and the incidence of adverse events. Secondary outcome measures included blood eosinophil counts, CRP serum levels, ANCA titers and PRD dosage. A relapse was defined as re-ocurrence or new onset of disease activity due to active CSS as checked by the BVAS score list. Relapses with life- or organ threatening organ involvement such as cardiac involvement with progressive ventricular arrhythmias were defined as major and requires an increase of PRD and cytotoxics. All other relapses were considered to be minor and were treated by a temporary limited increase of PRD. Persisting asthma or an isolated rise in blood eosinophils had no influence on the remission or relapse allo-

cation. ENT symptoms (*e.g.* polyposis nasi, sinusitis, anosmia) were included in the allocation to the remission or relapse groups, if there were signs of active disease (*e.g.* a new appearance or response to escalation of treatment).

Determination of antibodies against recombinant human IFN-α 2

Serum samples were screened for the presence of autoantibodies directed against recombinant human IFN-α by enzyme-linked immunoassay (ELISA) according to previously described protocols (24, 25). Briefly, 96-well microtiter plates were coated with rHuIFN-α (PBL Biomedical Laboratories, New Brunswick, USA) or Roferon A (Hoffman- La Roche, Basel, Swiss) at a concentration of 20 IE/ml in bicarbonate buffer (pH 9.6), overnight at room temperature (RT). Subsequently the plates were saturated with phosphate buffered saline containing 2% casein (PBS-C) for 1 hour at RT. After washing three times in PBS-Tween 20, sera diluted 1:50 in PBS with 0.1% BSA and 0.05% Tween 20, were incubated for 1 hour at room temperature. After washing bound IgG was detected by alkaline phosphatase-conjugated anti-human IgG (Dako, Hamburg, Germany). To exclude non-specific binding, a control plate was not coated with IFN-α. A monoclonal antibody against IFN-α (R&D, Wiesbaden, Germany) was used as positive control. A serum was regarded as positive if the absorbance was >3 SD higher than values obtained with healthy donors (n=80). Results were confirmed by immunoblot. Values were related to a set of calibrators to quantify the values in arbitrary units/ml.

Statistical analysis

Due to the character of the study, as an uncontrolled open label observational study, data were analysed descriptively. Values were given as medians and ranges Relapses were plotted according to the Kaplan-Meier method. Statistical analysis was performed using SPSS for Windows, version 12.0 (SPSS, Chicago, IL).

Results

Patient characteristics

Thirteen patients with CSS who had been in sustained remission for a median of 4 month following treatment with GC combined with either IFN-α (n=7), CYC (n=3), AZA (n=2), MTX (n=1) or leflunomide (n=1) were included in this observational study. At the time of study entry were on GC in a median dose of 5 mg/day (range: 0-10 mg).

Outcome

After a median follow up of 64 months (range 29–153) during maintenance treatment three of 13 patients were still receiving IFN-α. After a median of 63 months of therapy, IFN-α had been discontinued in nine patients for lack of efficacy (n=5), due to adverse events (n=2), or both (n=2). One patient died in a flare of acute respiratory failure of unknown origin at home. As reported by her relatives, she was seen by a foreign doctor since her practitioner was not available. No further clinical or laboratory data were collected. As no autopsy was performed, it is unknown whether an asthmatic attack, a relapse of CSS or an infectious complication was responsible for her death.

In total, during the whole observational period 21 relapses occurred in 9 patients after a median time of 17 months (range 5–46 months) from remission to the first relapse (Fig. 1) (32 relapses in 100 patient years). In 18 of the 21 relapses there was no evidence of immediate life- or organ-threatening disease and these flares responded well to an increase of IFN-α and PRD dose. Included in this group were 4 patients with new pulmonary infiltrates, but without significant impairment of pulmonary function (minor reduction of blood oxygen saturation and CO diffusion capacity). Bronchoalveolar lavage was performed in 2 of these 4 patients and confirmed active CSS by revealing eosinophilic alveolitis. A major relapse necessitating discontinuation of IFN-α occurred in 3 patients. One of these patients developed new onset pericarditis and worsening of preexisting ventricular arrhythmia and side effects at the same time (see below). In the second patient preexisting ventricular arrhythmia detoriated (increase of ventricular arrhythmias on 24h ECG). Echocardiography revealed pericarditis an a reduction of ejection fraction in both accompanied by an increase of the eosinophilc cationic protein serum

