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Short communication

Design of clinical trials for drug combinations: cytomegalovirus retinitis — foscarnet and ganciclovir. The CMV retinitis retreatment trial

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Abstract

The Cytomegalovirus Retinitis Retreatment Trial was a multicenter clinical trial designed to evaluate three treatments for the treatment of relapsed CMV retinitis; (1) foscarnet; (2) 'high-dose' ganciclovir, and (3) combination foscarnet and ganciclovir. Two hundred seventy-nine patients were enrolled and randomly assigned to one of these three regimens. Patients were followed monthly for 6 months and every 3 months thereafter. Outcomes of interest included: (1) mortality; (2) retinitis progression; (3) change in retinal area affected by CMV; (4) loss of visual field; (5) loss of visual acuity; (6) quality of life; and (7) treatment side effects.

Keywords: AIDS; Clinical trial; Combination antiviral therapy; Cytomegalovirus retinitis; Foscarnet; Ganciclovir

1. Introduction

Cytomegalovirus (CMV) is among most common opportunistic pathogens in patients with the acquired immunodefiency syndrome (AIDS) (Gallant et al., 1992; Hoover et al., 1993). With the advent of successful prophylaxis for *Pneumocystis carinii* pneumonia (PCP), disease due to CMV affects an estimated 45% of patients with AIDS sometime during the course of their disease (Hoover et al., 1993). Although multiple organs, including the eye, lung, gastrointestinal tract and central nervous system, may be affected by CMV, retinitis accounts for 85% of all CMV disease in patients with AIDS (Gallant et al., 1992). CMV retinitis is a necrotizing retinitis, which, if untreated, will spread throughout the entire retina over a period of months and result in total retinal destruction and blindness (Jabs et al., 1989). Hence, treatment of CMV retinitis is critical in preserving vision and the quality of life.

As of June 1995, two drugs were approved by the United States Food and Drug Administration (FDA) for the treatment of patients with CMV retinitis, foscarnet and ganciclovir. Both drugs are effective in controlling the retinitis but require long-term suppressive (maintenance) therapy to prevent relapse. Despite the use of maintenance

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therapy, relapse generally occurs (Studies of Ocular Complications of AIDS Research Group, (SOCA Research Group, 1994)), and the consensus is that with currently available therapy, virtually all patients will relapse given enough time. The reasons for relapse are unclear but likely include: (1) the limited intraocular penetration of systemically administered anti-CMV drugs; (2) the progressively failing immune system of patients with AIDS; (3) the development of resistance; or (4) a combination of factors.

Once relapse has occurred, the pace of relapse accelerates, i.e. the interval between successive relapses progressively shortens (SOCA Research Group, 1994). With each successive relapse, additional retina is irreversibly damaged, resulting in loss of visual field and ultimately visual acuity. Therefore, the CMV Retinitis Retreatment Trial (CRRT) was designed to address the question of which of these treatment regimens was best for relapsed retinitis: foscarnet, 'high-dose' ganciclovir, or combination foscarnet and ganciclovir.

2. Materials and methods

2.1. Study design

Patients with AIDS and either relapsed or persistently active CMV retinitis were eligible for the CRRT. Patients were randomized to one of three regimens: (1) reinduction with foscarnet followed by maintenance therapy with the highest approved dose; (2) reinduction with ganciclovir followed by maintenance therapy at twice the approved maintenance dose; or (3) combination therapy.

2.2. Treatment administration

Patients assigned to foscarnet were treated with induction therapy at 90 mg/kg every 12 h intravenously (IV) for 2 weeks followed by maintenance therapy at 120 mg/kg/day. Subsequent relapses were treated with the same reinduction and maintenance doses. Patients assigned to 'high-dose' ganciclovir were treated with induction therapy at 5 mg/kg every 12 h IV for 2 weeks followed by maintenance IV therapy at 10 mg/kg/day. Subsequent relapses were treated with induction at 7.5 mg/kg every 12 h for 2 weeks and maintenance therapy at 10 mg/kg/day. Patients assigned to combination therapy were kept on their previous maintenance regimen and the second drug was added at induction doses (foscarnet at 90 mg/kg every 12 h or ganciclovir 5 mg/kg every 12 h) followed by maintenance therapy with both drugs every day. The maintenance doses for combination therapy were ganciclovir at 5 mg/kg/day and foscarnet at 90 mg/kg/day. Subsequent relapses were treated with reinduction and maintenance with both drugs. Provisions were made in the trial design for changing to an alternate regimen either for persistent or recurrent toxicity or for failure to adequately control the retinitis. Treatment administration was not masked.

