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REVIEW

# Ophthalmologic complications of antiviral therapy in hepatitis C treatment

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## Abstract

Antiviral therapy consisting of interferon-alpha and ribavirin for chronic hepatitis C infection is associated with multi-system side-effects. Ophthalmologic complications are common and can be classified into two groups: interferon-associated retinopathy and atypical adverse events. Interferon-associated retinopathy has been investigated by multiple observational studies that have found widely divergent results. The clinical importance of this complication is, consequently, controversial. This review examines the literature with the specific goal of identifying the most important ophthalmologic issues facing the hepatologist prescribing antiviral therapy. Accordingly, it assesses the incidence of interferon-associated retinopathy, as well as its risk factors, pathogenesis, clinical manifestations and options for management using data from the observational studies. The likely benefit of a screening program, especially one targeting patients with the highest risk of developing interferon-associated retinopathy, is analysed. Atypical ophthalmologic adverse events occur less frequently than interferon-associated retinopathy during antiviral therapy for chronic hepatitis C infection. They often, however, lead to irreversible vision loss. We examine the reports of these adverse events - in individual case reports or case series and in the observational studies investigating interferon-associated retinopathy - to describe the spectrum of these adverse events, the likely outcome for patients and to highlight the most important areas of future clinical research.



**Key words:** Interferon; Hepatitis C; Ocular complications; Retinopathy

**Core tip:** Interferon-associated retinopathy is usually a benign, transient phenomenon with no lasting impact on visual function. It occurs in approximately 30% of patients receiving antiviral therapy for chronic hepatitis C infection. The main risk factors for its development appear to be hypertension and diabetes. Unless a clear benefit to patients can be shown, a screening program for the development of interferon-associated retinopathy is not justified. No conclusive evidence exists for a causal link between it and the atypical adverse events of antiviral therapy, which tend to cause irreversible vision loss.

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## INTRODUCTION

With 160 to 170 million infected people worldwide, hepatitis C virus (HCV) presents a major health care problem[1,2]. Current standard of care treatment consists of pegylated interferon alpha (PEG-IFNα) and ribavirin (RBV) for genotypes 2 to 6[3,4]. Boceprevir or telaprevir may be added to these for gentopye 1 infections[5]. Standard of care therapy is associated with side effects in many organs, the majority of which are attributed to interferon. Ophthalmologic complications can be classified into two groups: interferon-associated retinopathy and atypical adverse events.

## BACKGROUND

HCV, first identified in 1989, is a major cause of chronic liver disease[6,7]. It is the most common indication for liver transplantation in the Western world[8]. The natural course of HCV infection results in chronic disease in approximately 70% of patients, with the remaining 30% clearing the infection spontaneously[9]. Patients with chronic hepatitis C (CHC) infection can transmit HCV and are at risk of progression to liver cirrhosis and/or hepatocellular carcinoma[10].

The treatment of chronic hepatitis C infection has evolved over the past 20 years. Interferon alpha (IFNα) monotherapy was the first drug regimen found to induce viral clearance[11]. The combination of IFNα with oral RBV, a synthetic guanosine nucleoside, was subsequently found to increase the rate of viral clearance by 2-3 times[12,13]. Pegylation, the process of attaching IFNα to a polyethylene glycol moiety, both increased viral clearance and decreased the frequency of dosing of interferon to once weekly injections[14,15]. Most recently, treatment for HCV genotype 1 infection has been amended to include a third drug, either boceprevir or telaprevir, both of which are direct-acting antivirals[5].

## INTERFERON-ASSOCIATED RETINOPATHY

Interferon-associated retinopathy was first described by Ikebe *et al*[16] in 1990. It has been widely investigated since then. Our literature review identified 22 English-language reports of observational studies assessing its incidence and clinical features[17-38]. These studies all performed ophthalmological examinations during a course of antiviral therapy for chronic hepatitis C monitoring for interferon-associated retinopathy and atypical adverse events. They are summarised in Tables 1 and 2. Table 1 presents studies where more than half of the patients were treated with IFNα based regimens ($n$ = 10), whereas Table 2 presents studies with majority PEG-IFNα treated patients ($n$ = 12).