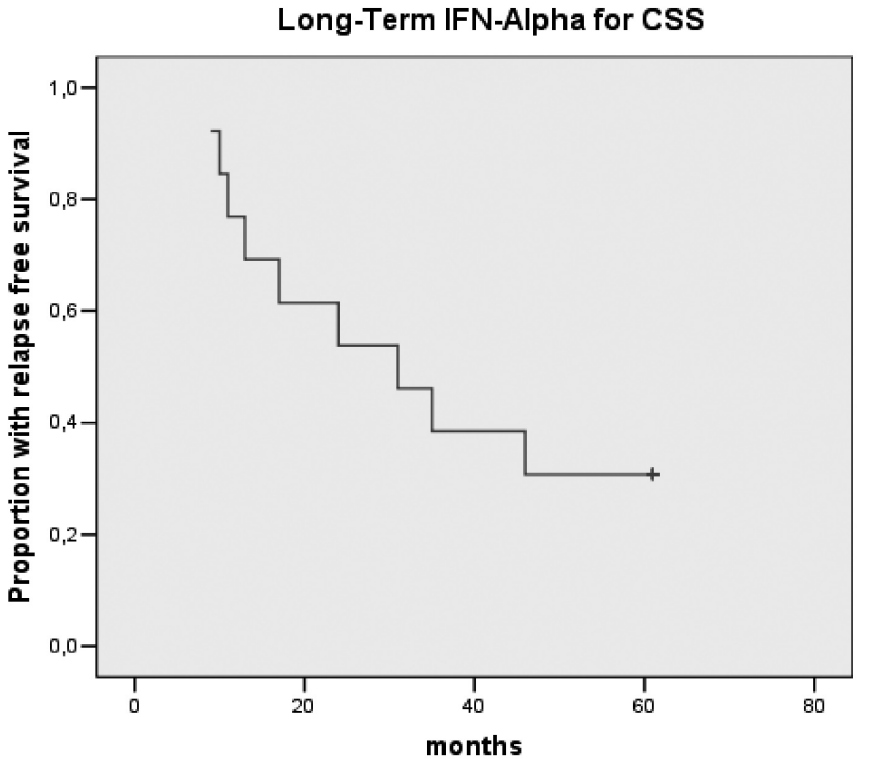

Fig. 1. Relapse free survival in 13 patients treated with IFN-α for maintenance of remission in Churg-Strauss syndrome.

Table I: Baseline characteristics of 13 patients with Churg-Strauss-syndrome treated for maintenance of remission with IFN-α.

Patient	Age (years)	Sex	Biopsy	DEI at first manifestation	DEI at study entry	FFS	BVAS at first manifestation	BVAS at study entry	Disease duration prior to study	Treatment prior to study entry	Duration of pre-treatment (months)	PRD (mg/d) at study entry	Anti asthmatics
2	55	f	P	7	4	0	15	9	36	IFN-α	2	10	topic
4	49	f	L	11	0	1	19	0	120	IFN-α	3	5	topic
5	54	f	Gi	15	2	2	30	6	69	IFN-α	6	8	topic
7	58	f	–	9	2	0	16	6	10	IFN-α	3	5	topic
9	42	f	–	11	0	1	24	0	42	IFN-α	3	6.25	topic
11	35	f	S	5	0	0	5	2	40	IFN-α	3	0	topic
12	45	m	S	11	0	1	16	0	84	IFN-α	4	7.5	topic
14	46	f	L, H, Gi	11	2	2	24	1	51	oCYC	2	8.75	topic
1	41	m	–	17	0	2	29	0	15	oCYC	12	5	topic
3	38	f	S	7	4	0	12	6	118	AZA	10	8	topic
6	26	f	S, Gi	13	2	2	21	0	24	pCYC	24	5	topic
8	62	m	S, L	9	0	0	17	0	36	pCYC	7	3	topic
10	35	f	S	13	2	2	28	0	228	MTX	25	3	topic+ p.o.

oCYC: daily oral cyclophosphamide; pCYC: intravenous cyclophosphamide; AZA: azathioprine; MTX: low-dose methotrexate; PRD: prednisolon; Manifestations of CSS: E: ENT; L: lower respiratory tract; K: kidney; EY: eyes; A: arthritis, myalgia; S: skin; H: heart; P: peripheral neuropathy; C: central-nervous system; Gi: gastrointestinal tract; B: constitutional symptoms; DEI: Disease Extent Index; BVAS: Birmingham Vasculitis Activity Score; FFS: Fife factor score.

level. The third patient suffered from a renal relapse with nephritic urinary sediment in combination with constitutional symptoms. In all three patients treatment was switched to cyclophosphamid and the dosage of prednisolone was raised to 1mg/kg bodyweight. In a fourth patient pulmonary infiltrates, constitutional symptoms and sinusitis (documented by MRI) coincided with an adverse event (see below) and lead to a switch to methotrexate. All four responded well to the induction therapy. Three patients developed a total of four episodes of increased asthmatic complaints measurable by an increase of total airway resistance that coincided with a raise in blood eosinophil counts which all responded to a temporary modest elevation of the prednisolone dose. The median dosage of IFN-α at first relapse was 9 million i.U./week s.c. (range 7.5–15), the median prednisolone dosage 5 mg (range 0-9).

