CYTOMEGALOVIRUS (CMV)-RELATED CHOROIDOPATHY: INDOCYANINE GREEN VIDEO-ANGIOGRAPHY (ICG-V) FINDINGS IN AIDS PATIENTS WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)*

J. Fernando Arévalo. M.D. **
Dario Fuenmayor-Rivera. M.D. ***

Abstract

Purpose: To compare intravenous fluorescein angiography (IVFA) to indocyanine green video-angiography (ICG-V) findings in cytomegalovirus (CMV) retinitis in patients with high active antiretroviral therapy (HAART) and to determine if ICG-V is a useful adjunct in the diagnosis of CMV-related choroidal inflammation.

Methods: Fluorescein angiography and ICG-V were prospectively performed in 13 consecutive eyes (8 patients) that presented with active CMV retinitis while on HAART. Angiograms were reviewed for specific features independently by the authors in a masked fashion. A comparison between IVFA and ICG-V findings was made.

Results: The mean CD4+ count of our patients was 160 cells/μL (range:77-350). On ICG-V, all eyes showed a hypofluorescent pattern that was maintained throughout the study. Nine of our cases had hyperfluorescence at some point during the study. The earliest hyperfluorescence was achieved 26.4 seconds (17-57.6) while maximum hyperfluorescence was achieved 147.1 seconds (18.1-315.6). Other findings on ICG-V included a late hyperfluorescent area of choroiditis in 9 (69.2%) eyes, and late frame hot spots in 7 (53.8 %) eyes. One case showed a previously undescribed choroidal ring-shaped hyperfluorescence in the macular area.

Conclusions: ICG-V in CMV-retinitis has distinct characteristics that are different from IVFA. ICG-V may be a useful non -invasive adjunct complementary to IVFA in the diagnosis of CMV-related choroiditis in patients with more immunologic and inflammatory response while on HAART.

* Presented in part at the American Academy of Ophthalmology and Pan-American Association of Ophthalmology Joint Meeting, Orlando, FL, October 1999

** Retina and Vitreous Service, Clinica Oftalmologica Centro Caracas, Caracas, Venezuela

*** The Instituto de Oftalmologia, Caracas, Venezuela

Correspondence and Reprints: J. Fernando Arevalo, M.D., Clinica Oftalmologica Centro Caracas, Centro Caracas PH-1, Av. Panteon, San Bernardino, Caracas 1010, Venezuela
E-mail:arevall@telcel.net.ve

Introduction

The recent introduction of protease inhibitors specific for human immunodeficiency virus (HIV) in the treatment of acquired immunodeficiency syndrome (AIDS) has allowed significant improvement in immune status in this group of patients.[1,2] There are 4 protease inhibitors currently available: ritonavir, indinavir, nelfinavir, and saquinavir. All of them competitively inhibit the protease-mediated cleavage of viral polyproteins, preventing the maturation of infectious virions resulting in inhibition of replication of HIV. This type of therapy has been called: high active antiretroviral therapy (HAART).

Cytomegalovirus (CMV) retinitis in AIDS patients usually occurs with a CD4+ lymphocyte count less than 50 cells/μL.[3-5] Typically it is characterized by a necrotizing retinitis with superficial hemorrhages and little or no intraocular inflammation, this last characteristic was so strong (before the HAART era) that in patients with necrotizing retinitis and vitreous inflammation another diagnosis had to be considered. Inflammation has been so far very rare in this group of patients, however there are some reports in the literature.[6-10] Serous macular exudation associated with CMV retinitis in patients with AIDS has been described.[6] Palestine and Frishberg described a patient with AIDS-related macular edema with cotton-wool spots, and other microvascular abnormalities.[7] Weinberg and Moorthy described an AIDS patient with cystoid macular edema (CME) associated with CMV retinitis [8]. It has been suggested that the severe immunodeficiency in patients with AIDS has a protective effect against inflammation-induced complications of necrotizing retinitis.[9] Recently, Karavellas et al. have described a new syndrome of immune recovery vitritis associated with inactive CMV retinitis, all their patients were on HAART.[10]

