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A randomized trial of high dose polyvalent intravenous immunoglobulin (HDIgG) vs. *Cytomegalovirus* (CMV) hyperimmune IgG in allogeneic hemopoietic stem cell transplants (HSCT)

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Abstract

Background and Objective. **The role of high dose intravenous IgG (HDIgG) and of hyperimmune CMV IgG (CMV-IgG) in patients undergoing allogeneic hemopoietic stem cell transplantation (HSCT) is still unclear. The aim of this study was to compare prophylactic CMV-IgG with HDIgGin a randomized prospective trial in allogeneic HSCT recipients: primary end point of the study was the occurrence of post-transplant CMV antigenemia (CMVAg-emia). Secondary end-points were severity of acute and chronic graft-versus-host disease (GvHD), infections and transplant related mortality (TRM).**

Design and Methods. **Patients were randomized to receive 100 mg/kg/week of CMV-IgG (group A; n=64) or 400 mg/kg/week of HDIgG (group B; n=64) from day –7 to day +100. The two groups were comparable for age, diagnosis, disease status, and acute graft-versus host (aGvHD) prophylaxis.**

Results. **The actuarial risk at 1 year of CMV antigenemia was lower for CMV-IgG (61% vs. 71%) but not significantly (p=0.37); CMVAg-emia occurred at the same interval from HSCT (47 vs. 48 days, p=0.9), with a comparable number of CMVAg positive cells (3 vs. 3 p=0.9). Eight patients died of interstitial pneumonia (IP) (4 in each group), two in group A of CMV-IP. Acute GvHD was scored as 0-I, II and III-IV in 39 vs. 35, 23 vs. 22 and 2 vs. 7 patients respectively for the two groups (p= not significant). The actuarial risk of developing acute GvHD grade II-IV was lower for CMV-IgG (39% vs. 45 %) but not significantly (p=0.43). Chronic GvHD scored as absent in 7 vs. 10 patients, limited in 39 vs. 37 and extensive in 19 vs. 17 patients respectively (p=not significant). Numbered days with intravenous antibiotics, days in hospital, days of fever, number of local and disseminated infections, number of patients with fever of unknown origin were not significantly different. Actuarial 1 year TRM is 18% vs. 19%, respectively (p=0.9).**

Interpretation and Conclusions. **This study confirms that CMV antigenemia is comparable in recipients of hyperimmune CMV-IgG and of polyvalent HDIgG, although the former had a 32% lower cost. It also shows that the potential immunomodulating effect on acute GvHD and transplant mortality is similar with 100 or 400 mg of IgG/kg/week: this is relevant, in view of the high cost of prophylactic HDIgG.**

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Immunodeficiency following myeloablative chemoradiotherapy and allogeneic bone marrow transplantation (BMT) can foster a variety of opportunistic infections,[1] including cytomegalovirus infections (CMV), one of the leading causes of morbidity and mortality. Acute GvHD, seropositive donors or recipients, HLA mismatching are all predictors of development CMV infection and/or disease.[2,3]

The use of high dose intravenous immunoglobulin (HDIgG) post-BMT is a controversial and expensive way of preventing infectious complications, after marrow or organ transplantation.[4] Studies in BMT recipients have used either polyvalent HDIgG or CMV-IgG, and both were found to prevent CMV infections;[5,6] similar results were achieved with immune plasma administered to seronegative patients not receiving granulocyte transfusions, with little effect however on the incidence and severity of GvHD.[7] Immune plasma does not protect patients at risk from CMV infection.[8] In general there was a decrease in the incidence of CMV infection compared to control groups, but the effect on CMV-disease was variable or absent.[9,10]

One unexpected finding was that prophylactic HDIgGs resulted in a significant decrease of the incidence and severity of GvHD in HLA identical and HLA non-identical graft recipients; gram-negative septicemia and local infections were also reduced, especially during the period of neutropenia.[11]

The aim of the present study was to test whether hyperimmune CMV-IgGis superior to polyvalent IgGin preventing CMV infections after allogeneic stem cell transplants. Primary end points of the study were CMV-antigenemia and CMV disease. Secondary end points were number of days with

Table 1. Clinical characteristics of patients.