### *What are the clinical manifestations of interferon-associated retinopathy?*

Interferon-associated retinopathy can be unilateral or bilateral and typical findings on slit lamp biomicroscopy or fundus photography are cotton wool spots and/or retinal hemorrhages (Figure 1). These lesions usually occur at the posterior pole within 2 disc diameters from the optic disc[20,39]. Most commonly, it has a benign course with no impact on vision (Tables 1 and 2). It usually self-resolves during a course of antiviral therapy, or shortly thereafter, without requiring a reduction in dose (Tables 1 and 2).

### *How common is interferon-associated retinopathy?*

The observational studies have found a wide range of incidence of interferon-associated retinopathy during antiviral treatment for chronic hepatitis C infection, from under 4% to over 60% (Tables 1 and 2). Different protocols of ophthalmologic follow up and differences in patient populations are the most obvious causes of these divergent results. Other potential contributors to be considered are RBV combination therapy versus interferon monotherapy and whether different forms and doses of interferon-α are more likely to develop interferon-associated retinopathy.

Observational studies that had infrequent or symptom-initiated ophthalmologic examinations were more likely to find a lower incidence of interferon-associated retinopathy than those with more rigorous ophthalmologic follow up (Tables 1 and 2). Interferon-associated retinopathy most commonly develops between 2 and 12 wk after the initiation of antiviral therapy[17,22,32,36]. It is a transient phenomenon lasting from a few weeks to years[30,32,36]. Study protocols that did not examine patients multiple times within the first 6 mo of starting treatment were predisposed to underreport rates of interferon-associated retinopathy[34,38]. Similarly, most patients who develop interferon-associated retinopathy have no visual symptoms (Tables 1 and 2). Thus, protocols that initiated ophthalmologic review only once a patient became symptomatic would, therefore, also result in underreporting[33,35]. Four of the five studies reporting the lowest incidences of interferon-associated retinopathy displayed at least one of these two factors[33-35,38].

Inclusion of patients with retinopathy at baseline skewed studies towards over-reporting of the incidence of interferon-associated retinopathy. No study has specifically assessed the clinical course of patients who have retinopathy from other causes prior to starting antiviral therapy, such as diabetes or hypertension. It is logical, however, that these patients would be at higher risk of having retinopathy during treatment than eyes without retinopathy at baseline. In the 22 observational studies considered in this review, 22 patients were identified as having retinopathy at baseline and 17 (77%) of these had progression of retinopathy[26,29,31]. In one trial, half

**Table 1 Incidence of interferon-associated retinopathy in observational studies during which more than half of the patients are treated with interferon-α based regimens for chronic hepatitis C**