Indocyanine green (ICG) is a dye that has several advantages over sodium fluorescein for visualization of choroidal vasculature. It is recognized that ICG provides better visualization of choroidal vessels. The dye absorbs (805 mm) and fluoresces (835 mm) in the near infrared ranged,[11-16] and visualization of fluorescence is possible through hemorrhage, lipid, retinal pigment epithelium (RPE), and xanthophyll. Indocyanine green is highly bound to protein and, therefore, leaks more slowly through the fenestrations of the choriocapillaris. Recent advances combining digital imaging systems with ICG fundus cameras have allowed high-resolution digital ICG videoangiography (ICG-V). Several reports have demonstrated the usefulness of ICG-V in the diagnosis of occult choroidal neovascularization secondary to age-related macular degeneration,[17-20] other chorioretinal disorders,[21-26] and choroidal tumors.[27-29]

The purpose of this study was to compare intravenous fluorescein angiography (IVFA) to ICG-V findings in cytomegalovirus (CMV) retinitis in patients with high active antiretroviral therapy (HAART) and to determine if ICG-V is a useful adjunct in the diagnosis of CMV-related choroidal inflammation.

Methods

Eight consecutive patients (13 eyes) with the clinical diagnosis of active CMV retinitis (Figure 1-A) were prospectively imaged with IVFA and ICG-V at the Instituto de Oftalmologia between May 1996 and May 1999. All patients were initially examined and a detailed fundus drawing completed, as well as fundus photography. All 8 patients then underwent ICG-V and IVFA.

All patients received HAART, which consisted of an HIV-1 specific protease inhibitor: saquinavir (Invirase, Hoffman-LaRoche, Nutley, NJ) 600 mg three times a day, and two reverse transcriptase inhibiting nucleosides: zalcitabine (Hivid, Hoffman- LaRoche) 0.75 mg three times a day, and zidovudine (AZT) 200 mg three times a day (Retrovir, Glaxo Wellcome).
Indocyanine green (Cardio-Green, Becton Dickinson Microbiology Systems, Cockeysville, MD) was prepared by adding a 25 mg dose to 2 ml

eyes. The ophthalmoscopic features of the 13 CMV retinitis eyes revealed a mean extention of retinitis of 31.4% of the retinal area. All eyes had active CMV retinitis. Retinitis was located in zones 1, 2, and 3 in 76.9% of cases. Retinitis was located at a mean 1,071 μ from de optic disc, and 3,4285 μ from the fovea. One (7.6%) of our cases had a concurrent retinal detachment. Another (7.6%) case had a cystoid macular edema (CME).

Indocyanine green video-angiography (ICG-V) features

On ICG-V, all eyes showed a hypofluorescent pattern that was maintained throughout the study. Nine cases had hyperfluorescence at some point during the study. Indocyanine green video-angiography findings (Table) show that the onset of fluorescence ocurred at 26.4 seconds (range: 17-57.6 seconds) and achieved a maximum at 147.1 seconds (range: 18.1-315.6 seconds) (Figure 1-B, C). Subretinal fluid and CME were not visualized with ICG-V. Choroidal vessels were seen in 9 eyes (69.2%) (Figure 1-B). In 7 cases (53.8%) choroidal vessels were seen first in the center of the area with retinitis, including one eye with a previously undescribed annular choroidal hyperfluorescence (Figure 2-A, B). Hot spots were visualized in the late phases of the angiogram in the 7 eyes (53.8 %) and their

Comparison of Intravenous Fluorescein Angiography (IVFA) and Indocyanine Green (ICG-V) (13 eyes) *

		ICG-V	IVFA
Earliest Hyperfluorescence (sec)		26.4 (range: 17-57.6)	44.8 (range: 21.3-94.6)
Phase:	Pre-arterial	NA	0
(N° of eyes)	Arterial	NA	0
	Laminar Venous	NA	9
Maximum Fluorescence (sec)		147.1 (range: 18.1-315.6)	209.5 (range: 49-339.3)
Phase:	Laminar Venous	NA	2
(N° of eyes)	Full Venous	NA	7
	Recirculation	NA	4
	Late		0
Choroidal Vessels (eyes)		9	3
Type:	Lacy	7	2
(N° of cases)	Diffuse	2	1
Location:	Center	7	2
(N° of cases)	Rim	0	0
	Diffuse	0	1
Caliber (μ)		380 (range: 200-1000)	112.5 (range: 100-125)
Subretinal Fluid (eyes)		0	1
Cystoid Macular Edema (eyes)		0	0
Late Hot Spots (eyes)		7	1
Size of spots (μ)		137.5 (range: 100-250)	100

