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EFFICACY AND TOLERABILITY OF INTERFERON ALPHA TREATMENT IN PATIENTS WITH CHRONIC CYSTOID MACULAR EDEMA DUE TO NON-INFECTIONOUS UVEITIS

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Abstract

Aim: To assess the efficacy and tolerability of interferon (IFN) alpha in chronic cystoid macular edema (CME) due to non-infectious uveitis.

Methods: Retrospective analysis of an interventional case series. IFN alpha-2a was administered at an initial dose of 3 or 6 million IU per day subcutaneously and tapered afterwards to the lowest possible dose to maintain the absence of CME. Treatment efficacy was assessed by optical coherence tomography.

Results: Twenty-four patients with chronic CME (median duration 36.0 months) due to non-infectious anterior (n=2), intermediate (n=18) or posterior (n=4) uveitis have been analysed. Ineffective pre-treatment included systemic corticosteroids (all patients), acetazolamide (22 patients) and at least one immunosuppressive drug (18 patients). IFN therapy was shown to be effective (= complete resolution of CME within 3 months, able to taper IFN) in 15 patients (62.5%), partly effective (= incomplete resolution of CME, unable to taper IFN) in 6 patients (25.0%) and not effective (= no response or recurrence of CME) in 3 patients (12.5%). IFN treatment was generally well tolerated. Common side effects including flu-like symptoms, fatigue or increased liver enzymes were dose dependent and led to discontinuation of IFN in only 1 patient.

Conclusion: Our data demonstrate IFN alpha to be an effective and well-tolerated therapy for chronic refractory uveitic CME.
Introduction

Cystoid macular edema (CME) is a serious complication of uveitis affecting approximately one-third of patients.[1] It represents one of the major causes of legal blindness in patients with intraocular inflammation.[2] Therefore, CME legitimates aggressive medical treatment including systemic or intravitreal corticosteroids, acetazolamide and immunosuppressive drugs.[3, 4] When a CME occurs in a condition of active uveitis, its management is mostly unproblematic if an early and adequate treatment of the intraocular inflammation is initiated.

In contrast, chronic uveitic CME still remains a therapeutic challenge. For us a CME is defined as ‘chronic’ if the uveitis itself appears quiescent (either burned out or well controlled by drugs) but, nevertheless, a CME is present that no longer responds to conventional anti-inflammatory therapy. For this refractory sight-threatening condition new therapeutic approaches need to be evaluated.

Interferon (IFN) alpha is a cytokine belonging to the subgroup of type I interferons that exerts strong antiviral, antiproliferative and various immunomodulatory effects. It is approved for the treatment of viral hepatitis and myeloproliferative syndromes, as well as for certain solid tumours and lymphomas.[5] However, during recent years IFN alpha has also been shown to be a very effective treatment for patients suffering from Behçet’s disease (BD) with inflammatory involvement of the posterior eye segment[6, 7] as well as for several cases of otherwise refractory uveitis.[8, 9] A particular finding in the BD patients was that IFN alpha treatment without additional acetazolamide or immunosuppressives led to complete resolution of CME.[10] This gave us the idea to use IFN alpha also in patients with chronic treatment-resistant CME due to non-BD uveitis. Thus, in January 2003 we started to treat our first patient. In 2006 we reported for the first time promising results of this novel approach in eight patients.[11]

After more than five years of experience, we now want to present a current update of our results on the efficacy and tolerability of IFN alpha treatment in patients with chronic treatment-resistant CME due to non-infectious uveitis.

Materials and methods

We present a retrospective analysis of an interventional case series that included 24 consecutive patients. To be eligible for IFN alpha treatment, patients had to suffer
from chronic CME due to non-infectious uveitis in at least one eye. CME had to be resistant to pre-treatment consisting of systemic or intravitreal corticosteroids and/or immunosuppressives of adequate dose and duration. To qualify for analysis, patients had to complete follow-up of at least 3 months after initiation of IFN therapy. Informed consent was obtained from all patients before the start of treatment.

Depending on bodyweight, IFN alpha-2a (Roferon-A™, Hoffmann-La Roche) was administered at an initial dose of 3 million (mio) IU (≤ 70 kg) or 6 mio IU (> 70 kg) per day subcutaneously. In 10 patients IFN alpha-2a was then tapered stepwise over 6 months to a dose of 3 million IU twice a week and finally discontinued (on the basis of the dosing schedule we use in BD patients). In the case of a relapse of CME in at least one eye of the patient, IFN alpha-2a was reinstituted at a dose of 3 mio IU every second day with subsequent tapering in order to evaluate the lowest maintenance dose to maintain the absence of CME. In the remaining 14 patients a different treatment regimen was used that did not discontinue IFN alpha-2a after 6 months. Dosing schedules for IFN alpha-2a are shown in Figure 1. In all patients, when IFN treatment was initiated the dose of previous immunosuppressives was halved, acetazolamide was tapered and oral corticosteroids were reduced to a maximum of 10 mg prednisolone per day as quickly as possible. To initiate IFN treatment, patients were admitted to hospital for 3–4 days; further treatment was performed in an outpatient setting. To lessen flu-like symptoms, paracetamol was additionally administered in the initial treatment phase.

