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Interferon associated retinopathy

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PERSPECTIVE

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Interferon associated retinopathy has been increasingly reported in Japan. In fact, most reports have appeared in the Japanese literature. In the present study, we review these articles.

Interferon was originally described as a factor capable of inducing antiviral activity.[1] Since then, the factor has been found to have antitumour activity in human neoplasms including metastatic renal cell carcinoma,[2] skin melanoma,[3] Kaposi's sarcoma,[4] and haemangiomatosis.[5] The agent also inhibits vascular endothelial cells[6] and regressed experimental iris neovascularisation.[7] In Europe, interferon has been used in an attempt to treat dendritic keratitis.[8] In the USA, it has been used mainly to treat subretinal neovascularisation in age related macular degeneration.[9–11] In Australia, antifibrotic effects of interferon have been employed to treat glaucoma filtering surgery and to manage ocular cicatricial pemphigoid.[12 13]

Interferons have been clinically used in the treatment of viral and malignant diseases. Subsequently, a variety of adverse effects of interferon use has been reported.[14] Quesada *et al* [14] noted toxic reactions from interferon, including acute side effects of an influenza-like syndrome consisting of fever, chills, myalgias, arthralgias, and headache. Fatigue has been the most prevalent chronic toxicity. Toxicities of the central nervous system, haematopoietic system, gastrointestine, renal function, skin, cardiovascular system, musculoskeletal system, and endocrine also have been described. However, these authors did not mention the ocular toxicity.[14]

Typical interferon associated retinopathy

In 1990, Ikebe and associates[15] first reported a 39 year old patient with retinal haemorrhages and cotton wool spots following intravenous administration of interferon. Since 1992, interferon therapy for viral hepatitis has been used at many hospitals in Japan; there are possibly more than 1.6 million patients with type C hepatitis in Japan and interferon use has been allowed by Health Insurance of Japan. Since 1993, ocular complications following interferon therapy have been reported mainly in Japan,[16–47] although Bauherz and associates,[48] Guyer and coworkers,[11] Klose *et al*,[49] and Vegh *et al* [50] have also demonstrated interferon associated ocular toxicity.

Typical ocular lesions include cotton wool spots and retinal haemorrhages at the posterior fundus, particularly around the optic disc.[16 21 22 32 37 40 43] Cotton wool spots and retinal haemorrhages may occur alone or together.[37 42] Retinal haemorrhages appear as superficial linear and patchy forms or as white centred bleeding. The retinopathy may develop unilaterally or bilaterally.[37] Blocking of background fluorescence by retinal haemorrhages and nonperfused areas at the cotton wool spots can be seen by fluorescein angiography.[21 37]

An initial dose (3×10^6, 6×10^6, or 9×10^6 U/day) of interferon is usually administered intravenously or intramuscularly three or six times per week for several weeks, and then the agent is gradually tapered. The retinopathy has reportedly developed 28 to 94 days,[17] 2 weeks to 5 months,[21] 2 weeks to 3 months,[22 43] 2–18 weeks,[35] and 2–15 weeks[42] after initiation of interferon therapy. The retinopathy may disappear spontaneously during therapy or rapidly after stopping therapy.[17 21 22 29 37] Despite the retinopathy, subjective complaints have been uncommon, and visual acuity has not always been impaired.[21 22 29 37] Most patients with interferon associated retinopathy can continue with the planned course of interferon therapy.

A large scale study of the incidence of interferon associated retinopathy has not been performed. Incidences of retinopathy in patients receiving interferon have been reported to be 18% (2/11),[25] 35.5% (12/34),[43] 40% (8/20,[16] 18/45[20]), 42% (10/24),[35] 46% (23/50),[32] 50% (10/20),[26] 61% (45/74),[22] 73.3% (22/30),[44] and 86% (43/50).[40] The incidence is thought to depend on the initial dose of interferon.[21 29 37 42] Particularly, patients receiving interferon, 9×10^6 U/day, six times per week, have shown a high frequency of retinopathy (Table 1).[42] The incidence also depends on the presence of diabetes mellitus (Table 1): patients with diabetes have shown a high frequency of retinopathy.[16 22 32 37 40 42] Also, the incidence is possibly influenced by the frequency of fundus examination,[40] because the subtle retinopathy may disappear after the long intervals between examinations. The incidences of interferon associated retinopathy in patients with type B hepatitis and malignant diseases are roughly similar to those with type C hepatitis.[21 22] No difference in the incidence of retinopathy between interferon alfa and beta has been found.[28 46]

