Non-pegylated and Pegylated Interferon Alpha-2a in Cutaneous T-cell Lymphoma and the Risk of Severe Ocular Side-effects

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Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of rare malignancies, primarily presenting in the skin (1, 2). Of these, mycosis fungoides (MF) represents the most frequent entity. Sézary syndrome (SS) is a type of CTCL, which, in contrast to MF, is characterized by the presence of malignant T-cells in the peripheral blood (3–5). For years, human recombinant interferon alpha-2a (IFNα-2a) was an important first-line treatment for MF stage >IIB and SS (6). Unfortunately, production of IFNα-2a was stopped in 2020 worldwide. Recently, pegylated forms of IFN emerged as alternative treatment options in CTCL, including pegylated IFNα-2a (PEG-IFNα-2a) (7, 8). However, since PEG-IFNα-2a is, to date, approved only for the treatment of viral hepatitis, its administration in CTCL represents an off-label approach. Whereas IFNα-2a had to be administered 3 times per week, its pegylated form leads to sustainably high blood levels with a single weekly dose (7, 9, 10). For both medications, the route of administration is a subcutaneous injection. This study reports on 4 patients with CTCL who received PEG-IFNα-2a at a weekly dosage of 180 µg as an off-label treatment, of whom 3 developed severe, drug-associated ocular side-effects. Furthermore, this study compared the risk of severe ocular side-effects with patients who received non-pegylated IFNα-2a. The aim of this study was to increase the awareness of PEG-IFNα-2a-induced ocular side-effects in patients with CTCL.

METHODS AND RESULTS

In this retrospective, observational, analysis, patients with CTCL who received IFNα-2a alone or IFNα-2a followed by off-label PEG-IFNα-2a between 2004 and 2020 at our centre at Department of Dermatology of the University Medical Center Mannheim, Germany were included. A total of 19 patients with SS and 8 with MF were identified. Four of these patients (3 with SS and 1 with erythrodermic MF stage IVA) received PEG-IFNα-2a as an off-label treatment for CTCL after manufacture production of non-pegylated IFN was stopped. All 4 patients were administered a PEG-IFNα-2a dosage of 180 µg once per week. Only ocular diseases that developed after initiation of IFNα-2a or PEG-IFNα-2a therapy were considered. Frequencies were compared using Fisher’s exact test.

Four of the 27 patients received off-label PEG-IFNα-2a treatment after IFNα-2a was discontinued. None of the 4 patients experienced relevant ocular symptoms during IFNα-2a therapy, whereas 3 of these patients (absolute risk 75.0%) developed severe ocular symptoms following conversion to pegylated IFNα-2a, forcing immediate discontinuation of therapy (Tables S1 and SII). In contrast, only 1 other patient (absolute risk 3.7%) developed severe ocular disease upon non-pegylated IFNα-2a therapy. As such, in the current study cohort, the risk of ocular severe adverse events was markedly and significantly higher upon PEG-IFNα-2a compared with non-pegylated IFNα-2a (relative risk 20.3, 95% confidence interval [95% CI]: 2.7–150.4, p=0.0035, Fisher’s exact test). All PEG-IFNα-2a-treated patients and 22 of the 27 IFNα-2a-treated patients (81.5%) received co-therapy with extracorporeal photopheresis (ECP). Despite ECP and paracetamol (to prevent flu-like side-effects) no matching medication/therapy of patients who developed ocular side-effects during PEG-IFNα-2a treatment was found. A list of all medications before and after onset of ophthalmological disorders is included in Table SII. One of the 3 PEG-IFNα-2a-treated patients who developed ocular side-effects had a medical history of cataract (patient 1). The medical histories of the other 2 patients were unremarkable concerning ocular diseases.

The single ocular adverse event observed upon non-pegylated IFNα-2a therapy represented microvascular branch occlusion of the superior temporal artery. In this patient, therapy was continued, but was complemented with acetylsalicylic acid (ASA). In the PEG-IFNα-2a-treated group, ocular side-effects included central retinal artery occlusion (Fig. 1), multiple infarcts of nerve fibre bundles, and drastic vision loss associated with sicca syndrome, which made discontinuation of therapy inevitable in all 3 patients (Table SII). We analysed all PEG-IFNα-2a-treated patients with regard to cardiovascular risk factors and events (11) to take other reasons for ocular diseases into account (Table SII). Notably, the 1 patient who did not develop ocular symptoms on PEG-IFNα-2a therapy has been prescribed ASA 100 mg as a daily medication for 5 years. All patients who developed ocular artery occlusion/infarcts either upon IFNα-2a or PEG-IFNα-2a therapy were approximately 70 years old (range 69–71 years), whereas the median age of all investigated patients at the time-point of IFNα-2a discontinuation was 66.5 years.