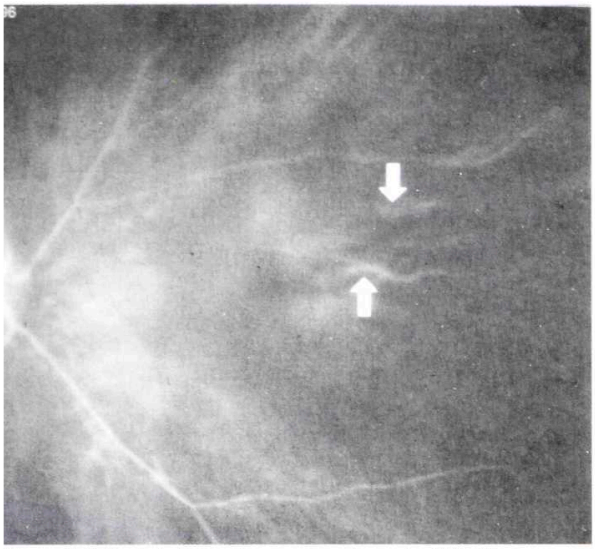

Figure 1-B. Early indocyanine green angiography (ICG-V) frame shows the onset of fluorescence

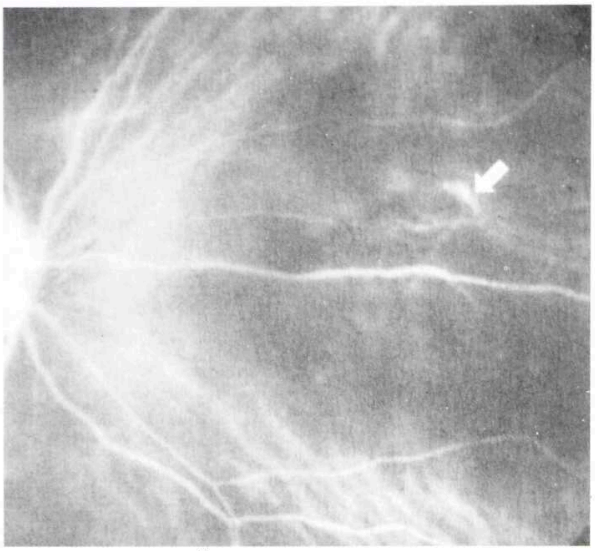

Figure 1-C. Maximum fluorescence on ICG-V

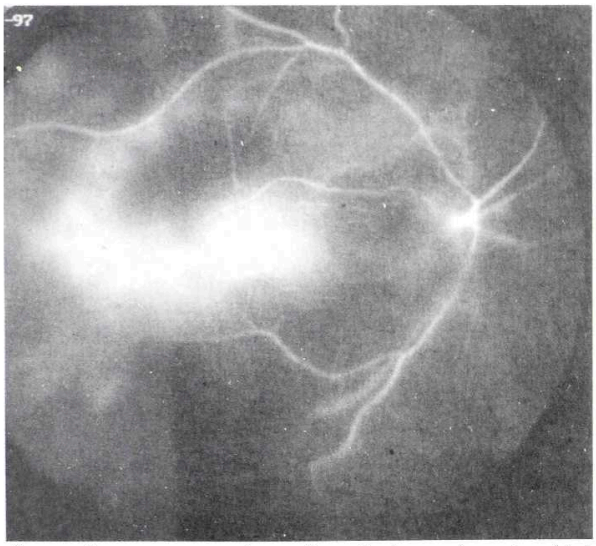

Figure 2-A. A previously undescribed annular choroidal hyperfluorescence of another patient with CMV retinitis imaged with ICG-V. Early fluorescence