The BVAS 1 score increased over time in the relapsing patients. The actual DEI at start of maintenance treatment (median 2, range 0–4) and at study end (median 2, range 0–5) did not differ. During maintenance treatment, IFN-α did not significantly reduce the prednisolone demand (median 6.25 mg/d at study entry, versus 5 mg/d at study end).

At study start the median eosinophil count was 470/nl (range 12 to 1040). In the patients suffering a relapse it raised to 1061/nl at relapse (30 -1908). CRP was elevated only in 2 patients at study start with 1.7 and 0.9 mg/dl, and negative in all patients remaining in remission at study end and positive in one suffering a relapse with 2.2 mg/dl. in only one patient in this cohort p-ANCA was detected at study start with stable titers during the treatment period.

Adverse events

In four patients IFN-α was discontinued due to adverse events: One patient developed autoimmune thyreoidits with hypothyroidism and positivity for antibodies against thyreoglobulin and thyroid microsomal antibodies. In two other previously reported cases cerebral leukoencephalopathy was observed, one in coincidence with a major cardiac relapse, the other as mentioned above in coincidence with a minor relapse (described in detail in (26)). (For patients' history, see Table II). One patient discontinued IFN-α despite complete remission due to a new onset of depression.

Four episodes of leucopenia (all in patients previously treated with CYC), the occurrence of aseptic abscesses in one patient and constitutional symptoms in another patient resolved after temporary reduction of the dose reduction IFN-α.

A total number of 23 infections (8 bacterial, 14 viral infections, one fungal) were noted. The 8 bacterial infections required oral anti-infective treatment (Table II). None of these infections was life-threatening or required hospitalisation. IFN-α and prednisolone were continued during the infections.

Prevalence of anti- IFN-α-antibodies

In view the high number of minor flares during long-term-treatment that responded to an increase of IFN-α dosage in most patients, the assessment of neutralising antibodies was performed in all patients who suffered from a relapse. Serum samples were stored prospectively during all visits and sera obtained before treatment, during remission and at the time of relapse were analysed. However, antibodies against IFN-α were found in none of these sera.

Discussion

In earlier studies, IFN-α proved to be a safe and effective treatment for the induction of remission in patients with active and refractory CSS (20). This report describes the first cohort of patients with CSS treated with IFN-α for maintenance of remission that has been reported till to date. This open lable observation study is limited by its small size with heterogeneous baseline characteristics including FFS from zero to two and the heterogeneous medications to induce remission, including IFN-α

Table II. Outcome and clinical course of 13 patients with Churg-Strauss-syndrome treated for maintenance of remission with IFN-α.

Patient	Side effects (management)	Relapses	Outcome
2	Constitutional symptoms (symptomatic treatment)	worsening of asthma and increase of blood eosinophil count	increase of IFN-α (remission)
4	Cerebral leukoencephalopathy (cessation of IFN-α); aseptic abscesses (n=3)	- pleuritis - eosinophilc alveolitis - worsening of asthma and increase of blood eosinophil count	switch to MTX (side effect) (side effects resolved)
5	Cerebral leukoencephalopathy (cessation of IFN-α); bronchitis, oral candidiasis (antiinfective treatment)	- pericarditis, arrhythmia	reintroduction of CYC (side effects resolved, remission)
7	Respiratory infections (n=2) (antiinfective treatment)	- eosinophilic alveolitis	death in acute respiratory failure (L?)
9	Transitory leucopenia (temporay dose reduction of IFN-α)	- sinusitis, pulmonary infiltrates, B	reintroduction of CYC (remission)
11	none	none	in remission with IFN-α
12	Leucopenia (dose reduction of IFN-α) Herpes zoster (antiinfective treatment) Laryngitis (symptomatic treatment)	- pulmonary inflitrates angina pectoris, sinusitis - new coronary stenosis, polyposis - enterocolitis, B	increase of IFN-α (remission)
14	New onset of depression (cessation of IFN-α)		switch to leflunomide
1	Transitory leucopenia (temporay dose reduction of IFN-α)	- ECG changes, asthma, sinusitis, B - ventricular arrhythmia, weight loss, neuropathy	increase of IFN-α (remission)
3	constitutional symptoms (symptomatic treatment) sinusitis (n=3) (antiinfective treatment)		in remission with IFN-α
6	Leucopenia (dose reduction of IFN-α) bronchits (n=3) (antiinfective treatment) sinusitis (n=3) (antiinfective treatment)	- ECG changes (ischemic), ventricular arrhythmia - 3x ventricular arrhythmia - eosinophilic gastric ulcers, increase in ventricular arrhythmia	initially increase of IFN-α, later CYC (remission)
8	none	none	in remission with IFN-α
10	autoimmune-thyroiditis (cessation of IFN-α) respiratory infections (n=3) (antiinfective treatment)	worsening of asthma and increase of blood eosinophil count	Switch to MTX (remission, euthyreosisunder treatment)

or conventional immunosuppressive agents.