Fig. 1. Ocular fundus of a patient 3 days after initiation of pegylated interferon alpha-2a therapy. Fundus images of (A) right and (B) left eye. (B) Central retinal artery occlusion of the left eye has been diagnosed.
**DISCUSSION**

Side-effects of interferon-treatment include ophthalmological disorders, such as retinopathy, retinal artery or vein occlusion and optic neuropathy, which can lead to a decrease or loss of vision (12, 13). Therefore, importantly, patients should be adequately informed about ocular side-effects and ophthalmological examinations are recommended before initiation of therapy with interferons. Furthermore, patients who develop drug-associated ophthalmological conditions should undergo immediate ophthalmological workup. In general, retinopathy and retinal artery or vein occlusion upon interferon-treatment are rare. However, in the current study cohort, 3 out of 4 patients with CTCL developed severe, intolerable ophthalmological conditions during treatment with PEG-IFNα-2a. These patients all received IFNα-2a treatment immediately before initiation of PEG-IFNα-2a. None of these 3 patients had relevant ophthalmological side-effects during non-pegylated interferon therapy. Hence, we conclude that the newly developed ocular diseases were very likely associated with PEG-IFNα-2a. Based on the current study analysis, the risk of severe ocular side-effects was more than 20 times higher with PEG-IFNα-2a therapy compared with its non-pegylated form in patients with CTCL.

In a phase I/II study by Schiller et al. (7) on 13 patients with MF stages IB to III who received PEG-IFNα-2a treatment, dosages of 180 µg (4 patients), 270 µg (6 patients) or 360 µg (3 patients) were administered once per week. According to the authors, at least 3 patients were treated at all dose levels. In the 180 µg dosage group, 50% of patients reached complete response (CR), while the other 50% experienced stable disease (SD). CR rates were even higher in the 270 µg dosage group (67%). Of the 3 patients receiving 360 µg, 1 patient each exhibited CR, PR or SD, respectively (each 33%). Frequent adverse events (AE) included laboratory abnormalities, fatigue, acute flu-like symptoms and hepatic toxicity. However, ocular side-effects upon PEG-IFNα-2a treatment were not observed in this study (7). It must be noted that, in contrast to the study by Schiller et al. (7), the PEG-IFNα-2a-treated patients at our clinic exhibited a higher disease stage (MF IVa and SS) and received co-therapy with ECP. Although it might be possible that vascular occlusion occurs more often in high-stage CTCL; for example, due to atypical lymphocytes, no evidence for this theory is found for CTCL in the literature. In addition, to our knowledge, no ocular side-effects due to the combination-treatment of ECP and IFN have been reported to date.

A review by Kunkler et al. on the treatment of 161 oncological patients identified interferon-α (2b) as the most frequent medication that caused ocular toxicity (14). Of note, a study by d’Alteroche et al. determined the usage of pegylated IFNα as a risk factor for retinopathy in patients with viral hepatitis (13). To date, the underlying mechanism is not clear. Possible causes for interferon-induced retinopathy include enhanced leukocyte adherence to the vascular endothelium, interferon-induced endothelial dysfunction and immune complex deposition in the retinal vasculature (12).

This is the first study reporting on severe ocular side-effects in patients with CTCL treated with PEG-IFNα-2a. Based on the current study analysis, usage of PEG-IFNα-2a in high stage CTCL is strongly limited due to an inadequate risk-benefit ratio resulting from severe vision-threatening side-effects. Clearly, our observation should be verified in a larger and more diverse sample before general conclusions can be drawn. There might also be an association with co-treatment or pretreatment. However, based on our experience, we very strictly evaluate the indication of PEG-IFNα-2a therapy in patients with CTCL at our clinic. Our data at least underscore the need for a close monitoring for ocular events in patients with CTCL receiving PEG-IFNα-2a. The current study aims to improve awareness of ocular side-effects following pegylated IFNα-2a therapy in patients with CTCL and to provide the basis for further studies on this topic in order to make CTCL therapy safer.

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The authors have no conflicts of interest to declare.

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