Eur J Cancer Clin Oncol, Vol. 25, No. 9, pp. 1365–1368, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Immunoprophylaxis of Cytomegalovirus Infections in Transplanted Patients

D. BRON and J. KLASTERSKY

Service de Médicine Interne et Laboratoire d'Investigation Clinique H. Tagnon, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, rue Héger Bordet 1, 1000 *Brussels, Belgium*

Abstract—*Cytomegalovirus causes severe infections in immunosuppressed patients and anti-viral treatments remain unsatisfactory. In an attempt to prevent lifethreatening CMV infections, immunoprophylaxis using hyperimmune immunoglobulins has been studied but led to conflicting results in the literature. The role of passive immunization in allogeneic marrow and renal transplant patients is discussed.*

INTRODUCTION

VIRAL opportunistic infections, primarily CMV infections, represent a major infectious problem in transplant patients [1]. Treatment remains unsatisfactory and immunoprophylaxis is still debated in the literature.

There are several reasons to support immunoprophylaxis in the prevention of CMV infection. Hyperimmune immunoglobulins have proven useful in the prevention of various viral infections such as hepatitis A or B, varicella, rubella and measles. Other rational bases derive from animal data showing that hyperimmune immunoglobulins or breast feeding from CMV seropositive mothers are able to protect immunosuppressed or newborn mice against CMV-induced interstitial pneumonia (IP). Also, after transplantation — particularly after allogeneic bone marrow grafts — both cellular and humoral immunity are impaired and it has been demonstrated that transplanted patients with higher antibody response to CMV antigens have a better outcome.

HYPERIMMUNE IMMUNOGLOBULINS IN ALLOGENEIC BONE MARROW TRANSPLANTED PATIENTS

The role of hyperimmune immunoglobulins (Ig) has mostly been studied in allogeneic transplant patients particularly susceptible to CMV infection [2]. The results of five controlled studies are summarized in Table 1.

The first study, published by Winston *et al.* [3], compares hyperimmune plasma with a control group. The difference in the incidence of CMV infection or IP is not significant. However, when one looks at the subgroup population who did not receive granulocyte transfusions this difference becomes highly significant. The role of granulocyte transfusion in CMV infection has been confirmed in another controlled study published by Meyers *et al.* [4]. This trial conducted in Seattle has also shown a significant decrease in CMV infections in the population treated with anti-CMV Ig, without concomitant granulocyte transfusions.

In a subsequent study published by Condie and O'Reilly [5], none of the patients received granulocyte transfusions. Hyperimmune Ig prophylaxis was compared with no treatment and also with prophylaxis using high doses of non-specific Ig. The difference between hyperimmune anti-CMV Ig and the control group was highly significant in terms of CMV infection as well as in terms of interstitial pneumonia. There were slightly less severe CMV infections in the group treated by non-specific Ig but this difference was not significant. In 1986, the Seattle group published another study in which patients receiving hyperimmune Ig were compared with control subjects [6]. In contrast to the study published in 1983, although none of the patients received granulocyte transfusions, the difference between hyperimmune immunoglobulins and controls was not significant but the percentage of CMV disease was particularly low in this study. In the second study published by Winston *et al.* [7], using high doses of non-specific Ig instead of plasma, the difference in interstitial pneumonia was significantly reduced but, actually, those immunoglobulins contained high levels of anti-CMV Ig.

Although none of these studies are really comparable because of variations in dose schedules and immunoglobin sources, it appears that the incidence of CMV infection is probably not significantly reduced whereas the incidence of severe CMV

Table 1. Anti-CMV Ig in allogeneic transplant patients

Authors (ref.)	Patients	No.	CMV infections (%)	Interstitial pneumonia (%)
Winston *et al.* [3]	Plasma	24	50	21*
	Controls	24	63	46
Meyers *et al.* [4]	Hyperimmune Ig	30	33*	7
	Controls	32	44	9
Condie and O'Reilly [5]	Hyperimmune Ig	17	0†	0†
	HD Ig	18	33	17
	Controls	20	50	30
Bowden *et al.* [6]	Hyperimmune Ig	22	24	5
	Controls	24	40	5
Winston *et al.* [7]	HD Ig	38	46	18†
	Controls	37	53	46

* Only significant in absence of granulocyte transfusions.
† $P < 0.05$.

