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Prof. Jin-Lei Wang
Director, Editorial Office
World Journal of Gastroenterology

Dear Professor Wang,

Please find enclosed the edited manuscript in Word format (file name: 4729-revision.docx)

Title: Ophthalmologic complications of antiviral therapy in hepatitis C treatment

Authors: Roderick O'Day, Mark C Gillies and Golo Ahlenstiel

The manuscript has been revised according to the reviewers' suggestions in keeping with the formatting guidelines (changes tracked).

In detail the following comments have been addressed (changes are marked in blue, underlined and bold):

1. The abstract has been revised and core tips section generated.
2. Format has been updated

Reviewer 01810532:

1. Reference have been added to the tables as suggested.
2. "*Timing of development of the IAR*" column:

We thank the reviewer for this suggestion but have decided not to include this column because we do not feel that the available data in the observational studies is sufficient to provide a robust answer to this issue. This is largely due to the diverse protocols of ophthalmic follow up used in these studies. As an example, three of the most recent and important observational studies have vastly different protocols for ophthalmic follow up: Vujosevic *et al* examined patients at baseline and then 3 monthly, Fouad *et al* at baseline, 12, 24 and 48 weeks and Mousa *et al* at baseline, 2, 4, 8, 12 and 24 weeks. The timing of onset of retinopathy is, accordingly, associated with the timing of ophthalmic follow up. A wide range of onset is seen in the

observational studies, mostly between two and twelve weeks. This is outlined in the text (page 6). If the editor feels, however, that this column would add to your readers understanding of this complication of antiviral therapy, we would be happy to include this information in table format.

Vujosevic S, Tempesta D, Noventa F, Mideni E, Sebastiani G. Pegylated interferon-associated retinopathy is frequent in hepatitis C virus patients with hypertension and justifies ophthalmologic screening. *Hepatology* 2012; **56**: 455-463 [PMID: 22331668 DOI: 10.1002/hep.25654]

Fouad YM, Khalaf H, Ibraheem H, Rady H, Helmy AK. Incidence and risk factors of retinopathy in Egyptian patients with chronic hepatitis C virus treated with pegylated interferon plus ribavirin. *Int J Infect Dis* 2012; **16**: e67-71 [PMID: 22115957 DOI: 10.1016/j.ijid.2011.09.022]

Mousa N, Besheer T, Gad Y, Elbendary A, Mokbel T, Abdel-Aziz A. Is combination therapy interferon and ribavirin in patients with chronic hepatitis C infection toxic for eyes? *J Ocul Pharmacol Ther* 2013; **29**: 345-348 [PMID: PMID: 23113644 DOI: 10.1089/jop.2012.0169]

Reviewer 00277503:

With regards to comments by this reviewer, we respectfully disagree. It is well established that IFN therapy, and not only in hepatitis C for that matter, is associated with a risk for ocular complications such as retinopathy. Thus, it is clearly mentioned in the product information for both, pegylated IFN-alpha 2a and 2b and therefore based on the product information alone treating physicians should be familiar with ocular complications of interferon therapy including retinopathy.

It is true that there is no high-quality controlled study to definitively delineate the causal link between antiviral therapy and the ocular events that occur during its use. However, with regards to interferon-associated retinopathy, we feel that there is little doubt that antiviral therapy is associated with this ocular event. This is an accepted fact in the literature, with over 20 observational studies undertaken to characterize it. We appreciate that there is a lack of controlled studies, nevertheless, a number of trials have monitored for the development of retinopathy in patients with untreated hepatitis C: For example, Schulman et al. during the course of their observational study followed 25 patients with hepatitis C that never received treatment and never developed retinopathy as compared to 42 patients that received interferon and ribavirin and had an incidence of *de novo* retinopathy of 69%. (**Schulman JA**, Liang C, Kooragayala LM, King J. Posterior segment complications in patients with hepatitis C treated with interferon and ribavirin. *Ophthalmology* 2003; **110**: 437-442 [PMID: 12578794]).

We would also like to highlight a few other issues. Firstly, our review is broader than an assessment of the incidence of interferon-associated retinopathy. We aim to address the key clinical questions of ocular safety faced by clinicians prescribing a course of antiviral therapy. The incidence of interferon-associated retinopathy is an important component of our review, however, we also discuss its clinical manifestations (including whether it causes vision loss), risk factors, pathogenesis and make suggestions as to its management and screening. Further, the atypical ocular events that have been found to occur during antiviral therapy are discussed and observations as to future studies are made. This therapy may have, however, ocular side

effects that need to be considered by the treating clinician. By focusing on the questions central to their patient, we hope that our review will be of use to the treating clinician.

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely Yours,



Dr. med. Golo Ahlenstiel

Clinical Senior Lecturer