2.3. Data collection

Baseline data collection included a history, complete ophthalmologic examination (including assessment of visual acuity), fundus photography, visual field testing, medical examination and laboratory evaluation of hematology, chemistry, CD4+ T cell count and CMV cultures of blood and urine. Patients were followed monthly for 6 months and every 3 months thereafter. An interval history, complete ophthalmologic examination, fundus photography and laboratory evaluation of hematology and chemistry were performed at each follow-up visit. Every 3 months, visual fields and a medical examination were performed.

2.4. Outcome measures

Outcomes of interest included: (1) mortality; (2) retinitis progression, assessed both by a masked grading of retinal photographs at the central Fundus Photograph Reading Center (FPRC) and by the clinician (SOCA Research Group, 1992); (3) increase in area of retinitis affected by CMV, assessed by the FPRC; (4) loss of visual field; (5) loss of visual acuity assessed by standardized logarithmic (ETDRS) visual acuity charts (SOCA

Research Group, 1992); (6) quality of life; and (7) treatment side effects.

3. Results

Recruitment of 279 patients was complete as of 6 March 1995.

4. Discussion

The CMV Retinitis Retreatment Trial was designed to address the issue of the best therapy for the treatment of CMV retinitis which has relapsed. The three treatment regimens were chosen for empiric reasons. The dose of foscarnet was the highest FDA-approved maintenance dose and was thought to be the highest tolerable dose. The dose of ganciclovir in this trial was twice the FDA-approved maintenance dose. With the availability of filgrastim (G-CSF) and sargrammostim (GM-CSF), higher doses of ganciclovir can be given, and they are often used in practice. Finally, the approach to combination therapy was the one used in preliminary case series of combination therapy (Dieterich et al., 1993; Kuppermann et al., 1993; Weinberg et al., 1994). Laboratory studies have reported that combination ganciclovir and foscarnet may have a synergistic effect on CMV replication (Freitas et al., 1989; Manischewicz et al., 1990), and case series of patients who have suffered frequent relapses of CMV retinitis have suggested that combination therapy may be effective when monotherapy is not (Dieterich et al., 1993; Kuppermann et al., 1993; Weinberg et al., 1994).

In summary, the CRRT evaluated treatments of relapsed CMV retinitis and the role of combination therapy as treatment.

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References

Dieterich, D.T., Poles, M.A., Lew, E.A., Mendez, P.E., Murphy, R., Addessi, A., Holbrook, J.T., Naughton, K. and Friedberg, D.N. (1993) Concurrent use of ganciclovir and foscarnet to treat cytomegalovirus infection in AIDS patients. J. Infect. Dis. 167, 1184–1188.

Freitas, V.R., Fraser-Smith, E.B. and Matthew, T.R. (1989) Increased efficacy of ganciclovir in combination with foscarnet against cytomegalovirus and herpes simplex virus type 2 in vitro and in vivo. Antiviral Res. 12, 205–212.

Gallant, J.E., Moore, R.D., Richman, D.D., Keruly, J. and Chaisson, R.E. (1992) Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodefiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. J. Infect. Dis. 166, 1223–1227.

Hoover, D.R., Saah, A.J., Bacellar, H., Phair, J., Detels, R., Anderson, R. and Kaslow, R.A. (1993) Clinical manifestations of AIDS in the era of *Pneumocystis* prophylaxis. N. Engl. J. Med. 329, 1922–1926.

Jabs, D.A., Enger, C. and Bartlett, J.G. (1989) Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch. Ophthalmol. 107, 75–80.

Kuppermann, B.D., Flores-Aguilar, M., Quinceno, J.I., Rickman, L.S. and Freeman, W.R. (1993) Combination ganciclovir and foscarnet in the treatment of clinically resistant cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. Arch. Ophthalmol. 111, 1359–1366.

Manischewicz, J.F., Quinnan, G.V., Jr, Lane, H.C. and Wittek, A.E. (1990) Synergistic effect of ganciclovir and foscarnet on cytomegalovirus replication in vitro. Antimicrob. Agents Chemother. 34, 373–375.

SOCA Research Group, in collaboration with the AIDS Clinical Trials Group. (1992) Studies of Ocular Complications of AIDS foscarnet-ganciclovir cytomegalovirus retinitis trial: 1. rationale, design, and methods. Controlled Clin. Trials 13, 22–39.

SOCA Research Group, in collaboration with the AIDS Clinical Trials Group. (1994) Foscarnet-ganciclovir cytomegalovirus retinitis trial. 4. Visual outcomes. Ophthalmology 101, 1250–1261.

Weinberg, D.V., Murphy, R. and Naughton, K. (1994) Combined daily therapy with intravenous ganciclovir and foscarnet for patients with recurrent cytomegalovirus retinitis. Am. J. Ophthalmol. 117, 776–782.