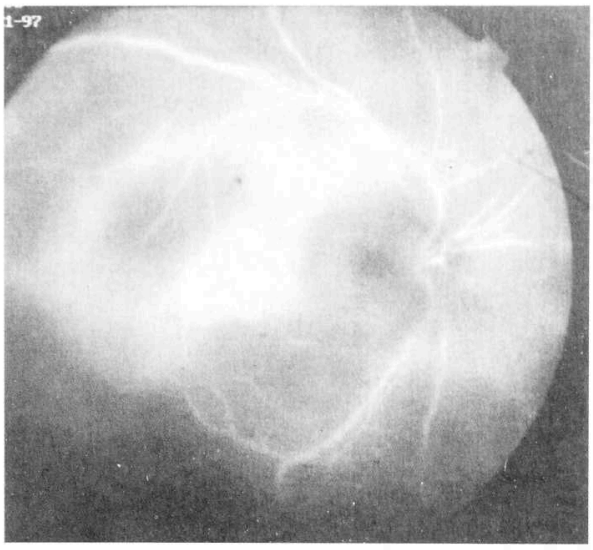

Figure 2-B. Maximum fluorescence

mean caliber was 137.5 μ (range: 100-250 μ) (Figure 3). None of eyes showed subretinal fluid and CME as seen on IVFA.

Intravenous fluorescein angiography (IVFA) Features

The IVFA findings (Table) detail that the onset of fluorescence occurred at 44.8 seconds (range: 21.3-94.6 seconds) and achieved a maximum at 209.5 seconds (range: 49-339.3 seconds) (Figure 4-A, B). In 9 cases (69.2%) the earliest fluorescence ocurred during the laminar or full venous phase of the angiogram, with the maximum fluorescence being reached during the full venous phase in 7 (53.8%), during the recirculation phase in 4 (30.7%), and during the laminar venous in two cases (15.3%). Choroidal vessels were seen in 3 eyes (23.0%). In 2 cases (15.3%) choroidal vessels

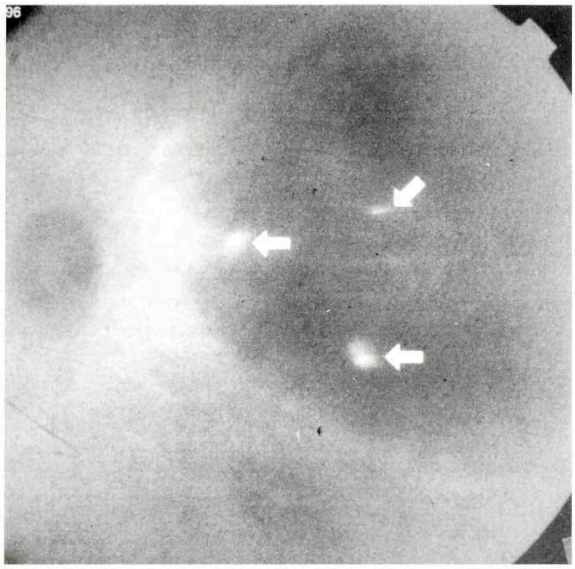

Figure 3. Hot spots are seen on late frames on indocyanine green videoangiography