| Study | IAR incidence | Country | Timing of examinations | Comment |
|---|---|---|---|---|
| Nagaoka *et al*[17] | 22 of 36 (61%) | Japan | Baseline, 2, 4, 8, 16 and 24 wk | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. Age was a risk factor for the development of IAR. HTN and DM were not. Atypical adverse events: nil reported. |
| d'Alteroche *et al*[18] | 36 of 144 (25%)[1] | France | Baseline and then 3 monthly | IAR: No reduced VA in eyes that developed IAR. No dose reduction for management of IAR. HTN (9 of 11), receiving PEG-IFNα and older age were more likely to develop retinopathy. Insufficient numbers with DM ($n$ = 1). Atypical adverse events: nil reported. |
| Okuse *et al*[19] | 14 of 73 (19%) | Japan | Baseline, 2, 4, 12 and 24 wk | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. HTN significantly associated with development of IAR (5 of 15), T2DM not (1 of 2). Atypical adverse events: nil reported. |
| Schulman *et al*[20] | 27 of 42 (64%) | United States | Baseline and then 2-3 monthly for 4-20 mo | IAR: therapy discontinued in two patients with multiple CWS, one with mild decrease in VA. All other patients with IAR continued with treatment. High doses of interferon used, up to 5MIU/d. HTN was not predictive of the development of IAR. Insufficient eyes for analysis of DM as risk factor ($n$ = 2). Atypical adverse events: permanent peripheral monocular scotoma in 1 patient. Disc edema in 1 patient with a background of rheumatoid arthritis; no long term vision loss. |
| Jain *et al*[21] | 8 of 19 (42%) | Canada | Baseline and then monthly | IAR: no change in VA in any patient with retinopathy. IAR resolved during study period in all but one patient. No dose reduction for management of IAR. Atypical adverse events: nil reported. |
| Saito *et al*[22] | 28 of 81 (35%) | Japan | Baseline and then 2 weekly | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. IAR was more likely in older patients and those with DM and/or HTN. Atypical adverse events: nil reported. |
| Kadayifcilar *et al*[23] | 7 of 20 (35%)[2] | Turkey | Baseline, monthly during treatment and 1 yr after completing treatment. | IAR: one of 7 with CWS at the macular had dose reduction by 1/2 for decreased VA. Full resolution in 4 wk. Otherwise no dose reduction for IAR. 16 of 20 patients had backgrounds of chronic renal failure. Atypical adverse events: unilateral BRVO in 1 patient with a background of CRF resulting in normal visual acuity at 12 mo but residual upper quadrantanopia. |
| Sugano *et al*[24] | 6 of 25 (24%) | Japan | Baseline and then 4 weekly | IAR: not available. Atypical adverse events: not available. |
| Kawano *et al*[25] | 36 of 63 (57%) | Japan | Baseline, 1, 2 and 4 wk and then 4 weekly until 6 mo after completing treatment | IAR: no dose reduction for 35 of 36 patients with IAR. Significantly higher incidence of retinopathy in patients with diabetes (11 of 12) and HTN (4 of 5). Atypical adverse events: severe RH in 1 patient with a background of DM; no long term vision loss. |
| Hayasaka *et al*[26] | 14 of 40 (35%)[3] | Japan | 1 mo prior to starting treatment and 2 weekly during treatment. | IAR: no reduced VA in eyes that developed IAR Not clear, but seems that interferon was ceased if developed IAR. Three patients with retinopathy at baseline all showed progression. Atypical adverse events: nil reported. |

[1]Twelve patients treated for chronic hepatitis B infection were excluded from the incidence data shown; [2]Sixteen patients treated for chronic hepatitis B infection were excluded from the incidence data shown; [3]Three patients that had baseline diabetic retinopathy were excluded from the incidence data shown. BRVO: Branch retinal vein occlusion; CRF: Chronic renal failure; CWS: Cotton wool spots; DM: Diabetes; HTN: Hypertension; IAR: Interferon-associated retinopathy; MIU: Million international units; PEG: Pegylated; IFN: Interferon; RBV: Ribavirin; RH: Retinal hemorrhage; VA: Visual acuity; VEGF: Vascular endothelial growth factor.

of the patients with retinopathy at baseline had resolution of retinopathy during treatment[31]. In the other trials that identified patients with retinopathy, all eyes with baseline retinopathy had progression during the course of treatment.

When patients with baseline retinopathy and studies with suboptimal ophthalmologic follow up are excluded, 313 of 1007 (31%) patients developed interferon-associated retinopathy with a range of 8%-64% (Tables 1 and 2). The size of this corrected range implies that these factors do not fully explain the wide range of incidence of interferon-associated retinopathy.

Differences in the dose and type of interferon used in the observational studies have been proposed as key reasons for the wide range of incidence of interferon-associated retinopathy found. Early studies of IFNα for

**Table 2 Incidence of interferon-associated retinopathy in observational studies during which more than half of the patients were treated with pegylated interferon-α based regimens for chronic hepatitis C**