	Total	*Group A*	*Group B*	*p*
Number	128	64	64	
Age (y)				
median (range)	35.5(11–56)	33.5(17–55)	36(11–56)	NS**
Recipient gender				
male/female	87/41	43/21	44/20	NS*
Donor age (y)				
median (range)	32.5(1–66)	32(1–57)	32.5(1–66)	NS**
Donor genders				
male/female	63/65	37/27	26/38	NS**
Disease				
SAA	9	6	3	NS*
AML	43	20	23	NS*
CML	34	18	16	NS*
ALL	18	9	9	NS*
others	28	14	14	NS*
Disease status				
CP– CR1	84	48	36	NS*
CR2	16	7	9	NS*
Advanced	27	8	19	NS*
CMV status (d/r)				
–/–	2	0	2	
+/–	8	4	4	
–/+	17	12	5	
+/+	101	48	53	
Days from diagnosis to HSCT				
Median (range)	236(31–4413)	234(40–3452)	226(31–4413)	NS°

**Fisher's exact test. °Mann–Whitney test.*
Abbreviations: Group A=CMV–IgG; Group B=polyvalent.
SAA=severe aplastic anemia, CML=chronic myelogenous leukemia, AML=acute myelogenous leukemia, ALL=acute lymphoblastic leukemia, CMV=cytomegalovirus, HSCT=hemopoietic stem cell transplantation, CR=complete remission, CP=chronic phase.

fever, days in hospital, incidence and severity of acute GvHD and transplant mortality.

Materials and Methods

Patients

One hundred twenty-eight patients underwent hemopoietic stem cell transplantation from HLA identical siblings at our Institute between 1992 and 1996. Informed consent was obtained from all patients. Clinical details of patients are outline in Table 1. The two groups were comparable for age, diagnosis, disease status at transplant, and time between diagnosis to transplantation (Table 1).

Transplantation

All patients were transplanted in our institute between 1992 and 1996. The conditioning regimen was cyclophosphamide (CY)(120 mg/kg) (n=10) (group A, n=7, group B, n=3), CY plus total body irradiation (TBI)(n=84) (group A n=43, group B n=41) and CY plus busulphan (16 g/kg)(BU) or Thiotepa (TT)(5-15 mg/kg)(n=34) (group A n=14, group B n=20). TBI was delivered to patients in total dose of 9.9-12 Gy in 3-6 fractions. Prophylaxis for acute graft-versus-host disease (GvHD) was mainly cyclosporin A (CSA) with (n=113) or without (n=15) short course methotrexate (MTX). The distribution of patients who were not given MTX was marginally different between groups (11 vs 4, p=0.05). Ninety four patients received HLA identical bone marrow grafts (group A n=52, group B n=42), and 34 patients received HLA identical peripheral blood hemopoietic stem cells (group A n=12, group B n=22).[12,13] The median number of infused cells was 5.2 (range 1.9-25.8) vs. 6.1 (range 3-23.3)$\times 10^8$/g BW for the two groups, respectively (p=0.09). The cells were transfused over 24 hours after the last fraction of TBI. Neither prophylactic nor therapeutic granulocyte transfusions were used in the study patients. All blood products were irradiated and transfused to patients via leukocyte filters resulting in significant leukocytes depletion. All patients received oral trimethoprim-sulphomethoxazol to prevent *Pneumocystis carinii* infection, intravenous acyclovir 500 mg/m^2 every eight hours, form day –1 to +30 and after that acyclovir per os 800 mg four times per day. Patients who developed CMVAg-emia were treated pre-emptively with ganciclovir and/or foscavir as we have previous reported.[14]

Study design

Hyperimmune CMV-IgG. Group A received 100 mg/kg/week hyperimmune CMV-IgG (Cytotect, Biotest, Germany) from day –7 to day +100: this preparation has been reported to contain a titer of neutralizing antibodies of 1:1,000.[15] The cost for the average 60-kg weight patient was 7,714 USD.

Polyvalent IgG. Group B received 400 mg/kg/week of polyvalent IgG (Sandoglobulin, Sandoz, Switzerland) from day –7 until day +100: this preparation has been shown to have a titer of neutralizing CMV antibodies of 1:50.[15] The cost for the average 60-kg weight patient was 11,314 USD.

End points

The primary end point of the study was the incidence of CMVAg-emia and CMV disease. Secondary end points were: IgG levels after HSCT, number of days with fever, days in hospital, incidence and severity of acute GvHD and transplant mortality.

CMV status at transplantation

Two donor/recipient pairs were CMV seronegative before HSCT (–/–), 8 pairs had a positive donor in to a negative recipient (+/–), 17 had a negative donor in to a positive recipient (–/+) and 101 were both positive (+/+) (Table 1).

CMV lower matrix protein pp65

All patients were monitored weekly until day +100, and then at regular intervals as outpatients,

Table 2. Transplantation characteristics.

