Transpl Int (1994) 7 [Suppl 1]: S232–S234

I. Lautenschlager
K. Höckerstedt
K. Salmela

Good and impaired response to ganciclovir treatment of severe CMV infections in liver transplant recipients

I. Lautenschlager (✉) · K. Höckerstedt
K. Salmela
Transplantation Laboratory,
University of Helsinki,
P.O. Box 21 (Haartmaninkatu 3),
SF-00014 University of Helsinki,
Finland

Abstract In this study we investigated good and impaired clinical responses to ganciclovir treatment of severe CMV disease in 23 adult liver transplant patients. CMV episodes were diagnosed by direct immunodetection of CMV-specific antigens in blood leukocytes and by viral cultures. The patients were monitored weekly for CMV antigenemia during the antiviral treatment. Sixteen out of 23 patients recovered from CMV episodes with the standard ganciclovir therapy of 2 weeks. Seven patients demonstrated an impaired response to ganciclovir and had to be treated for longer than 2 weeks (29 ± 9 days). The patients with an impaired response to ganciclovir also demonstrated higher CMV antigenemia levels compared to those with good a response, and all still had antigenemia after 2 weeks' therapy. Thus, most severe CMV infections in liver transplant patients subsided with ganciclovir treatment of 2 weeks, but impaired responses also occurred and patients had to be treated for several weeks with ganciclovir before they recovered from CMV.

Key words CMV · Ganciclovir · Liver transplantation

Introduction

The incidence of cytomegalovirus (CMV) infection among liver transplant recipients is high and 40–70% of these patients develop a symptomatic CMV disease [7, 9, 10]. A variety of clinical manifestations of CMV, such as fever, leukopenia, trombocytopenia, pneumonia, enteritis, and hepatitis have been described [12]. In recent years, new rapid diagnostic methods and effective antiviral drugs have eased the clinical management of these patients.

Ganciclovir is a potent antiviral drug inhibiting the replication of CMV. It is a congener of deoxyguanosine that is phosphorylated and incorporated into replicating viral DNA with subsequent inhibition of both viral chain elongation and DNA polymerase activity [5]. The virostatic activity of ganciclovir appears to be limited to viruses of the herpes family, including CMV. Ganciclovir is a therapeutically safe and effective agent for the treatment of severe CMV infections after liver transplantation [1, 4, 6]. However, impaired clinical responses have also been recorded [3].

New rapid laboratory methods have made it possible to diagnose active CMV infection from blood leukocytes by specific antibodies in a few hours [13]. The quantitative antigenemia test has been demonstrated to be helpful in monitoring the response to antiviral therapy [14]. In this study, we investigated good and impaired clinical responses to ganciclovir treatment of severe CMV infections in liver transplant patients monitored by the CMV-antigenemia test.

Patients and methods

Twenty-three out of the 62 adult liver allograft recipients receiving a liver allograft during the years 1989–1992 developed a severe CMV disease in the early (31 ± 16 days) posttransplant period. The basic immunosuppression consisted of triple therapy with azatioprine, cyclosporine A, and methylprednisolone. No acute rejection episodes or courses of intensified immunosuppression were associated with the CMV disease episodes described here.

The diagnosis of CMV infection was based on direct immunodetection of CMV in blood leukocytes by using a monoclonal antibody against CMV-specific antigens (pp65, Biotest Pharma, Frankfurt, Germany) and Immunoperoxidase staining [14], and on viral cultures from blood, urine, biopsies, and bronchoalveolar lavations (BAL). In all patients with antigenemia, the diagnosis of CMV infection was confirmed by positive viral cultures. Three of the 23 CMV disease episodes were primary infections. The CMV infections were treated with intravenous ganciclovir 10 mg/kg per day for 14 days. In patients with life-threatening CMV pneumonia (5/23), CMV hyperimmune globulin was administered. During antiviral treatment, the patients were monitored weekly for CMV antigenemia. In cases of symptomatic disease not responding to the antiviral treatment after 14 days and in persisting CMV antigenemia, ganciclovir therapy was prolonged until the clinical signs subsided and no CMV was detectable. The correlation of the clinical response to ganciclovir and the level of CMV antigenemia was studied retrospectively. The level of CMV antigenemia was expressed as the number of CMV positive cells/50000 leukocytes [13].