The main outcome criterion of the analysis was the efficacy of IFN treatment assessed as the response of CME which was measured by optical coherence tomography (OCT) at each visit. It was defined as:

- ‘effective’ if a complete resolution of CME was seen within 3 months and the dose of IFN alpha-2a could be tapered;
- ‘partly effective’ if an incomplete resolution of CME within 3 months was observed, the dose of IFN alpha-2a could not be tapered and/or acetazolamide could not be discontinued;
- ‘not effective’ if no response of CME was seen or a recurrence of CME occurred within 3 months.

As a secondary outcome criterion, development of visual acuity (VA) was measured in European decimals and converted to logMAR for computing. According to recommendations of the Standardization of Uveitis Nomenclature (SUN) Working
Group, improvement of VA was defined as a decrease, and worsening of VA as an increase of at least 0.3 logMAR (= 3 lines).[12]
To exclude contraindications but also to control side effects during IFN treatment, patients were seen by our group’s internists before starting treatment and, if indicated, during follow-up. Routine blood parameters including complete blood count and liver enzymes were measured every 4–6 weeks.

Results
Characteristics and detailed results of patients are shown in Table 1. Twenty-four patients (9 male, 15 female) with a total of 40 affected eyes were analysed. The median age of patients at the start of IFN treatment was 50.0 years (lower quartile (Q1) 42.0 years; upper quartile (Q3) 66.0 years; mean 51.0 years; range 19–74 years). Two-thirds of the patients suffered from bilateral CME. Localization of the uveitis was anterior in 2 patients (8.3 %), intermediate in 18 patients (75.0 %) and posterior (Birdshot chorioretinopathy) in 4 patients (16.7 %). An underlying systemic disorder was detectable in 1 patient with intermediate uveitis, who suffered from multiple sclerosis. Median duration of CME before IFN therapy was calculated for 36.0 months (Q1 24.8 months; Q3 85.0 months; mean 56.9 months; range 16–132 months). The uveitis itself was quiescent in all patients and did not necessitate any change or intensification of treatment at the timepoint when IFN was started.
Ineffective pre-treatment for CME consisted of systemic corticosteroids in all patients, acetazolamide in addition in 22 patients and at least one additional immunosuppressive drug in 18 patients. Intravitreal drugs (triamcinolone and/or bevacizumab) were administered in 6 patients; in 9 patients surgical treatment of CME by pars plana vitrectomy had been performed. The median follow-up for all patients accounts for 21.0 months (Q1 11.8 months; Q3 42.8 months; mean 27.9 months; range 1–65 months).
Figure 2 provides an overview of the efficacy of IFN treatment. This was shown as effective in 25 eyes of 15 patients (62.5 % each) and partly effective in 10 eyes of 6 patients (25.0 % each). It has to be considered as not effective in only 5 eyes of 3 patients (12.5 % each). Pre-existing neutralizing auto-antibodies against IFN alpha (titre >1000 ng/ml) were most probably the reason for non-response in one of these patients (no. 8) and led to discontinuation of treatment after 1 month (the only patient
in the series who, exceptionally, did not complete the required follow-up of 3 months). Another of these 3 non-responding patients (no. 7) developed new auto-antibodies against IFN alpha with a recurrence of CME (IFN therapy stopped after 3 months) in both eyes.

Table 2 shows the development of mean foveal thickness and VA within the first 3 months of IFN treatment and, at the end of follow-up, relating to efficacy of IFN treatment. As shown in Figure 3, in the vast majority of patients CME responded very quickly to IFN treatment, demonstrating a remarkable decrease after 3 days and an almost complete resolution already within 2 weeks.

In 8 patients IFN therapy was discontinued after six months in the complete absence of CME. One patient (no. 6) was lost to follow-up then. In the remaining 7 patients CME relapsed, in 6 patients within 1–3 months and in 1 patient after 22 months. Therefore IFN therapy had to be reinstated, again demonstrating efficacy. Currently, 2 patients have been off IFN for 4 and 8 months, respectively, without recurrence of CME to date, after IFN treatment for 63 and 61 months, respectively. Six patients with a follow-up longer than 24 months (median 49 months, range 27–65 months) are in stable remission of CME at the timepoint of analysis with very low IFN doses between 0.5 mio IU every fifth day and 3 mio IU every third day.