Table 2. Doses and schedule of anti-CMV immunoglobulins (Ig)

Authors (ref.)	Source	Route	Doses of Ig	Schedule
Winston *et al.* [3]	Plasma	IV	10 ml/kg (150 mg/kg)	Day −7, 3, 30, 45, 60, 75, 90, 120
Meyers *et al.* [4]	α-CMV Ig	IM	6 ml/m² (±70 mg/kg)	Day −4, −2, 0, 1 × week→ day 77
Condie and O'Reilly [5]	α-CMV Ig	IV	200 mg/kg	Day 25, 50, 75
Vuvan *et al.* [8]	α-CMV Ig	IV	200 mg/kg	1 × week→ day 100
Bowden *et al.* [6]	α-CMV Ig	IV	150 mg/kg	Day −5, −1, +6, +20, +34, +48, +62

disease such as interstitial pneumonia seems to be significantly decreased.

The best schedule and the optimal period to start the immunoprophylaxis are difficult to define. Trials using anti-CMV Ig are detailed in Table 2. The doses of Ig vary from 70 to 200 mg/kg. Other non-randomized studies reported good results with higher doses of Ig (500 mg/kg) but these data are not superior to those expected with lower doses. In three studies [3, 4, 6] Ig were given before transplantation whereas one study started the day of transplantation [8] and one study started 3 weeks after transplantation [5]. Since the period of severe combined immunodeficiency starts several weeks after TBI and CT, it is probably not important to start the treatment before transplantation. Also, although several studies use a weekly schedule, the half-life of immunoglobulin is 3 weeks and it is thus probably not necessary to give these Ig more than every 3 weeks. However, when GVHD occurs, Ig survival is shortened and the frequency of Ig administration should be increased.

Another question concerns the respective role of immunoglobulins in CMV seronegative recipients and in CMV seropositive recipients. In six studies, the patient's CMV status is available. In Winston *et al.*'s study [3], using hyperimmune plasma, there are too few seropositive patients to draw a conclusion but the feeling of the author is that less CMV infection occurred in the four patients treated with Ig than in the five patients treated without Ig. In the study published by the Seattle group, all patients were seronegative and, in the absence of granulocyte transfusions, hyperimmune Ig were effective [4]. This is also the case in the study conducted by Condie and O'Reilly, in which most of the patients were seronegative and effective prevention with hyperimmune Ig was demonstrated [5]. In this study, data on the few seropositive patients are not known. In another study conducted in Germany, hyperimmune Ig at two different dosages were effective; in this study, the majority of the patients were seropositive suggesting that these Ig are also effective in seropositive patients. Finally, in Schmeiser *et al.*'s study, prevention of CMV infection was mostly marked in seronegative patients in which only 6% of CMV infection developed whereas 48% of CMV infection appeared in seropositive patients [9]. Ig are effective in seronegative patients and it is likely that they do play a role in seropositive patients. However, new studies with larger numbers of patients are required to confirm the protective role of Ig.

HYPERIMMUNE IMMUNOGLOBULINS IN RENAL TRANSPLANT PATIENTS

CMV is also a problem after renal transplantation in which CMV infection can induce graft failure or leukopenia. Little data are available in terms of

immunoprophylaxis and only one randomized study has been published [10]. This study, analyzing the role of intravenous Ig in CMV negative renal transplant recipients receiving a graft from a CMV positive donor, demonstrated a significantly reduced incidence of virologically confirmed CMV syndrome as well as CMV-induced leukopenia. Most of the other complications related to CMV diseases (hepatitis, thrombocytopenia, graft loss, pneumonia) decreased but, because of the low numbers, none of those were significant. It is concluded that hyperimmune Ig do play a role in the prevention CMV-related complications after renal transplantation as well as after BMT.