Results

All the 23 cases of severe CMV infection investigated here were first episodes of CMV infection after transplantation. In addition to general symptoms, the patients had one or several organ manifestations of CMV infection (hepatopathy, 13; pneumonia, 7; gastrointestinal, 3). The clinical CMV disease and CMV antigenemia responded well to the recommended 14 days' course of ganciclovir treatment in 16 patients. Three of these patiens also received CMV hyperimmune globulin. One patient died of aspergillosis a few weeks after recovery from CMV disease.

In seven patients, neither the disease symptoms nor CMV antigenemia responded to ganciclovir in the recommended 14 days and the treatment was extended to 29 ± 9 days. Due to persistent viremia and severe symptoms (hepatopathy and gastroenteritis), one patient was subsequently treated with foscarnet. Two patients with CMV pneumonia were additionally treated with hyperimmune globulin. All seven patients finally recovered from the CMV infection. Two patients died from other infections, one from bacterial sepsis and the other from aspergillosis a few weeks after recovery from the CMV disease. All three patients with a primary CMV infection belonged to this group of patients with impaired response

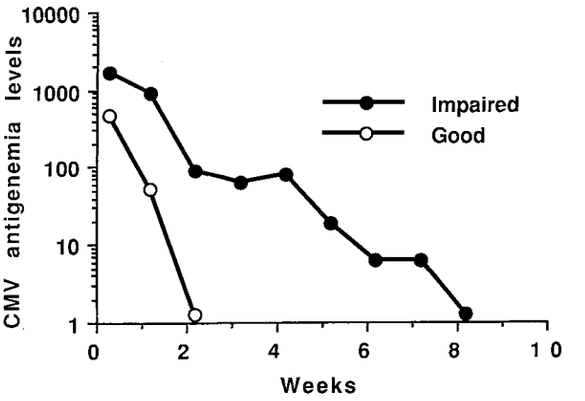

Fig. 1 CMV antigenemia levels of patients with good (open circles) and impaired responses (closed circles) to ganciclovir treatment

to ganciclovir. There was no significant difference in the severity of the disease in two groups or between primary infections and reinfections/reactivations.

The quantitative demonstration of CMV antigenemia levels in the ganciclovir-treated patients is shown in Fig. 1. The patients with an impaired clinical response to ganciclovir had higher CMV antigenemia levels before, and significantly higher levels ($P < 0.05$) after 1 week of treatment compared to those with a good response. After 2 weeks of treatment, the poorly responding patients still had a significant level of antigenemia, while the virus was no longer found in the blood of the good responders.

Discussion

The efficacy of ganciclovir therapy for severe CMV infection in hepatic allograft recipients has been reported by several authors [1, 4, 6, 8]. Ganciclovir has revolutionized the treatment of CMV disease, and with this treatment transplanted patients infrequently die of an overt CMV disease. In spite of successful therapeutical results of ganciclovir treatment, impaired responses have been recorded [5], and even ganciclovir resistant CMV infections have been reported in other groups of immunodeficient patients [2].

In our study, the impaired response to ganciclovir was associated with a prolonged and high level of CMV antigenemia. None of these patients had previous courses of ganciclovir treatment, thus reducing the likehood of induced ganciclovir resistance of the CMV strains as the cause of prolonged disease. Whether or not ganciclovir treatment should be prolonged until the virus is eradicated from the blood of a patient with subsiding symptoms is not established. However, the association of

severe and prolonged CMV infection with liver allograft dysfunction and deterioration in the patients general condition seemed obvious in our seven cases and this fact encouraged us to continue the active eradication of the virus, which was achieved by a much longer than recommennded antiviral treatment. Intravenous administration of ganciclovir is usually well tolerated and from the economical and practical point of view is easily carried out. The frequent monitoring of the level of CMV antigenemia provides a reliable diagnostic tool in the follow-up of the response to antiviral treatment.