Atypical interferon associated ocular complications

In addition to retinal haemorrhages and cotton wool spots, uncommon ocular lesions develop after the start of

Table 1 Initial dose of interferon alfa-2b

Initial dose of interferon alfa-2b (U/day, 6 times per week)	*Patents without diabetes mellitus (n=49)*		*Patients with diabetes mellitus (n=9)*	
	Retinopathy		*Retinopathy*	
	Absent (n=30)	*Developed (n=19)*	*Absent (n=2)*	*Developed (n=7)*
3×10^6	13	4 (23%)	2	0 (0%)*
6×10^6	11	6 (35%)	0	3 (100%)*
9×10^6	6	9 (60%)	0	4 (100%)*

*p<0.01, Kruskal–Wallis rank test, adapted from Hayasaka *et al*.[42]

interferon therapy. Visual acuities in patients with the atypical toxicity of interferon have sometimes been impaired.

Kado and coworkers[18] reported on a 61 year old woman with type C hepatitis who received interferon alfa 6×10^6 U/day. The patient had vitreous haemorrhage in the left eye, and her left visual acuity decreased to 0.01. Miyamoto and associates[17] described a 27 year old woman with type C chronic hepatitis and sarcoidosis who was receiving interferon alfa. The patient complained of visible floaters in both eyes 38 days after starting interferon therapy. Iridial nodules, cells and snowball opacities in the vitreous, and periphlebitis in the retina were found. The authors believed that deterioration of sarcoidosis associated uveitis may have been induced by interferon alfa.[17] Kubo and associates[31] showed prolonged retinal changes in a patient with type C hepatitis after interferon had been discontinued. Chen *et al*[43] reported on a patient in whom retinopathy did not resolve for a long time after the start of interferon therapy. This patient had chronic active hepatitis, diabetes mellitus, and systemic hypertension. The authors recommended that periodic fundus examinations be performed during a patient's interferon therapy.[43] Retinal microaneurysms have also been found in patients receiving interferon alfa.[22 32 37] Hayasaka *et al*[37] found subconjunctival haemorrhages in three patients treated with interferon alfa. Bauherz *et al*[48] described bilateral oculomotor nerve paralysis induced by interferon alfa in a patient with hairy cell leukaemia. Yoshitoshi and associates[23] reported a 65 year old woman with type C chronic active hepatitis in whom panophthalmitis developed 6 days after interferon alfa 10^7 U/day. The patient's right eye was enucleated. Histopathological study showed massive infiltration of inflammatory cells in the ocular tissues. The bacterial culture was negative. The authors believed that immunological dysfunction may have been involved in the pathogenesis of panophthalmitis in this patient.[23] Ayaki[34] reported on a 56 year old man with type C hepatitis and diabetes mellitus in whom neovascular glaucoma in the left eye developed 2 months after the start of interferon alfa 6×10^6 U/day, three times a week. He believed that interferon may have been a factor in the development of neovascular glaucoma in this patient. Miyamura *et al*[27] and Saitoh *et al*[30] described aggravation of diabetic retinopathy in patients treated with interferon for chronic type C hepatitis. Kawamoto *et al*[28] reported central retinal vein occlusion in three patients treated with interferon. Branch retinal vein occlusion occurred in two patients during interferon therapy.[17 41] The patients had decreased visual acuity in the affected eyes.[17 41] A patient with branch retinal artery occlusion during interferon therapy was reported.[22]