SOURCES OF IMMUNOGLOBULINS

Winston *et al.* published a control study using hyperimmune plasma [3]. The rationale for using plasma is based on animal data but animal data have also shown that only the 7S fraction, containing the specific IgG, was useful in the prevention of CMV. In addition, plasma always represents a higher risk of transmission of infectious diseases and usually contains lower titers of antibody. Intramuscular injection is the usual route used for viral prophylaxis but the maximum doses are limited by the pain at the injection site, and it seems that higher doses of immunoglobulins are necessary to prevent CMV infection than to prevent other viral infections. Also, at least 4 days are required to reach adequate circulating levels of anti-CMV immunoglobulins. For all these reasons, a large majority of the studies have used intravenous hyperimmune Ig allowing higher titer of circulating anti-CMV antibody.

In order to circumvent the use of human donors, human monoclonal antibody technology brings real promise in the search for new sources of anti-CMV antibodies. Such a human monoclonal IgG has been obtained in our laboratory and preliminary *in vitro* data indicate that this antibody can prevent CMV-induced myelosuppression [11].

MECHANISM OF ACTION

The mechanism of action of this anti-CMV immunoglobulin is not fully understood [12, 13]. It has been shown that specific anti-CMV immunoglobulins in immunosuppressed patients—with diminished response to CMV antigen, with lower production of interferon after virus infection — increase the level of specific immunoglobulins with cytotoxic or neutralizing activities. It is also likely that the increase of IgG level in the serum and respiratory tract decreases the risk of infectious problem including CMV. Ig activate the complement system and increase host defense.

In four studies mentioned earlier, IVIG have been associated with a decrease in the incidence of graft versus host disease (GVHD) [3–5, 13]. This decrease in GVHD has also been reported with specific and non-specific IV immunoglobulins.

This important effect could be related to anti-lymphocytes antibodies or to a blockade of FC-receptor on CD8 lymphocytes (CD8-lymphocytes) being involved in the process of GVHD). It is well known that CMV infection is correlated with the incidence of GVHD and a reduced incidence of GVHD probably has an indirect effect in the prevention of CMV reactivation or CMV infection [14].

ROLE OF SCREENED BLOOD PRODUCTS

There are ample data indicating that primary CMV infection occurring among seronegative patients is usually, if not exclusively, due to transmission of virus in blood products, including the marrow itself [14]. Recently, the Seattle group published a very relevant study of seronegative patients showing the role of blood products screened for CMV [6]. As illustrated in Table 3, although Ig does decrease the incidence of CMV infection, this difference becomes only significant when screened blood products are used in parallel with hyperimmune Ig and it seems that this effect could be related only to the screened blood. The authors suggest that, in CMV-negative patients receiving marrow from CMV-negative donor, the use of screened blood products can completely prevent CMV infection.

The important role of screened products in CMV negative recipient has been demonstrated in two other centers [15, 16]. The addition of screened products significantly reduced the incidence of CMV infection when combined with hyperimmune Ig vs. Ig alone. Unfortunately, a control with only screened blood products is missing in both of the latest studies and it is difficult to isolate the role of screened blood products from the role of Ig.

Table 3. Role of screened blood products in CMV propylaxis

Authors (ref.)	No. patients	Treatment	% CMV infection
Bowden *et al.* [6]	22 (CMV^-)	IVIG	24
	28 (CMV^-)	Screened blood	13*
	23 (CMV^-)	IVIG + screened blood	5*
	24 (CMV^-)	Controls	40
Ash *et al.* [15]	20 (CMV^-)	IVIG + screened blood	0*
	22 (CMV^-)	IVIG	12
	19 (CMV^-)	Controls	32
Kapoor *et al.* [16]	38 (CMV^+)	IVIG + screened blood	32
	56 (CMV^-)	IVIG + screened blood	0

IVIG: intravenous immunoglobulins.
* $P < 0.05$.