In conclusion, most liver transplant patients recover from CMV disease with the standard ganciclovir therapy of 2 weeks. If impaired responses to the standard therapy occur, prolonged antiviral treatment is necessary.

Acknowledgements This study was supported by the Finnish Academy of Science, the Sigrid Juselius Foundation, and the University of Helsinki, Finland.

References

1. Erice A, Jordan MC, Chace BA, Fletcher C, Chinnock BJ, Balfour JJ (1987) Ganciclovir treatment of cytomegalovirus disease in transplant recipients and other immunocompromised host. JAMA 257:3082–3087
2. Erice A, Chou S, Biron KK, Starrat SC, Balfour HH, Jordan MC (1989) Progressive disease due to ganciclovir-resistant cytomegalovirus in immunocompromised patients. N Engl J Med 320:289–293
3. Faulds D, Heel RC (1990) Ganciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infection. Drugs 39:597–636
4. Harrison MA, De Girolamini PC, Jenkins RL, Hammer SM (1988) Ganciclovir therapy of severe cytomegalovirus infections in solid organ transplant recipients. Transplantation 46:82–88
5. Matthew T, Boehme R (1988) Antiviral activity and mechanisms of action of ganciclovir. Rev Infect Dis 10:490–494
6. Paya CV, Hermans PE, Smith TF, Rakela J, Wiesner RH, Krom RAF, Torres VE, Sterioff S, Wilkowska W (1988) Efficacy of ganciclovir in liver and kidney transplant recipients with severe cytomegalovirus infection. Transplantation 46:229–234
7. Paya CV, Hermans PE, Wiesner RH, Ludwig J, Smith TE, Rakela J, Krom RAT (1989) Cytomegalovirus hepatitis in liver transplantation: prospective analysis of 93 censecutive orthotopic liver transplantation. J Infect Dis 160:752–758
8. Salmela K, Höckerstedt K, Lautenschlager I, Eklund B, Isoniemi H, Holmberg C, Ahonen J (1990) Ganciclovir in the treatment of severe CMV disease of liver transplant recipients. Transplant Proc 22:238–240
9. Sayage LH, Gonwa TA, Goldstein RM, Husberg BS, Klintmalm GB (1989) Cytomegaloinfection in orthotopic liver transplantation. Transplant Int 2:96–101
10. Signh N, Dummer JS, Kusne S, Breing MK, Amstrong JA, Makowta L, Strazl TE, Ho M (1988) Infections with cytomegalovirus and other herpesviruses in 121 liver transplant recipients transmitted by donated organ an effect of OKT3 antibodies. J Infect Dis 158:124–131
11. Stratta RJ, Schaefer MS, Markin RS, Wood RP, Kennedy EM, Langnas AN, Reed EC, Woods GL, Donovan JP, Pillen TJ, Duckworth RM, Shaw BW (1989) Clinical patterns of cytomegalovirus disease after transplantation. Arch Surg 124:1443–1450
12. Stratta RJ, Schaefer MS, Markin RS, Cushing KA, Donovan JP, Wood RP, Langnas AN, Reed EC, Woods GL, Zetterman RK, Sorrel MF, Pillen TJ, Shaw BW (1991) Ganciclovir therapy for viral disease in liver transplant recipients. Clin Transplant 5:287–293
13. Van den Berg AP, Van der Bij W, Van Son WJ, Anema J, van der Giessen M, Schirm J, Tegzess AM, The TH (1989) Cytomegalovirus antigenemia as a useful marker of symptomatic cytomegalovirus infection after renal transplantation – report of 130 censecutive patients. Transplantation 48:991–995
14. Van der Bij, Torensma R, Van Son WJ, Anema J, Schrim J, Tegzess AM, The TH (1988) Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leucocytes. J Med Virol 25:179–188