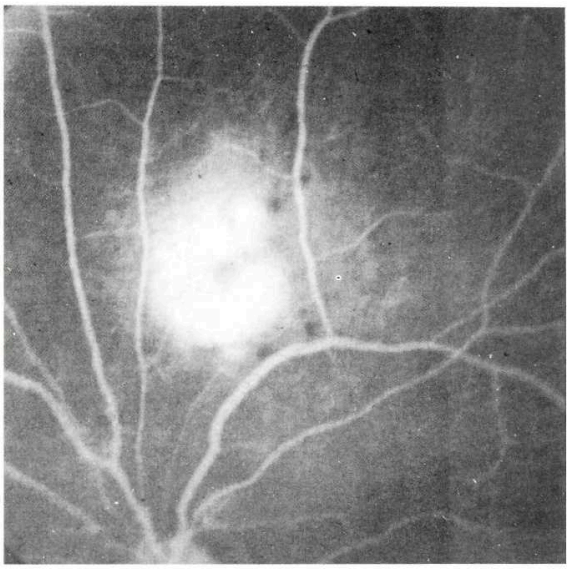

Figure 4-B . Maximum fluorescence during IVFA

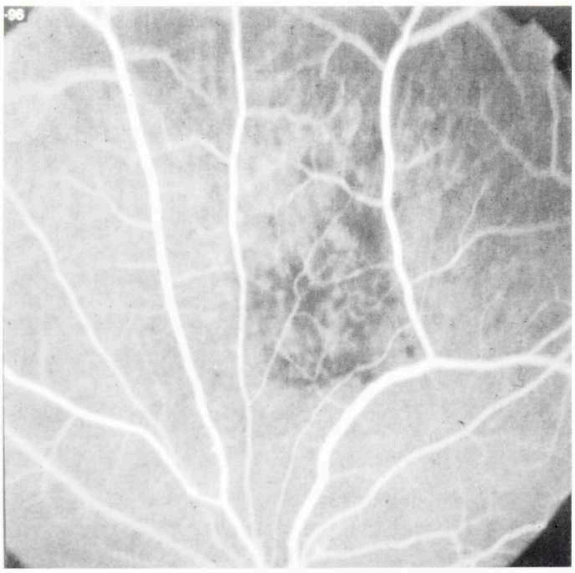

Figure 4-A Intravenous fluorescein angiography (IVFA) frame showing the onset of fluorescence

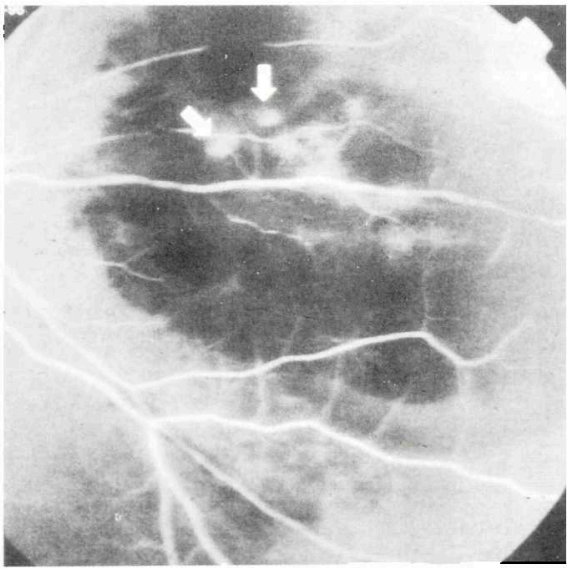

Figure 5-A Hot spots seen on late frames on IVFA

were seen in the center of the area with retinitis and their mean caliber was 112.5 µ (range: 100-125 µ). Hot spots were visualized in the late phases of the angiogram in 1 eye (Figure 5-A). Areas with lack of perfusion were seen in 7 eyes (53.8%) (Figure 5-B): hypofluorescent center, hyperfluorescent plaques, and subretinal fluid were seen in 1 eye each (7.6%). None of the eyes showed the late hypofluorescence and localized hyperfluorescence as seen on ICG-V.

Discussion

Cytomegalovirus retinitis in AIDS patients very rarely manifests with intraocular inflammation. Serous macular exudation associated with CMV retinitis in patients with AIDS has been described[6]. Palestine and Frishberg described a patient with AIDS-related macular edema with cotton-wool spots, and other microvascular abnormalities. [7] Weinberg and Moorthy described an AIDS patient with cystoid macular edema (CME) associated with CMV retinitis.[8] It has been suggested that the severe immunodeficiency in patients with AIDS has a protective effect against inflammation-induced complications of necrotizing retinitis.[9] Recently, Karavellas et al. have described a new syndrome of immune recovery vitritis associated with inactive CMV retinitis, all their patients were on HAART.[10] Advances in infrared imaging technology have improved the resolution of the ICG angiograms over the past years and recent reports have focused on the use of ICG in identifying choroidal pathology, especially those that are poorly defined on fluorescein angiography. [17-20]

