SHORT COMMUNICATION

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

Jana D. ALBRECHT[1–3], Nadia NINOSU[1], Denise BARRY[1], Thomas ALBRECHT[4], Marthe-Lisa SCHAARSCHMIDT[1], Sergij GOERDT[1] and Jan P. NICOLAY[1–3]*

*[1]Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, DE-68167 Mannheim, [2]Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, [3]Section of Clinical and Experimental Dermatology, Medical Faculty Mannheim, Heidelberg University, Mannheim and [4]Institute of Pathology, Heidelberg University Hospital, University of Heidelberg, Heidelberg, Germany. *E-mail: jan.nicolay@umm.de*

Accepted May 4, 2022; Epub ahead of print May 4, 2022
Acta Derm Venereol 2022; 102: adv00722. DOI: 10.2340/actadv.v102.2487

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 >IIA 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 manufactural 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 SI 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 SI). 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 SI). 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.

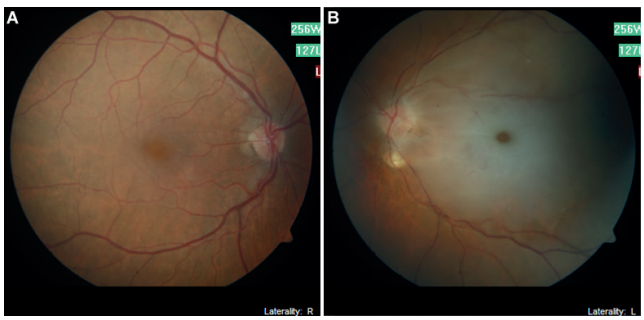

Fig. 1. Ocular fundus of a patient 3 days after initiation of pegylated interferon alpha-2a therapy. Fundus images of (A) right and (B) left eye. (B) Central retinal artery occlusion of the left eye has been diagnosed.

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.

ACKNOWLEDGEMENTS

The authors thank Professor Christel Weiss (Department of Medical Statistics, Biomathematics and Information Processing, Medical Faculty of the University of Heidelberg, Germany) for statistical analysis and Dr Ann-Katrin Regensburger (Department of Ophthalmology, University Hospital Wuerzburg, Germany) for providing the ocular fundus images.

The authors have no conflicts of interest to declare.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127: 2375–2390.
2. Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007; 110: 479–484.
3. Dobos G, Pohrt A, Ram-Wolff C, Lebbe C, Bouaziz JD, Battistella M, et al. Epidemiology of cutaneous T-cell lymphomas: a systematic review and meta-analysis of 16,953 patients. Cancers (Basel) 2020; 12: 2921.
4. Pulitzer M. Cutaneous T-cell lymphoma. Clin Lab Med 2017; 37: 527–546.
5. Dippel E, Assaf C, Becker JC, von Bergwelt-Baildon M, Beyer M, Cozzio A, et al. S2k guidelines – cutaneous lymphomas update 2016 – Part 1: classification and diagnosis (ICD10 C82 – C86). J Dtsch Dermatol Ges 2017; 15: 1266–1273.
6. Dippel E, Assaf C, Becker JC, von Bergwelt-Baildon M, Beyer M, Cozzio A, et al. S2k guidelines – cutaneous lymphomas update 2016 – Part 2: treatment and follow-up (ICD10 C82 – C86). J Dtsch Dermatol Ges 2018; 16: 112–122.
7. Schiller M, Tsianakas A, Sterry W, Dummer R, Hinke A, Nashan D, et al. Dose-escalation study evaluating pegylated interferon alpha-2a in patients with cutaneous T-cell lym-

phoma. J Eur Acad Dermatol Venereol 2017; 31: 1841–1847.
8. Husken AC, Tsianakas A, Hensen P, Nashan D, Loquai C, Beissert S, et al. Comparison of pegylated interferon alpha-2b plus psoralen PUVA versus standard interferon alpha-2a plus PUVA in patients with cutaneous T-cell lymphoma. J Eur Acad Dermatol Venereol 2012; 26: 71–78.
9. Harris JM, Martin NE, Modi M. Pegylation: a novel process for modifying pharmacokinetics. Clin Pharmacokinet 2001; 40: 539–551.
10. Zeuzem S, Welsch C, Herrmann E. Pharmacokinetics of peginterferons. Semin Liver Dis 2003; 23: 23–28.
11. Callizo J, Feltgen N, Pantenburg S, Wolf A, Neubauer AS, Jurklies B, et al. Cardiovascular risk factors in central retinal artery occlusion: results of a prospective and standardized medical examination. Ophthalmology 2015; 122: 1881–1888.
12. Rentiya ZS, Wells M, Bae J, Chen KJ, Chao AN, Turgeon N, et al. Interferon-alpha-induced retinopathy in chronic hepatitis C treatment: summary, considerations, and recommendations. Graefes Arch Clin Exp Ophthalmol 2019; 257: 447–452.
13. d'Alteroche L, Majzoub S, Lecuyer AI, Delplace MP, Bacq Y. Ophthalmologic side effects during alpha-interferon therapy for viral hepatitis. J Hepatol 2006; 44: 56–61.
14. Kunkler AL, Binkley EM, Mantopoulos D, Hendershot AJ, Ohr MP, Kendra KL, et al. Known and novel ocular toxicities of biologics, targeted agents, and traditional chemotherapeutics. Graefes Arch Clin Exp Ophthalmol 2019; 257: 1771–1781.