| Study | IAR incidence | Country | Timing of examinations | Comments |
|---|---|---|---|---|
| Mousa *et al*[27] | 8 of 98 (8%) | Egypt | Baseline, 2, 4, 8, 12 and 24 wk then every 3 mo | IAR: seven of 8 patients with IAR had no reduction in VA. No dose reduction for management of IAR. Combined DM and HTN gave relative risk of 6.5 of developing IAR. Atypical adverse events: vitreous hemorrhage from retinal tears with retinal detachment requiring vitrectomy in 1 patient, final visual outcomes were not described. |
| Fouad *et al*[28] | 22 of 84 (26%) | Egypt | Baseline, 12, 24 and 48 wk and 1 mo after completing treatment | IAR: no reduced VA in eyes that developed IAR. Three patients with IAR developed retinal hemorrhages and treatment was ceased. Logistic regression found HTN (9 of 12) and DM (13 of 16) to be predictors of developing IAR. Atypical adverse events: NAION in 2 patients and optic neuritis in 1 patient, final visual outcomes for these patients were not described. |
| Vujosevic *et al*[29] | 21 of 97 (22%)[1] | Canada | Baseline, 3 and 6 mo and 3 mo after completing treatment | IAR: all patients with pre-existing retinopathy, 9 patients, had worsening of retinopathy during treatment. Factors associated with developing IAR were age, metabolic syndrome, HTN, cryoglobulinemia and pre-existing intraocular lesions. Using multivariate analysis only HTN was a significant predictor of developing IAR. Insufficient number of patients with DM ($n$ = 5). Atypical adverse events: bilateral BRVO in one patient with a background of HTN resulting in irreversible vision loss in the left eye only. |
| Lim *et al*[30] | 5 of 10 (50%)[2] | Korea | Baseline and then 3 weekly for 6 mo | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. Atypical adverse events: unilateral CRVO in 1 patient with a background of DM resulting in irreversible vision loss. |
| Mehta *et al*[31] | 18 of 64 (28%)[3] | United States | Baseline, 3 and 6 mo | IAR: no reduced VA in eyes that developed IAR. 1 of 88 ceased treatment for asymptomatic IAR. Male only cohort. HTN and DM not significant predictor of developing IAR. Poor follow up rates - 69% had an eye exam within the first 12 weeks of starting treatment. Atypical adverse events: nil reported. |
| Kim *et al*[32] | 11 of 32 (34%) | Korea | Baseline, 4, 8, 12, 16, 24, 36 wk | IAR: no reduced VA in eyes that developed IAR alone. No dose reduction for management of IAR. All retinal lesions spontaneously resolved. 91% of retinopathy developed within 2 mo, but 1 occurred at 4 mo. HTN significantly associated with development of IAR (6 of 10), T2DM not (1 of 2). Atypical adverse events: unilateral BRVO in 1 patient with background of HTN resulting in irreversible vision loss. |
| Panetta *et al*[33] | 7 of 183 (4%) | United States | Baseline and repeat examination when visually symptomatic | IAR: three patients ceased treatment. Two with visual symptoms associated with IAR. 46% of patients had HTN and 16% had DM - neither predictive of developing IAR. Atypical adverse events: nil reported. |
| Malik *et al*[34] | 3 or 38 (8%) | United Kingdom | Baseline, 3 and 6 mo. Low follow up rates | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. Atypical adverse events: nil reported. |
| Andrade *et al*[35] | 5 of 34 (15%) | Spain | Baseline, at cessation of treatment and when visually symptomatic | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. Higher serum VEGF in patients with retinopathy and/or subconjunctival hemorrhage. Atypical adverse events: cystoid macular edema in 1 patient, final visual outcomes were not described. |
| Ogata *et al*[36] | 25 of 69 (36%) | Japan | Baseline and then regularly for 6 months | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. 46% (13 of 28) treated with IFNα developed IAR compared to 29% (12 of 41) treated with PEG-IFNα. Atypical adverse events: no details. |
| Chisholm *et al*[37] | 5 of 10 (50%) | United Kingdom | Baseline, 2, 4, 8, 12 and 24 wk and 12 wk after completing treatment | IAR: no dose reduction for management of IAR. Atypical adverse events: nil reported. |
| Cuthbertson *et al*[38] | 4 of 25 (16%) | United Kingdom | 3 mo after starting treatment or when visually symptomatic | IAR: no reduced VA in eyes that developed IAR. No dose reduction for management of IAR. Atypical adverse events: nil reported. |

[1]Nine patients that had baseline retinopathy were excluded from the incidence data shown. All 9 had progression of retinopathy; [2]Thirty-six of the 46 patients treated for chronic hepatitis B infection were excluded from the incidence data shown; [3]Ten patients that had baseline diabetic retinopathy were excluded from the incidence data shown. Five of these had resolution of retinopathy on subsequent eye exams. BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; DM: Diabetes; HTN: Hypertension; IAR: Interferon-associated retinopathy; NAION: Non-arteritic anterior ischemic optic neuropathy; PEG: Pegylated; IFN: Interferon; RBV: Ribavirin; VA: Visual acuity; VEGF: Vascular endothelial growth factor.