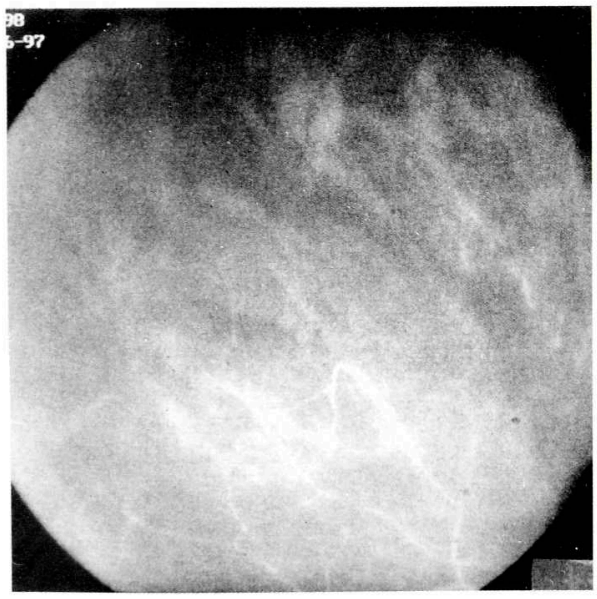

Figure 5-B. Lack of perfusion seen on IVFA

We describe 9 eyes (69.2%) with active CMV retinitis imaged with ICG-V and IVFA in whom a CMV-related choroidopathy can be visualized. All of our patients were on HAART for at least five months, and had a mean CD4+ count of 160 cells/μL.

Comparison of fluorescence with intravenous fluorescein angiography reveals that hyperfluorescence onset occurred at 90 seconds, this hyperfluorescence increased up to 120 seconds, and in the late phases of the IVFA the hyperfluorescense persisted. On ICG-V, hypofluorescence onset occurred early at 30 seconds. This hypofluorescence increased up to 120 seconds, and in the late phases of the ICG-V the hipofluorescence persisted (Figure 6 and Table).

Our study was not design to determine the nature of the observed hypofluorescence or hyperfluorescence on ICG-V in patients with active CMV retinitis. However, we believe that active CMV not only affects the retina but also the retinal pigment epithelium (RPE) (hypofluorescence), and the choroid (hyperfluorescence). In addition, HAART may be responsible for a more inflammatory reaction as the immune system recovers accounting for our findings on ICG-V not observed before HAART was instituted.

Limitations of our study include the fact that ICG-V is still evolving and more information may emerge on other fundus lesions that could have similar appearances. In addition, the recommended technique of dye injection does not include calculation and dilution of Cardio-Green on a weight basis. These factors may contribute to variations in the time of onset, time of maximal hyperfluorescence, and subjective intensity interpretations. Other limitations that this study has include the small number of cases evaluated, the lack of an objective method of measurement of degree of fluorescence, and the lack of a matched control group.

In summary, our study suggests that ICG-V in CMV-retinitis has distinct characteristics that are different from IVFA. ICG-V may be a useful

