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A. P. van den Berg
I. J. Klompmaker
B. G. Hepkema
A. S. H. Gouw
E. B. Haagsma
S. P. Lems
T. H. The
M. J. H. Slooff

Cytomegalovirus infection does not increase the risk of vanishing bile duct syndrome after liver transplantation

A. P. van den Berg (✉) · T. H. The
Department of Clinical Immunology, University Hospital Groningen, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands

I. J. Klompmaker · E. B. Haagsma
Department of Gastroenterology and Hepatology, University Hospital, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands

B. G. Hepkema · S. P. Lems
Department of Transplantation Immunology, University Hospital, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands

A. S. H. Gouw
Department of Pathology, University Hospital, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands

M. J. H. Slooff
Department of Hepatobiliary and Pancreatic Surgery, University Hospital, P.O. Box 30.001, NL-9700 RB Groningen, The Netherlands

Abstract Cytomegalovirus (CMV) infection and HLA-DR sharing have been reported to be associated with the development of vanishing bile duct syndrome (VBDS) after liver transplantation. We retrospectively analyzed the importance of these risk factors for VBDS in 126 consecutive recipients of a first transplant. In contrast to previous studies, CMV was monitored strictly using the antigenemia assay, a quantitative marker of the viral load. Patient and graft survival were comparable in patients with and without CMV infection. The incidence of VBDS was low, regardless of the CMV infection status or degree of HLA-DR sharing. Improvements in the early diagnosis and treatment of CMV infection may have eliminated its negative influence on graft survival.

Key words Cytomegalovirus · VBDS · HLA-DR · Liver transplantation

Introduction

It has been reported that cytomegalovirus (CMV) infection, in combination with a one or more HLA-DR antigen match between donor and recipient, is associated with a tenfold increase in the relative risk of vanishing bile duct syndrome (VBDS) after orthotopic liver transplantation (OLT) [1]. Others have shown that HLA-DR match increases the incidence of CMV hepatitis, which in its turn increases the risk of VBDS fourfold [2]. Not all groups have been able to confirm these data, however [3].

High-quality virological monitoring is a prerequisite for studies on the relation between CMV infection and specific clinical events. The CMV antigenemia assay that has been developed in our laboratory is a sensitive and specific test to diagnose active CMV infection [4, 5]. It provides a quantitative estimate of the actual viral load, which makes it particularly useful to study the pathogenetic role of CMV on immunological events after transplantation. We analyzed the relation between CMV infection, HLA-DR matching, and VBDS in a cohort of patients who were meticuously monitored for CMV infection.

Materials and methods

Clinical management

A total of 126 consecutive adult recipients of a first OLT and surviving for at least 4 weeks formed the study population. The median duration of follow-up was 30 (range 1–100) months. Immunosuppression consisted of prednisolone, cyclosporin, and azathioprine, with a 1-week induction course of cyclophosphamide [6].

Acute rejections were documented by biopsy and treated with methylprednisolone pulses or a steroid recycle; in cases of steroid resistance, a course of rabbit ATG was given (Bijleveld et al., submitted for publication).

CMV seronegative recipients preferentially received a liver from a seronegative donor. No hyperimmunoglobulin or high-dose acyclovir prophylaxis against CMV were given. Generally, no specific measures were taken in case of asymptomatic CMV infection. When CMV disease occurred, immunosuppression was tapered according to protocol: prednisolone was reduced to 10 mg daily and azathioprine to 50 mg daily, whereas the cyclosporin dosage was kept unchanged. Ganciclovir was started when CMV disease persisted or when organs were involved. Immunosuppression was restored to normal levels when symptoms had subsided, antigenemia had decreased, and an antibody response had occurred.

CMV monitoring

CMV infection was diagnosed by weekly monitoring of antigenemia, viremia, and serology, as previously reported [5]. Biopsies were performed when organ involvement was clinically suspected.

HLA-DR typing

The two-colour fluorescence method using sets of locally obtained, well-characterized allo-antisera was used [7].