In the effective and partly effective patients concomitant medication could be remarkably tapered during follow-up. Right at the start of IFN therapy, 14 patients were each on prednisolone, acetazolamide or immunosuppressives. Only 3 patients were undergoing no other therapy at initiation of IFN treatment. At the end of follow-up, concomitant medication included low-dose prednisolone in 12 patients. However, only 3 patients were still on acetazolamide, and only 5 patients on immunosuppressives. Seven patients did not need any other therapy.

Side effects occurred frequently during IFN therapy. They included typical flu-like symptoms, especially after the first and second injection (23 patients), fatigue (10 patients), increased liver enzymes (9 patients), leucopenia (6 patients), alopecia (5 patients), transient detection of anti-thyroid auto-antibodies without developing clinical symptoms (2 patients), fibromyalgia and mild depression (1 patient each). Side effects were mostly dose dependent, improved during tapering of IFN alpha treatment, and led to its discontinuation in 1 patient only (no. 16; patient’s personal decision due to persisting fatigue).
<table>
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<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age at init of IFN therapy (yrs)</th>
<th>Diagnosis</th>
<th>Previous treatment (History)</th>
<th>Medication at initiation of IFN therapy</th>
<th>Duration of CME (days)</th>
<th>Eye</th>
<th>Foveal thickness in OCT (µm)</th>
<th>Visual acuity (VA, logMAR)</th>
<th>Response</th>
<th>Follow-up (months)</th>
<th>Foveal thickness in OCT (µm)</th>
<th>Visual acuity (VA, logMAR), and IFN dose at the end of follow-up</th>
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### Table 2

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<th>Mean foveal thickness and range (µm)</th>
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<td>3 days on IFN</td>
<td>2 weeks on IFN</td>
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<td>'Effective’ eyes</td>
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<td>571 (300–1020)</td>
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<td>528 (210–1000)</td>
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</table>
Discussion

CME represents a sight-threatening complication of uveitis and therefore necessitates enhanced therapeutic efforts, especially if it becomes chronic. In our case series of patients with quiescent uveitis but long-lasting and refractory CME, IFN alpha was very effective, demonstrating remission or partial remission of CME in 87.5% of patients or 87.5% of eyes, respectively. We were surprised by the quick response of CME to IFN therapy. However, our data do not show any correlation between the grade of efficacy of IFN therapy and the duration of CME or the underlying uveitis condition (anterior, intermediate or posterior).

To date, it is unknown how long after the occurrence of CME an improvement in vision may still be possible, should an effective treatment be found. Hence, for us, the primary aim of IFN treatment was not to gain an increase in VA but to prevent patients from further loss of vision. In our analysis, out of 35 eyes, in which IFN treatment was demonstrated to be effective or partly effective, 34 eyes showed an improvement or at least maintenance of VA during follow-up compared to values before IFN therapy. As long as there are no exact parameters to predict visual development in eyes with chronic CME, in our opinion it is absolutely indicated to undertake therapeutic efforts as well in eyes with very long-lasting CME.

So far, we are unable to answer the question of whether and when IFN treatment can be discontinued without a relapse of CME. Our attempt to stop IFN therapy after six months was not successful. Perhaps this was too early. The question of IFN discontinuation was also hampered by the fact that several patients were not willing to stop IFN therapy because they were concerned about possible relapses of CME. Probably, we have to consider that IFN alpha, similar to other immunomodulating drugs, will not be able to cure long-lasting CME. However, our results in patients with several years of follow-up demonstrate that it is possible to maintain the long-lasting absence of CME with very low IFN doses.

Although side effects occurred frequently, IFN treatment was generally well tolerated. Most of the side effects were of mild to moderate severity and dose dependent. Only one patient decided to discontinue treatment. In the remaining patients, this was neither medically necessary nor desired by the patients. For them the advantages of the therapy clearly outweighed its side effects. Overall, we observed the same spectrum of side effects that has been reported in patients with BD treated with IFN alpha.[6] However, the frequency of particular side effects, such as fatigue or
increased liver enzymes, was higher in our patients than in those with BD. This may be due to the fact that, on average, our patients were significantly older. Whereas BD patients are usually between 20 and 40 years old at the start of IFN treatment, 50 % of the patients in our analysis were older than 50 years, 25 % even older than 66 years. Moreover, in several of our patients concomitant medication included mycophenolate mofetil which was not, as we do with immunosuppressives in BD patients, discontinued before initiation of IFN alpha and which may have contributed to increasing liver enzymes.

Only one patient (no. 8) had no side effects at all, including no flu-like symptoms, which represent the most common side effect of IFN alpha affecting more or less all patients after the first and second injection. In this patient we detected pre-existing auto-antibodies against IFN alpha. To date, we have no explanation for this phenomenon. However, it confirms our experience that the occurrence of flu-like symptoms after initiation of IFN therapy might be a positive sign with regard to the response of a patient. Thus, if a patient displays no flu-like symptoms at all or, as happened in patient no. 7, therapy ceases to have an effect after the initial response, anti-IFN auto-antibodies have to be excluded.