Additional data are still required to understand if a combination of Ig and screened blood products is superior to screened blood products only. This question is particularly important in CMV-negative recipients receiving marrow from a CMV-positive donor.

CONCLUSIONS

Additional controlled studies are still required to better understand the role of Ig, particularly in view of the cost of this product. Trials are particularly needed in seropositive transplant patients, in seronegative transplant patients with a seropositive donor, or in blood donor centers where screened products are not available.

Hyperimmune Ig are not useful in seronegative recipient with a seronegative donor and screened blood transfusions given the excellent prevention obtained with screened blood products only. The Ig are not useful when unscreened granulocyte transfusions are administered because Ig are probably not able to neutralize such a large inoculum of virus. Finally, promising results with the prophylactic use of Acyclovir in seropositive recipient should encourage studies combining chemoprophylaxis and immunoprophylaxis.

REFERENCES

1. Wingard JR, Chen DYH, Burns WH *et al.* Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. *Blood* 1988, **71**, 1432–1437.
2. Sullivan KM. Immunoglobulin therapy in bone marrow transplantation. *Am J Med* 1987, **83**, 43–45.
3. Winston DJ, Pollard RB, Ho WG *et al.* Cytomegalovirus immune plasma in bone marrow transplantation recipients. *Ann Intern Med* 1982, **97**, 11–18.
4. Meyers JD, Leszczynski J, Zaia JA *et al.* Prevention of cytomegalovirus immune globulin after marrow transplantation. *Ann Intern Med* 1983, **98**, 442–446.
5. Condie RM, O'Reilly RJ. Prevention of cytomegalovirus infection by prophylaxis with an intravenous, hyperimmune, native, unmodified cytomegalovirus globulin. *Am J Med* 1984, **76**, 134–141.
6. Bowden RA, Sayers M, Flournoy N *et al.* Cytomegalovirus immune globulin and seronegative blood products to prevent primary cytomegalovirus infection after bone marrow transplantation. *N Engl J Med* 1986, **314**, 1006–1010.
7. Winston DJ, Ho WG, Lin CH *et al.* Intravenous immunoglobulin for modification of cytomegalovirus infections associated with bone marrow transplantation. *Am J Med* 1984, **76**, 128–133.
8. Vu Van H, Fiere D, Chomel J *et al.* Prophylaxis against cytomegalovirus infection after BMT with gammaglobulins. *Exp Hematol* 1985, **13**, 105.
9. Schmeiser T, Arnold R, Wiesneth M, Bunjes D, Heimpel H, Heit W. CMV-IgG-hyperimmunoglobin for the prevention of CMV-infection in BMT-recipients. *Bone Marrow Transplantation* 1986, **1**, 64.
10. Snydman DR, Werner BG, Heinze-Lacey B *et al.* Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal-transplant recipients. *N Engl J Med* 1987, **317**, 1049–1054.
11. Bron D, Lagneaux L, Delforge A, Klayme S, Stryckmans P. Role of human monoclonal anti CMV antibody in CMV-induced myelosuppression. *Blood* 1988, **72**, 261a.
12. Berkman SA, Lee ML, Gale RP. Clinical uses of intravenous immunoglobulins. *Sem Hematol* 1988, **25**, 140–158.
13. Occhini D, Bacigalupo A, Van Lint MT *et al.* Prophylactic high-dose IV IgG in bone marrow transplantation: a randomized trial. *Bone Marrow Transplantation* 1986, **1**, 57–58.
14. Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. *J Infect Dis* 1986, **153–3**, 479–488.
15. Ash RC, Bratanow NC, Raybould T *et al.* Prevention of primary cytomegalovirus infection in allogeneic bone marrow transplant patients by cytomegalovirus-negative blood products and anti-cytomegalovirus intravenous immunoglobulin. *Blood* 1986, **68**, 297a.
16. Kapoor N, Tutschka PJ, Copelan EA. Prevention of fatal CMV infection by administration of intravenous gammaglobulin. *Blood* 1987, **70**, 308a.