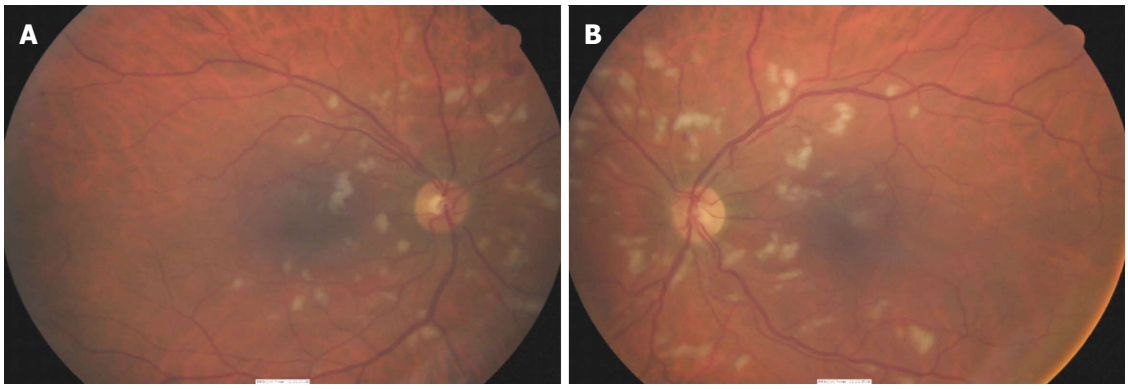


**Figure 1 Fundus photographs of a 60-year-old male treated with high dose interferon-α for renal cell carcinoma.** These images show bilateral, typical interferon-associated retinopathy consisting of cotton wool spots and retinal hemorrhages surround the optic disc.

age-related macular degeneration found that the incidence of interferon-associated retinopathy was dose-dependent[40]. Consistent with this, the study with the highest incidence analysed in this review used the highest dose of interferon: 3-10 million units IFNα subcutaneous injection daily[20]. It has also been proposed that PEG-IFNα, which has a ten-fold longer serum-half life than conventional IFNα, may cause interferon-associated retinopathy more readily[36]. This would contrast with the systemic side effect profile of PEG-IFNα, which appears to be similar to conventional IFNα[14,15]. One large study found a significantly higher incidence of interferon-associated retinopathy in patients treated with PEG-IFNα than patients treated with IFNα of 45% *vs* 19%[18]. Two other smaller trials have found contradicting non-significant trends[32,36]. Ultimately, the significance of this issue is questionable since it is unlikely that small differences in the incidence of interferon-associated retinopathy, which is largely benign, will alter these use of PEG-IFNα over IFNα or the dose used to treat chronic hepatitis C infection.

The effect of ribavirin on the incidence of interferon-associated retinopathy is unclear due to conflicting results found by the observational studies that addressed this issue. It is used for its synergistic effect with interferon therapy, but does not result in HCV eradication as a monotherapy[12,13]. Conjunctivitis is the only ophthalmologic adverse event regularly associated with RBV[41]. It has, however, been suggested that combination therapy with RBV may increase the risk of interferon-associated retinopathy as compared to interferon monotherapy[21,30]. Lim *et al*[30] found a significantly higher rate of interferon-associated retinopathy in patients with chronic hepatitis C infection treated with PEG-IFNα and RBV combination therapy than patients with chronic hepatitis B infection treated with PEG-IFNα monotherapy, that is 50% *vs* 14%. These results are difficult to interpret as chronic hepatitis C infection is associated with a hypercoagulable state, which itself may confer an increased risk of developing interferon-associated retinopathy[42]. Further studies are required to determine the impact of RBV on the development of interferon-associated retinopathy.