	Total	Group A	Group B	p
Donor type				
HLA id sibling (BM)	94	52	42	0.09*
HA id sibling (PBSC)	34	12	22	0.03*
Conditioning regimen				
CY	10	7	3	0.16*
CY+TBI	84	43	41	0.42*
CY+ BU or TT	34	14	20	0.15*
Acute GvHD prophylaxis				
CSA+MTX	113	53	60	0.05*
CSA	15	11	4	0.05*
No of infused cells				
median (range)	5.5 (1.9-25.8)	5.2(1.9-25.8)	6.1(3-23.3)	0.008°
BM	4.8 (1.9-13.6)	4.75(1.9-13.6)	4.9(3-8.3)	0.088°
PBSC	12.9(5.8-25.8)	12.8 (6-25.8)	13 (5.8-23)	0.8°

**Fisher's exact test. °Mann–Whitney.*
Abbreviations: Group A=CMV–IgG; Group B=polyvalent. SAA=severe aplastic anemia, CML=chronic myelogenous leukemia, AML=acute myelogenous leukemia, ALL=acute lymphoblastic leukemia, CMV=cytomegalovirus, HSCT=hemopoietic stem cell transplantation, CR=complete remission, CP=chronic phase.

for the presence of pp65-positive cells in peripheral blood by immunoperoxidase stain, as described previously,[16] using a mixture of C10 and C11 (CLONAB CMV, Bites) antibodies and peroxidase staining. CMV-positive cells were expressed as positive cells/200,000 cells.

Statistical analysis

Statistical analysis was performed on the basis of the intention-to-treat principle. The Mann-Whitney test was used to compare means for continuous variables between groups. Fisher's exact test was used for 2×2 tables. Kaplan-Meier curves were used for survival, relapse and transplant-related mortality incidence as also the actuarial incidence of CMV antigenemia and incidence of acute GvHD grade II-IV.[17]

Results

Engraftment

All patients had a complete daily blood count until day +30 and at least weekly as outpatients for 6 months and in every visit after that. All patients achieved engraftment. Median day to reach polymorphonuclear cells (PMN) > 500×10^9/L was 15 days (range 10-25) for both groups (p=0.97).

CMV-antigenemia

Seventy nine patients (54%) developed CMVAgemia, 37 (58%) patients of group A vs. 42 (66%) of group B (p=0.23). The median day to develop antigenemia for group A was 47 days (range 18-139) vs. 48 days for group B (range 2-104)(p=0.9). Median number of CMV-positive cells was 3 (range 1-82) for group A vs. 3 (range 1-124) for group B (p=0.9) and the maximum number of CMVAg positive cells was 5 (range 1-150) and 7 (range 1-124) for two groups, respectively (p=0.8). Ten out of 64 patients (16%) from group A and 8/64 (13%) patients from group B developed interstitial pneumonia (p=0.97).

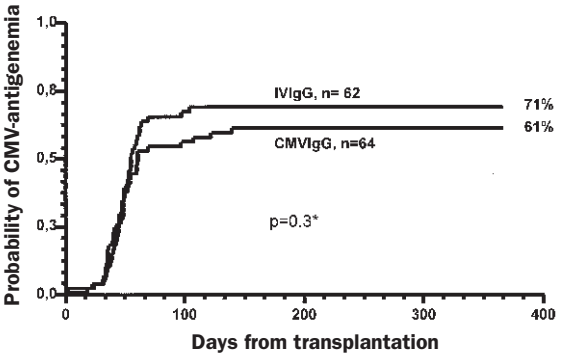

Figure 1. Actuarial probability to develop CMV antigenemia for patients at risk (*log rank).

The actuarial risk of developing CMV antigenemia was 61% vs. 71% (p=0.15) for the two groups respectively (Figure 1) and was not influenced by the CMV status of donor.

Acute GvHD (aGvHD)

The median day to develop aGvHD was 17 (7-99) for the whole group. For 39 (61%) of group A and 35 (55%) of group B was scored as grade O-I respectively (p= 0.29), 25 vs 29 as grade II-IV (39% vs. 45%, p=0.29)(Table 3). The actuarial incidence to develop acute GvHD grade II-IV was 39% vs. 45%, respectively (p=0.77)(Figure 2). The incidence of CMV-antigenemia was not statistically significant for two groups, for different grades of acute GvHD (for grade O-I, p=0.9, for grade II, p=0.2, and for grade II-IV, p=0.5). In addition, there was no age impact in the incidence of acute GvHD (data not shown).

Serum IgG levels

Serum levels of immunoglobulin were measured every week. The median levels AF IgG were significantly higher in patients of group B as compared with patients of group A, at time intervals 0-20, 21-50, 51-100 days after transplantation (p<0.0001). The levels were decreased and similar in the two groups after day +100, after the discontinuation of IgG prophylaxis (p=0.4)(Figure 3).