To date, the possible mode of action of IFN alpha in CME can only be hypothesized. Keeping in mind the previous failure of anti-inflammatory and immunosuppressive drugs, the underlying mechanism of chronic uveitic CME is assumed to be not or not only inflammation but more probably a diffuse damage of the blood–retina barrier. Thus the effect of IFN alpha we have seen here might be different from an only anti-inflammatory or immunomodulating one. What we have clinically observed in our patients could correlate with the results of Gillies and Su, who in 1995 postulated that IFN alpha-2b, which is very similar to IFN alpha-2a, enhances the barrier function of bovine retinal microvascular endothelium in vitro. In their experiments IFN alpha-2b increased the electrical resistance in monolayers of bovine retinal capillary cells, decreased their permeability to inulin and enhanced their morphological differentiation. In contrast, IFN gamma did not demonstrate these effects. Thus, the authors hypothesized that IFN alpha might have therapeutic potential in diseases characterized by leakage of the vascular endothelium.[13]

There are some factors which may limit the evidence of this study, such as its retrospective nature, the heterogeneity of the patients regarding the type of uveitis
(anterior, intermediate or posterior) as well as the non-standardized dosing regimens for IFN and the concomitant medications.

In summary, our data demonstrate that IFN alpha is an effective and well-tolerated therapeutic option for long–lasting, otherwise refractory uveitic CME and therefore signifies a considerable advance in the treatment of such patients. However, there are still open questions that need to be answered in the near future regarding optimized dose regimens, co-medication, the possibility of discontinuation as well as better understanding of the exact mode of action.

References


Legends

Table 1:
Patient characteristics, previous and concomitant medication, follow-up and development of foveal thickness and visual acuity during IFN treatment.
Abbreviations: AU = anterior uveitis; IU = intermediate uveitis; PU = posterior uveitis; Ster = steroids; Acet = acetazolamide; MMF = mycophenolate mofetil; CsA = cyclosporine A; MTX = methotrexate; Aza = azathioprine; Cyclo = cyclophosphamide; Triam = triamcinolone; Bevac = bevacizumab; ppV = pars plana vitrectomy; Pred = prednisolone; OD = right eye; OS = left eye; OU = both eyes; E = effective; PE = partly effective; NE = not effective; Flu = flu-like symptoms; Fat = fatigue; Alop = alopecia; Liv = increased liver enzymes; Leuk = leucopenia; Fibro = fibromyalgia; Ant = auto-antibodies; Depr = depression; NAV = not available; NAP = not applicable.

Table 2:
Development of foveal thickness and visual acuity within the first 3 months of IFN treatment and at the end of follow-up in relation to the grade of efficacy. Abbreviation: NAP = not applicable.

Figure 1:
Dosing regimens for IFN alpha-2a.

Figure 2:
Overview of the efficacy of IFN treatment in the 24 patients.

Figure 3:
Development of foveal thickness in the 40 eyes.
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Competing Interest: None declared.
Patients no. 1-8, 12, 13

BW > 70 kg

- 6 mio IU per day for 1 month
- 4.5 mio IU per day for 1 month
- 3 mio IU per day for 1 month
- 3 mio IU every 2nd day for 1 month
- 3 mio IU 3x/week for 1 month
- 3 mio IU 2x/week for 1 month
- Stop of IFN

In case of a relapse

- 3 mio IU every 2nd day for 1 month
- 3 mio IU every 3rd day for 1 month
- 3 mio IU every 4th day for 1 month
- Further tapering to the lowest possible dose

Patients no. 9-11, 14-24

BW ≤ 70 kg

- 3 mio IU per day for 2 months
- 3 mio IU every 2nd day for 2 months
- 3 mio IU every 3rd day for 1 month
- 3 mio IU every 4th day for 1 month
- Further tapering to the lowest possible dose

- 6 mio IU per day for 1 month
- 4.5 mio IU per day for 1 month
- 3 mio IU per day for 1 month
- 3 mio IU every 2nd day for 1 month
- 3 mio IU 3x/week for 1 month
- 3 mio IU 2x/week for 1 month
- Stop of IFN
24 patients
Chronic uveitic CME

3 patients
IFN alpha-2a not effective

21 patients
Response to IFN alpha-2a

15 patients
IFN alpha-2a effective

6 patients
IFN alpha-2a partly effective

8 patients
IFN alpha-2a discontinued after 6 months in remission of CME

1 patient
Lost to follow-up

7 patients
No discontinuation of IFN alpha-2a after 6 months

7 patients
Re-institution of IFN alpha-2a due to relapse of CME