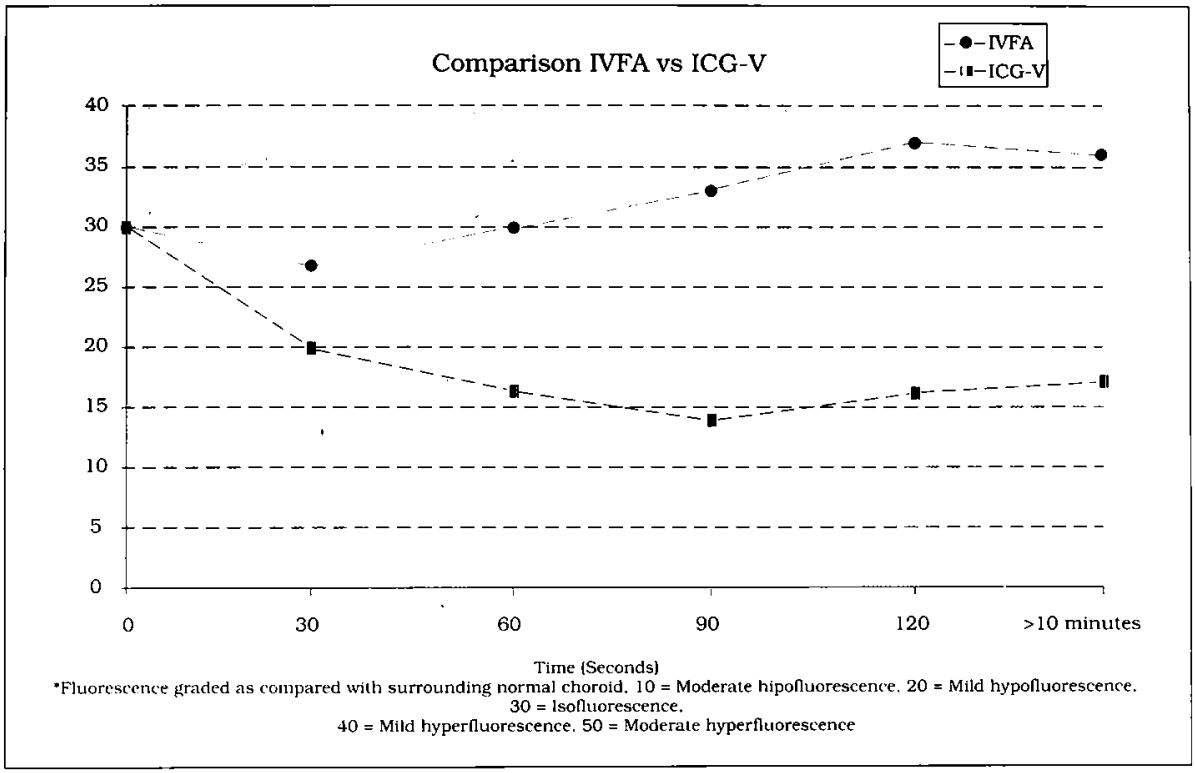

Figure 6. Graph comparing the fluorescence of Cytomegalovirus retinitis throughout intravenous fluorescein angiography (IVFA) and indocyanine green video-angiography (ICG-V). On IVFA, the hyperfluorescence onset occurred at 90 seconds, this hyperfluorescence increased up to 120 seconds, and in the late phases of the IVFA the hyperfluorescence persisted. On ICG-V, hypofluorescence onset occurred early at 30 seconds. This hypofluorescence increased up to 120 seconds, and in the late phases of the ICG-V the hypofluorescence persisted.

non invasive adjunct complementary to IVFA in the diagnosis of CMV-related choroiditis in patients with more immunologic response while on HAART.

References

1. Stein D, Drusano G, Steigbigel R, et al. Two-year follow-up of patients treated with indinavir 800 mg q8h. Presented at the Fourth Conference on Retroviruses and Opportunistic Infections; January 24, 1997; Washington, DC

2. Lederman M, Connici E, Landay A, et al. Partial immune reconstitution after 12 weeks of HAART (AZT, 3TC, ritonavir): preliminary results of ACTG 315. Presented at the Fourth Conference on Retroviruses and Opportunistic Infections; January 24, 1997; Washington, DC

3. Holland GN, Pepose JS, Pettit TH, et al. Acquired immune deficiency syndrome: Ocular manifestations. Ophthalmology 1983;90: 859-873

4. Kuppermann BD, Petty JG, Richman DD, et al. Correlation between CD4+ counts and prevalence of cytomegalovirus retinitis and human immunodeficiency virus-related noninfectious retinal vasculopathy in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 1993; 115: 575-582

5. Lowder CY, Butler CP, Dodds EM, Secic M, Recillas C, Gilbert C. CD8+ Lymphocytes and cytomegalovirus in patients with acquired immunodeficiency syndrome. Am J Opthalmol 1995; 120: 283-290

6. Gangan PA, Besen G, Munguia D, Freeman WR. Macular serous exudation in patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. Am J Opthalmol 1994; 118: 212-219

7. Palestine AG, Frishberg B. Macular edema in acquired immunodeficiency syndrome-related microvasculophaty. Am J Ophthalmol 1991; 111: 770-771

8. Weinberg DV, Moorthy RS. Cystoid macular edema due to cytomegalovirus retinitis in a patient with acquired immune deficiency syndrome. Retina 1996; 16: 343-344

9. Maguire AM, Nichols CW, Crooks GW. Visual loss in cytomegalovirus retinitis caused by cystoid macular edema in patients without the acquired immune deficiency syndrome. Ophthalmology 1996; 103: 601-605