Table 3. Results.

	Total	Group A	Group B	p
CMV antigenemia				
CMV (N/Y)	49/79	27/37	22/42	0.23*
no. CMV+ cells	3 (1-124)	3 (1-82)	3 (1-124)	0.9°
days CMVAg	48 (2-139)	47 (18-139)	48 (2-104)	0.9°
max no. cells	6 (1-150)	5 (1-150)	7 (1-124)	0.8°
Acute GvHD				
O-I	74/128	39/64	35/64	0.29*
II	55/128	23/64	22/64	0.5*
II-IV	9/128	2/64	7/64	0.8*
median day	17 (7-99)	17 (7-99)	17 (7-56)	0.67°
Chronic GvHD				
no	17	7	10	0.3*
limited	75	38	37	0.5*
extensive	36	19	17	0.4*
Causes of death				
leukemia relapse	16	6	10	
acute GvHD	6	2	4	
infections	3	2	1	
others	5	2	3	
interstitial pneumonia	8	4	4	
Days PMN > $500x10^9$/L				
median (range)	15 (10-25)	15 (10-25)	15 (10-25)	0.97°
Survival (months)				
median (range)	23 (7.7-50)	23 (7.7-50)	25.3 (9.7-48)	0.5°

**Fisher's exact test. °Mann-Whitney.*
Abbreviations: Group A= CMV-IgG; Group B= polyvalent. HDIgG GvHD=graft versus host disease, CMV=cytomegalovirus, max=maximum, PMN=polymorphonuclear cells, mo=months.

Infections

The incidence of infections was comparable between groups. The number of local/disseminated infections in the two groups were as follows: 22/14 for group A vs 24/22 for patients in group B. The latter is of borderline significance (p=0.08). Fever of unknown origin developed in 8 vs 9 patients, respectively.

Interstitial pneumonia developed in 18 patients (10 vs 8 for two groups respectively). CMV was the cause of IP in 2 patients in group A; 4 vs 7 patients developed fungal pneumonia. Fever of unknown origin develop in 8 out of 9 patients, respectively.

Survival, relapse and transplant-related mortality (TRM)

The 4 years actuarial survival (69% vs. 60%, p=0.35), relapse rate (20% vs. 31%, p=0.1) and TRM (18% vs. 19%, p=0.9) were not statistically significant between two groups (Figure 4).

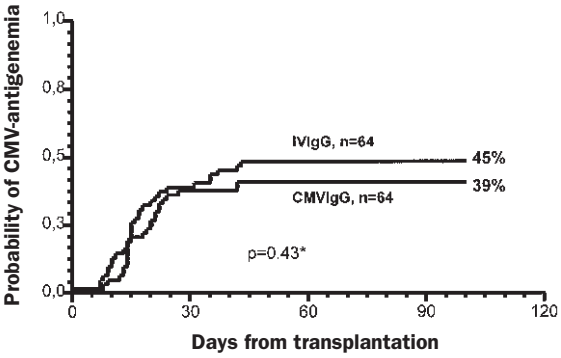

Figure 2. Actuarial probability to develop acute GvHD grade II-IV (*log rank).

Causes of death

Fifiteen (23%) patients from group A, and 22 (34%) from group B died (p=0.12) of leukemia relapse (5 vs. 10 deaths for two groups respectively), interstitial pneumonia (IP) (4 patients in each group), acute GvHD (2 vs 4) or infections (2 from group A and 1 from group B).

Discussion

The use of intravenous immunoglobulin after bone marrow transplantation has been reported to decrease CMVAg-emia and infections:[11,18] similar results were reported with the use of immune plasma, especially in seronegative patients.[5,8] Cytomegalovirus immunoglobulin has been reported to be effective as a single agent in the treatment of cytomegalovirus pneumonia[19] especially in combination with drugs such as ganciclovir and/or foscavir.[20,21]

In this prospective randomized study, we have shown that hyperimmune CMV-IgG has a statistically non significant advantage compared to polyvalent HDIgG in preventing CMV infections after allogeneic HSCT, although the amount of neutralizing antibodies given to the patient with the hyperimmune preparation was five times greater than in the polyvalent IgG preparation.[15] The risk of CMV-antigenemia was 10% less in the CMV-IgGgroup (p=0.3) and CMV disease was comparable. Therefore, a large dose of specific CMV IgG given until day +100, in association with a high dose of acyclovir, does not seem to prevent CMV infections in allogeneic HSCT recipients. The conclusion that could be drawn is that CMV antibodies are relatively ineffective in preventing CMV reactivation or infections, in agreement with a recent study.[22] CMV disease was rare, but it should be said that all patients received pre-emptive therapy at the time of CMV antigenemia. This approach has been shown to prevent or control CMV infections,[23] whereas ganciclovir prophylaxis at engraftment must still