### *Why does interferon-associated retinopathy occur?*

The pathogenesis of interferon-associated retinopathy is yet to be fully elucidated. Its clinical manifestations, cotton wool spots and retinal hemorrhages suggest an ischemic mechanism. These changes are most commonly associated with diabetes or hypertension[43,44]. It has been proposed that endothelial dysfunction, as evidenced by the failure of dilatation of retinal arterioles in response to wall shear stress in eyes that subsequently developed interferon-associated retinopathy, is the central process leading to retinal ischemia[17]. Endothelial dysfunction, it is proposed, causes platelet aggregation and leukocyte adherence to vascular endothelium[17]. These "immune complexes" act as microthrombi and cause focal retinal infarction[39]. This hypothesis is supported by data suggesting IFNα may promote pro-thrombotic autoantibody production mediated by T cell activation[45]. Further, IFNα may increase production of the highly potent intravascular aggregator of platelets, plasma-activated complement 5[24]. Moreover, IFNα increases leukocyte adherence to the vascular endothelium resulting in leukocyte trapping in the retinal microcirculation[46].

### *Does interferon-associated retinopathy causes vision loss?*

Cotton wool spots and retinal hemorrhages are not usually associated with vision loss. They would if they occurred at the central macula, but the *fovea centralis* is avascular. Nevertheless, there are at least two reported cases of irreversible visual disturbance after interferon-associated retinopathy that consisted of cotton wool spots and/or retinal hemorrhages only, i.e. that were not associated with an atypical adverse event[20,47]. One patient developed a permanent peripheral monocular scotoma in the same eye due to interferon-associated retinopathy consisting of cotton wool spots and retinal hemorrhages only[20]. The other patient developed permanent bilateral reduced visual acuity and visual field defects after isolated interferon-associated retinopathy[47]. Such cases, however, are rare; in most patients isolated interferon-associated retinopathy causes no impact on visual func-

tion (Tables 1 and 2). Indeed, in the 1289 patients, only 1 had interferon-associated retinopathy that caused vision impairment[20] (Table 1). Importantly, vision loss that occurs whilst taking antiviral therapy is usually due to the development of an atypical adverse event.

### Are there any groups that are at greater risk for developing interferon-associated retinopathy?

Hypertension and diabetes mellitus appear to be risk factors for the development of interferon-associated retinopathy; however, this has not been established unequivocally. Such a finding would be theoretically consistent with the proposed pathogenesis of interferon-associated retinopathy. The same methodological problems that resulted in the diversity in the incidence of interferon-associated retinopathy found by the observational studies described above also apply to this issue. Compounding this, the numbers of patients with diabetes or hypertension that developed interferon-associated retinopathy in most studies were too small to enable meaningful statistical analysis (Tables 1 and 2).

Observational studies of standard of care therapy for chronic hepatitis C infection during which at least 10 patients developed interferon-associated retinopathy identified diabetes and hypertension as its main risk factors[28,29,31,32] (Table 2). Fouad *et al*[28] performed a comprehensive study of 84 patients treated with standard of care therapy in Egypt with extensive ophthalmologic follow up. Their study, which included a number of patients with hypertension and diabetes, 12 and 16 respectively, found that both predicted the development of interferon-associated retinopathy using logistic regression analysis. By contrast, Mehta *et al*[31] found higher rates of interferon-associated retinopathy in patients with hypertension and diabetes, but the differences were not statistically significant. Their study had sufficient numbers of patients with these conditions - 13 patients with diabetes mellitus and 31 with hypertension - however, ophthalmological follow up was poor with less than 70% of patients receiving an eye exam within 12 weeks of starting standard of care therapy. Both Vujosevic *et al*[29] and Kim *et al*[32] performed observational studies with good numbers and adequate ophthalmologic follow up. They both found hypertension to be a significant predictor of the development of interferon-associated retinopathy using univariate and multivariate analysis. Diabetes mellitus was not found to be a significant predictor of the development of interferon-associated retinopathy using multivariate analyses in either, but the cohorts only had 5 and 2 patients with diabetes mellitus, respectively. In Vujosevic *et al*[29], a higher percentage of patients with diabetes mellitus developed interferon-associated retinopathy on univariate analysis. There were insufficient numbers of patients with diabetes mellitus in earlier studies involving IFNα to assess its effect[18-20]. Studies with adequate numbers of patients with diabetes mellitus tended to find it as a risk factor for the development of interferon-associated retinopathy.