10. Karavellas MP, Lowder CY, Macdonald JC, Avila CP, Freeman WR. Immune recovery vitritis associated with inactive cytomegalovirus retinitis: A new syndrome. Arch Ophthalmol 1998; 116: 169-175

11. Baker KJ. Binding of sulfobromophthalein (BSP) sodium and indocyanine green by plasma alpha 1 lipoproteins. Proc Soc Exp Biol Med 1966; 122-957- 63

12. Leevy CM, Bender J, Silverberg M, Naylor J. Physiology of dye extraction by the liver: comparative studies of sulfobromophthalein and indocyanine green. Ann NY Acad Sci 1963; 111: 161- 175

13. Goresky CA. Initial Distribution and rate of uptake of sulfobromophthalein in the liver. Am J Physiol 1964; 207: 13-26

14. Kogure K, David NJ, Yamanouchi U, Choromokos E. Infrared absorption angiography of the fundus circulation. Arch Ophthalmol 1970; 83: 209-214

15. Flower RW, Hochheimer BF. Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography. Johns Hopkins Med J 1976; 138: 33-42

16. Benson RC, Kues HA. Fluorescence properties of indocyanine green as related to angiography. Phys Med Biol 1978; 23:159- 163.

17. Yannuzzi LA, Slakter JS, Sorenson JA, Guyer DR, Orlock DA. Digital indocyanine green videoangiography and choroidal neovascularization. Retina 1992; 12: 191-223

18. Sorenson JA, Yannuzzi LA, Slakter JS, Guyer DR, Ho AC, Orlock DA. A pilot study of digital indocyanine green videoangiography for recurrent occult choroidal neovascularization in age-related macular degeneration. Arch Ophthalmol 1994; 112: 473-479

19. Yannuzzi LA, Hope-Ross M, Slakter JS, et al. Analysis of vascularized pigment epithelial detachments using indocyanine green videoangiography.Retina 1994; 14: 99-113

20. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, Hope-Ross M, Orlock DR. Digital Indocyanine-green videoangiography of occult choroidal neovascularization. Ophthalmology 1994; 101: 1727-

21. Guyer DR, Puliafito CA, Mones JM, Friedman E Chang W, Verdooner SR. Digital indocyanine gree angiography in chorioretinal disorders. Ophthalmolog 1992; 99: 287-291

22. Dhaliwal RS, Maguire AM, Flower RW, Arribas NI Acute posterior multifocal placoid pigmer epitheliopathy: an indocyanine green angiographi study. Retina 1993; 13: 317-325

23. Yuzawa M, Kawamura A , and Matsu M.Indocyanine green videoangiography findings i Harada's disease. Jpn J Ophthalmol 1993; 37: 456-46

24. Guyer DR, Yannuzzi LA, Slakter JS, Sorenson JA, H Ac, Orlock D. Digital indocyanine gree videoangiography of central serous chorioretinopathy Arch Ophthalmol 1994; 112: 1057-1062

25. Ie D, Glaser BM, Murphy RP, Gordon LW, Sjaarda RN and Thompson JT. Indocyanine green angiography i multiple evanescent white-dot syndrome. Am Ophthalmol 1994;117: 7-12.

26. Yuzawa M, Kawamura A , and Matsui M Indocyanine green videoangiography findings in acut posterior multifocal placoid pigment epitheliopathy Acta Ophthalmológica 1994; 72: 128-133

27.Shields CL, Shields JA, De Potter P. Patterns c Indocyanine green videoangiography of choroidc tumours. Br J Ophthalmol 1995;79: 237-245

28. Sallet G, Amoaku WMK, Lafaut BA, Brabant P, De Laey JJ. Indocyanine green angiography of choroidc tumours. Graefe's Arch Clin Exp Ophthalmol 1995; 233 677-689

29. Piccolino FC, Borgia L, and Zinicola E. Indocyanine green angiography of circumscribed choroidc hemangiomas. Retina 1996; 16: 19-28

30. Kim JW, Freeman WR, el-Haig W, et al. Baseline characteristics, natural history, and risk factors to progression in eyes with stage 2 macular holes. Result from a prospective randomized clinical trial. Vitrectomy for Macular Hole Study Group. Ophthalmology 1995 102: 1818-1828