After the successful use for induction of remission, the long-term administration of IFN-α was only partially effective for the maintenance of remission in the present study. Relapses were frequent, but life- and/or organ-threatening relapses occurred in only three patients with severe cardiac and pulmonary manifestations. One patient, who previously was in stable remission, died of respiratory failure of unknown origin. As an autopsy was not preformed, an association with CSS or its treatment can not be excluded.

The French Vasculitis Study Group described a cohort of 64 CSS patients within a group of 278 patients with different vasculitic disease entities (11). In that study, during a median follow-up of 88 months 20.3% of the CSS patients relapsed, irrespective of the treatment regimen they received. Median time to relapse was similar to our cohort (17 (median) *vs*. 24.6 (mean) months). In a larger cohort of French CSS patients (7) the time from remission to relapse was even longer (69 months), but some relapses occurred very early, too. In accordance with the French data, Solans found in his cohort of 32 CSS patients from Spain a relapse rate of 28% (27). Another cohort, treated with MTX for maintenance of remission showed a relapse rate of 40% occurring early after a median of 9 months after remission (15). However, the overall higher rate of relapses in the present trial compared to the above mentioned studies is most likely related to the fact that mostly patients with previous treatment failure and thus more aggressive disease were included in this study.

A decline in therapeutic efficacy of recombinant IFN-α during long-term administration has been correlated with the development of antibodies against IFN-α in patients with chronic hepatitis C (24, 25), chronic myelogenous leukemia (28), hairy-cell leukaemia (29) and carcinoid tumours (30). The fact that an increase in IFN-α dose was effective for the treatment of most relapses in this study raised the question whether antibodies against IFN-α were present in these patients. We therefore determined the presence of antibodies against recombinant IFN-α2b in sera at the time of relapse, but none of the sera contained anti-IFN-α2b antibodies. Hypothetically, the lack of neutralising antibodies may be a result of the concomitant prednisolone therapy in our patients. The IFN-α receptor is expressed on human eosinophils and ligation of the receptor reduces the release of cytotoxic mediators such as ECP and eosinophil derived neurotoxin. In T cells, which express the IFN-α receptor also, IFN-α reduces the expression of eosinophil activating cytokines,

particularly interleukin-5 (IL-5). Since CSS is characterised by a TH-2 dominated cytokine profile and increased expression of IL-5 and IL-13 (2, 31), the beneficial effect of IFN-α in CSS is possibly related to a harmonisation of the skewed cytokine profile by reducing the release of TH-2 cytokines from T cells. (32). Hypothetically, the lack of efficacy during long-term administration might be related to a down-regulation of IFN-α receptors as a result of long-term IFN-α therapy. Unfortunately, no fresh cells were sampled at the start of the study and during relapse to test this hypothesis.

The spectrum of adverse events related to IFN-α in this study was broad and the incidence of adverse events was high. We observed one case of autoimmune-thyreoiditis, two cases of leucoencephalopathy (26) and one case of depression, most notably, 23 episodes of mild to moderate infections in all 13 patients studied (including 8 bacterial with need of antimicrobial treatment: 12.3/100 patient years). The incidence of infections with methotrexate (15) was lower (8.9/100 patient/years) and the data from the French Vasculitis Study Group indicate a lower incidence for the cyclophosphamid treated patients too (28.6% of 77 patients in an observation period of 88.5 months in all subgroups of patients with different vasculitides, *e.g.* 3.9/100 patient/years).

Conclusion

The attempt to avoid cyctotoxic side effects of cyclophosphamide and to reduce the number of relapses by modulating the eosinophils with interferon-α did not fulfil the expectations raised by the data from the induction of remission-trial (20). Recombinant interferon-α is only partially effective in the maintenance of remission in patients with Churg-Strauss syndrome. Due to numerous side effects and infections its use should be restricted to patients with an increased risk for relapse and contraindications against or intolerance of conventional immunosuppressive therapies. Therefore new strategies as the monoclonal antibody targeting IL5 (mepolizumab), that is introduced in special forms of the hyperosinophilic syndrome (33) are needed and are already subject of ongoing trials for Churg-Strauss syndrome.

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