No other patient characteristics that have been assessed have been found to predict the development of interferon-associated retinopathy (Tables 1 and 2). Older age has been suggested to represent a greater risk for its development, but this has not been a consistent finding[17,19,22,29]. The larger studies that assessed risk factors identified above did not implicate age, with the exception of Fouad *et al*[28], Vujosevic *et al*[29], Mehta *et al*[31] and Kim *et al*[32]. An association of age with the development of interferon-associated retinopathy may be because it is also associated with a higher risk of diabetes and hypertension.

### If a patient develops interferon-associated retinopathy, what should be done?

There is a growing body of clinical experience that it is safe to continue standard of care therapy with no dose reduction in patients who develop interferon-associated retinopathy so long as they do not have reduced visual acuity or other visual symptoms which would suggest the development of an atypical adverse event (Tables 1 and 2). Various dose reduction and cessation regimens aiming to minimise the impact of interferon-associated retinopathy have been used. One study described the dose reduction regimens used by two clinicians in their management of 38 patients with interferon-associated retinopathy over 10 years[18]. This study did not compare outcomes between the groups. In fact, no formal comparator studies have assessed different strategies of managing standard of care dosing in patients who develop interferon-associated retinopathy. There is, therefore, no good evidence to guide whether interferon therapy should be modified or discontinued when interferon-associated retinopathy has been diagnosed. It is, however, well established that dose reduction of interferon increases the risk of treatment failure. Thus, dose reduction should be considered carefully.

### Should we screen for interferon-associated retinopathy?

No consensus has been reached regarding the need to screen for interferon-associated retinopathy. Cuthbertson *et al*[38] argue that due to the low incidence of interferon-associated retinopathy and its generally benign course there is no need for routine screening. By contrast, Vujosevic *et al*[29] support a screening program targeting hypertensive patients, who they found to be at greater risk of developing interferon-associated retinopathy. Mousa *et al*[27] propose that screening should only be for patients with both diabetes and hypertension, but not those with either in isolation. On the other end of the spectrum, Schulman *et al*[20] considered close ophthalmological follow up for all patients as appropriate.

We propose that screening for interferon-associated retinopathy should only be performed if it meets the following criteria: (1) it can be used to predict the patients at risk for developing pathology that causes irreversible visual impairment; and (2) early treatment of these patients will reduce the chance of the development of that pathology. As discussed above, interferon-associated

retinopathy, with a few exceptions, has a generally benign course. Screening for interferon-associated retinopathy may be justified if it can be proved that eyes that develop it are more likely to develop an atypical adverse event, which in turn causes poor visual outcomes. Evidence of such a relationship does not exist to date. In addition, it would need to be established that early detection would enable an intervention that reduces the severity of that atypical adverse event. For example, it would need to be shown that strict risk factor control after the diagnosis of interferon-associated retinopathy prevents the development of an atypical adverse event[48]. With the current state of the evidence, a screening program for interferon-associated retinopathy, even one including only those patients at high risk of developing it, does not appear to be justified.

## ATYPICAL ADVERSE EVENTS

Many atypical ophthalmologic adverse events have been encountered during antiviral therapy for chronic hepatitis C infection. The most common of these are retinal vein occlusion (RVO)[21,29,30,32,49-55], and non-arteritic anterior ischemic optic neuropathy (NAION)[28,49,56-59]. Other atypical adverse events that have been reported include ocular myasthenia[60,61], optic neuritis[62], Vogt-Koyanagi-Harada disease[49,63-67], ocular sarcoidosis[68,69], ocular toxocariasis[70], neurovascular glaucoma[71], conjunctival hemorrhage[20,26,35], macular edema[72-74], oculomotor nerve palsy[75], trichomegaly[23] and retinal detachment[76].

The mechanisms that cause an atypical adverse event may be distinct from the ischemic mechanism thought to be responsible for interferon-associated retinopathy. For example, there is growing evidence that interferon is directly toxic to the optic nerve[62,77,78]. Chisholm *et al*[37] found high levels of subclinical retinal toxicity, measured as aberration on multifocal electro-retinogram, in patients treated with IFNα and ribavirin. The electro-retinogram changes were not correlated with clinical signs of interferon-associated retinopathy, cotton wool spots an retinal hemorrhages[37].