Definitions

CMV infection was defined by the detection of antigenemia or viremia, or by demonstration of a significant antibody rise [6]. CMV disease required the presence of laboratory evidence of CMV infection, a compatible clinical syndrome, and the absence of alternative causes of the symptoms. Diagnosis of VBDS required the complete absence of interlobular or small bile ducts in 50 % or more of portal tracts, with or without arteriopathy with intimal proliferation and foamy macrophage infiltration [8].

Statistics

Graft and patient survival rates were calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate statistical significancy. The Wilcoxon rank test for unpaired data and the chi-square test were used where indicated. All tests were performed two-sided, with P values of 0.05 or less being considered as statistically significant. In addition, 95 % confidence interval (CI) levels are given where appropriate.

Results

CMV infection and patient and graft survival

CMV infection occurred in 85 of the 126 patients (67 %). Infection was primary in 14, and secondary in the remaining 71 patients. Clinical manifestations occurred in 61 patients, comprising fever with or without arthralgia, myalgia, and malaise ($n = 48$), fever with biochemical evidence of hepatitis ($n = 11$), or pneumonitis ($n = 2$); 25 patients received ganciclovir because of CMV disease. No patient died as a direct result of CMV infection.

Infection was diagnosed by the presence of antigenemia in 79 patients; a serological response occurred in 82. Antigenemia permitted a presymptomatic diagnosis in the majority of cases and was valuable in the management of infection. Patient and graft survival rates at 2 years were 84 % and 81 %, respectively, and were not different in patients with and without CMV infection.

Table 1 Incidence of vanishing bile duct syndrome (VBDS) in relation to cytomegalovirus (CMV) infection and HLA-DR matching between donor and recipient (*CI* confidence interval)

CMV infection	HLA-DR antigen match	Incidence of VBDS (95 % CI)
No	0	2/22 9 % (1–29)
No	≥ 1	0/19 0 % (0–18)
Yes	0	2/55 4 % (4–13)
Yes	≥ 1	1/30 3 % (0–17)

VBDS

VBDS developed in five (4 %) patients at a median of 3 (range 2–12) months after OLT. Occurrence of VBDS was not related to patient age of sex, cold ischemia time, or operative blood loss. As expected, acute rejection was a risk factor for VBDS [relative risk (RR) 13.4, $P < 0.05$], as was steroid-resistant rejection (RR 12, $P < 0.05$). VBDS occurred in three patients with CMV infection; in all of them, CMV infection preceded VBDS. The RR of VBDS associated with CMV infection therefore was 0.72 (95 % CI 0.13–4.16, $P > 0.1$). VBDS was not related to the maximal CMV load during infection, occurrence of CMV disease, or CMV hepatitis. The risk of VBDS in relation to CMV infection and HLA-DR matching is given in Table 1. No evidence for a pathogenetic role of CMV infection, HLA-DR matching, or their combination was found.

Discussion

These data do not support claims by other groups that CMV infection, alone or in conjunction with a HLA-DR match, is pathogenetically linked to VBDS. Our study was retrospective, but the protocol for CMV monitoring was strict and intensive, and the management of CMV infection and disease was uniform, thus minimizing the potential for bias. It is difficult to explain the conflicting data from Cambridge/King's College [1] and Pittsburgh [2] on the one hand, and those from the Mayo Clinics [3] and our center, on the other. However, VBDS is generally preceded by one or more episodes of

acute rejection. More intense immunosuppressive treatment may have promoted the development of CMV infection and facilitated its detection. Thus, CMV infection might just be a reflection of increased alloreactivity. Alternatively, a period of tapering of immunosuppression that was too prolonged might have precipitated the onset of irreversible rejection. Accurate monitoring of viral replication using the antigenemia assay may have prevented undue underimmunosuppression. Finally, antiviral treatment may have limited the amount of damage directly by interruption of the cytopathogenic effects of viral replication, and indirectly, by limiting the cytotoxic T cell response to viral antigens.

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