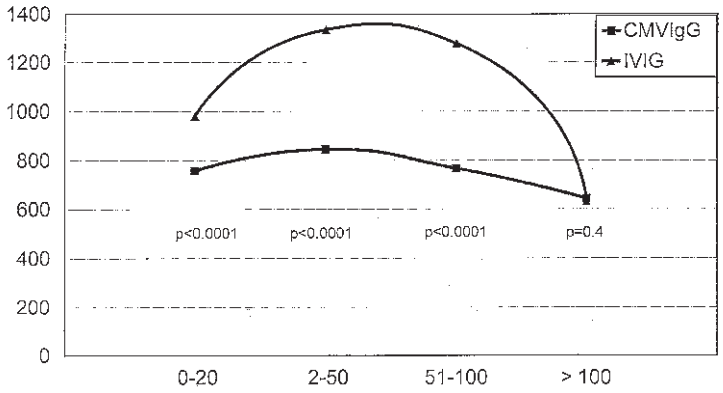

Figure 3. Serum levels of IgG after transplantation. Significant higher levels are seen in patients receiving polyvalent immunoglobulin as compared to patients receiving lower dose ($p < 0.0001$). After day +100, serum IgG levels are comparable.

prove to be superior in terms of survival.[23,24]

We have shown that the IgG levels in recipients of HDIgG were significantly higher ($p< 0.00001$) when compared to hyperimmune CMV. Therefore, we have been administering prospectively a larger dose of IgG to a randomly chosen group of patients and have achieved significantly greater serum IgG levels, although the overall incidence of local/disseminated infections was superimposable.

The mechanisms of action of immunoglobulin is poorly understood. Activation of complement system, increase of phagocytosis and granulocyte chemotaxis, increase of levels of virus-neutralizing antibody and serum antibodies to endotoxins, decreased bacterial attachment to mucosal surfaces have all been proposed, but immunoregulatory functions are also a possible mechanism of action.[11] Immunoglobulin now has an established role in treatment of autoimmune diseases such as autoimmune thrombocytopenia.[25,26] Possible mechanisms are the competitive blockage of Fc receptors on macrophages surface, providing a signal for the elimination of the cells or preventing them from recognizing target tissues.[27] The current used dose of IgG is 400-1,000 mg/kg/week, which results in antibody replacement, enhanced neutralization and augmented opsonization-phagocytosis. In the present study we found no significant differences using 100 or 400 mg/kg/week, in keeping with recently reported results of two double-blind studies showing that the immunomodulating action of immunoglobulin is comparable in different doses.[28,29]

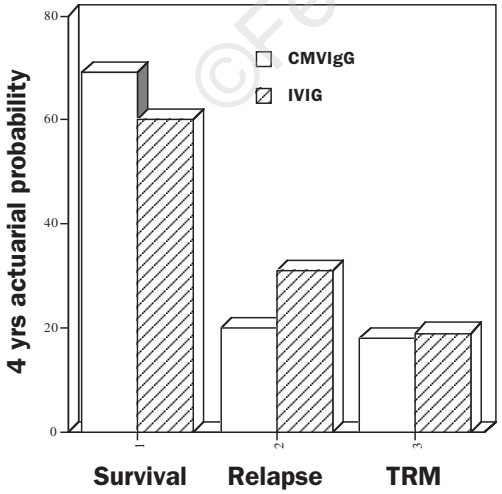

Figure 4. Four years actuarial probability of survival (69% vs 60%), relapse rate (20% vs 31%), and TRM (18% vs 19%) for groups A and B, respectively.

An important issue is the cost of a high dose of IgG after allogeneic BMT. CMV-IgG given at the dose of 100 mg/kg is 32% less expensive than 400 mg/kg of HDIgG, and therefore comparable results in this study were achieved at a lower cost.

This consideration, together with the fact that 100 and 400 mg/kg of IgG seem to be equivalent in modulating acute graft versus host disease has prompted us to open a prospective randomized trial comparing 100 vs 400 mg/kg/week of polyvalent IgG: the results will be comparable if this will cut the cost of IgG post-HSCT significantly.

Contributions and Acknowledgments

AB was responsible for the conception of the study, its design, funding, direct supervision and for reviewing the manuscript. MTVL was responsible for randomization and data handling. TL, FG, DO, NM, GB, SB were responsible for patient care. PZ was responsible for data handling and for drafting the article.

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Disclosures

Conflict of interest: none.

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