Atypical complications of antiviral therapy often result in dramatic, irreversible vision loss. In an exhaustive review of NAION that occurred during interferon therapy, half of the 36 documented cases of this complication suffered from permanent visual dysfunction[56]. Similarly, in a recent review of RVO during interferon-α therapy, only 4 of 14 cases had full recovery of vision[53]. Other atypical complications also lead to long-term visual impairment. In particular, inflammatory complications of antiviral therapy, such as Vogt-Koyanagi-Harada disease, also tend to have poor visual outcomes[49,67]. In the 22 observational studies identified by our literature review involving 1287 patients treated with antiviral therapy for chronic hepatitis C infection, 12 (0.93%) patients developed an atypical adverse event. Five (0.39%) of these led to documented irreversible vision loss and 4 (0.31%) did not describe final visual outcomes (Tables 1 and 2).

The relationship between interferon-associated retinopathy and the atypical complications of antiviral therapy is unclear. Indeed, there is limited evidence that atypical adverse events are caused by interferon treatment and not merely due to chance[56]. The most common complications, AION and RVO, are both vascular in nature. It has been suggested that there may be common elements between the pathogenesis of these complications and interferon-associated retinopathy[49,56]. Certainly, there are many cases in the literature where AION and RVO are concomitant with interferon-associated retinopathy[51,55,79]. As the atypical complications are the key causes of vision loss during antiviral therapy and interferon-associated retinopathy is common and well-described, any relationship between them should be explored in depth.

## THE FUTURE

The standard of care regimen is in the process of a major re-evaluation after two major breakthroughs. Firstly, multiple HCV-specific direct-acting antivirals are at various stages of development and two of these have been approved for the treatment of genotype 1 HCV infection[80-83]. Secondly, a host genetic polymorphism near the interleukin-28B (IL28B) gene on chromosome 19 that strongly predicts spontaneous and standard of care-induced recovery from infection was identified by four groups in 2009 and 2010[84-87].

Despite the advent of direct-acting antivirals, it is likely that PEG-IFNα will remain an integral part to HCV treatment regimens for the foreseeable future[5]. When used as monotherapy, rapid virological resistance develops *in vivo* to the first generation direct-acting antivirals - telaprevir and boceprevir - inhibiting antiviral response[88]. Moreover, the antiviral activity of these first generation direct-acting antivirals, the only approved by the FDA, appears genotype specific[89]. Accordingly, they are presently recommended for use in genotype 1 chronic HCV only[5]. Investigations of second generation direct-acting antivirals are currently under way, so eventually we very likely will have interferon free-regimens[90,91]. RBV, however, remains a core component of most of these regimens.

A controversial issue at present is whether patients, particularly those with IL-28B non-responder genotypes, should defer treatment for chronic hepatitis C infection until new, more effective regimens become available[92]. Considering that the most common interferon-associated retinopathy seems to be largely benign in most patients, we do not feel that there is enough evidence for the potential risk for ophthalmologic complications to significantly impact this discussion as the most common is largely benign and there is no obvious, established link between interferon and the rarer, more severe adverse events.

## CONCLUSION

In summary, the most common complication of antiviral

therapy for chronic hepatitis C infection is interferon-associated retinopathy. This is usually a benign, self-limiting phenomenon with no lasting impact on visual function. It occurs in approximately 30% of patients undergoing standard of care therapy, however, there is significant variability in its incidence in observational studies. Hypertension and diabetes mellitus appear to be the most important risk factors for its development. The rarer, atypical adverse events of antiviral therapy often cause irreversible vision loss. The most common of these are RVO and NAION. To date, no definitive pathogenic link has been proven between antiviral therapy or interferon-associated retinopathy and any of the various atypical adverse events. If such a relationship can be found, screening for interferon-associated retinopathy may be justified as a means to prevent the development of an atypical adverse event. Newer direct-acting antivirals are likely to outpace further study into this area, making interferon-free antiviral therapy likely in the next 5 years.

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