Preretinal haemorrhage associated with sudden visual impairment occurred during interferon therapy.[39] Tadokoro and associates[38] reported on a 41 year old man with type C active hepatitis in whom optic disc oedema in the left eye developed after initiation of interferon therapy. His visual acuity was not impaired. Despite continuation of interferon therapy, the disc oedema gradually decreased. The authors believed that the use of interferon may have been related to the disc oedema.[38]

Atypical interferon associated ocular complications have been found in a small number of patients. The single reports may represent coincidences and not have any association with interferon use. For instance, two cases of branch retinal vein occlusion may be the expected finding in the population treated. The visual acuity in patients with atypical complications may sometimes be impaired. Typical interferon associated retinopathy develops mainly in the first 3 months, and atypical toxicities occur during the therapy. Patients should be examined before starting interferon to look for pre-existing retinopathy; if any is present, interferon should not be used or the patient should be monitored closely—for example, monthly. If no retinopathy is present, less frequent examinations may be performed, such as at 3 months, unless the patient notes decreased vision. The treatment should be discontinued if visual acuity decreases or severe ocular toxicity occurs.

Risk factors and pathogenesis of interferon associated retinopathy

Diabetes mellitus is reportedly a risk factor in the development and progression of interferon associated retinopathy.[16 22 27 30 32 37 40 42 45]

Systemic hypertension has also been suspected in the development of the retinopathy.[21 32 40] Patients' age,[35 37 40] arterial sclerosis,[31] erythrocyte count,[22 32] leucocyte count,[22] platelet count,[16 18 19 29 46] haemoglobin,[21 29 46] serum glutamate oxaloacetate transaminase,[22] serum glutamate pyruvate transaminase,[22 28 36] triglyceride,[40] and total cholesterol[40] levels have been examined as possible risk factors, but the results have been negative or inconclusive.

Pathogenesis of interferon associated retinopathy is unknown, although some investigators have suggested deposition of the immune complex at the vessels[17] and immunological dysfunction.[23] To our knowledge, no histopathological study of typical interferon associated retinopathy has been done.

Animal experiments for ocular toxicity of interferon

Vegh and coworkers[50] investigated the toxicity of injecting human fibroblast interferon intravitreally in rabbit eyes, and found that a single intravitreal injection of 166 660 U/0.1 ml was non-toxic to ocular structures as demonstrated by electroretinographic and histological examination. Abe and associates[51] studied the long term administration of interferon to mice. Their results showed that the retinal vascular bed was occluded in mice that were pretreated with urethane but not in mice without pretreatment. The authors believed that a diseased retina is a prerequisite for the development of retinal vessel occlusion with interferon.[51]

Hepatitis C virus associated retinopathy

Abe and associates[52–54] reported on patients with possible hepatitis C virus associated retinopathy. Retinal haemorrhages and cotton wool spots developed in patients with chronic hepatitis C virus infection unassociated with interferon therapy.[52–54] To our knowledge, no other investigators have reported hepatitis C virus associated retinopathy. It is possible that the pathogeneses of interferon associated retinopathy and hepatitis C virus associated retinopathy may be related. Also, it is probable that pre-existing retinal vascular disease, such as diabetes or retinopathy associated with hepatitis C, may predispose one to develop retinopathy secondary to interferon.

Conclusion

Two weeks to 3 months after the start of interferon therapy, retinal haemorrhages and cotton wool spots develop. The incidence of retinopathy depends on the initial dose of interferon. The retinopathy disappears spontaneously during therapy or rapidly after stopping the therapy. Despite the retinopathy, most patients have had good visual acuity. However, a small number of patients have had impaired vision. In particular, patients with diabetes mellitus have shown a high frequency of development and progression of retinopathy during interferon therapy. Patients should be examined before starting interferon to look for pre-existing retinopathy. If any is present,

interferon should not be used or the patient should be monitored closely—for example, monthly. If no retinopathy is present, less frequent examinations might be performed, such as at 3 months, unless the patient notes decreased vision. If severe ocular toxicity occurs, interferon therapy should be discontinued.

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