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Prevention and Treatment of Cytomegalovirus Infections with Interferons and Immune Globulins

Summary: With the exception of congenitally-infected infants, cytomegalovirus infection is generally benign in persons with normal host defenses. In contrast, among immunosuppressed patients, these infections may be severe and sometimes fatal. Treatment of cytomegalovirus infection with presently available antiviral agents including interferons has not been successful. Prevention of infection has been successful in several circumstances, however. Cytomegalovirus is transmitted by blood products from seropositive donors, and screening to remove seropositive blood products or freezing to destroy leukocytes has been effective among neonates, cardiac transplant patients and renal dialysis patients. An alternative approach used among marrow transplant patients is passive immunization of seronegative patients with plasma or globulins with high antibody titers against cytomegalovirus. Alpha interferon given prophylactically has been effective in delaying virus reactivation and reducing the severity of infection among seropositive renal transplant patients. All of these approaches, as well as the continued development of more effective antiviral agents, will be needed for control of cytomegalovirus infection.

Zusammenfassung: *Prävention und Behandlung von Cytomegalovirus-Infektionen mit Interferonen und Immunglobulinen.* Bei Personen mit normaler körpereigener Abwehr nimmt die Cytomegalovirus-Infektion im allgemeinen einen benignen Verlauf – ausgenommen Säuglinge mit konnataler Infektion. Bei immunsupprimierten Patienten ist der Verlauf hingegen schwer, manchmal tödlich. Die Therapie der Cytomegalovirus-Infektion war bisher mit den derzeit verfügbaren antiviralen Substanzen einschließlich der Interferone nicht erfolgreich. Durch verschiedene Maßnahmen gelang es jedoch, die Infektion zu verhüten. Cytomegalovirus wird durch das Blut von seropositiven Spendern übertragen. Das Screening zur Aussonderung seropositiver Blutprodukte und Gefrieren der Blutprodukte zur Zerstörung der Leukozyten waren bei Neugeborenen, Herztransplantat-Empfängern und Hämodialyse-Patienten wirksam. Bei Knochenmarkstransplantat-Empfängern wurde als Alternative die passive Immunisierung seronegativer Patienten mit Plasma oder Globulinen mit hohen Antikörpertitern gegen Cytomegalovirus eingesetzt. Prophylaktische Gabe von alpha-Interferon verzögerte die Virus-Reaktivierung und verminderte bei seropositiven Nierentransplantat-Empfängern die Schwere der Infektion. Um die Cytomegalovirus-Infektion unter Kontrolle zu bringen, wird es nötig sein, alle diese Methoden einzusetzen und weiterhin an der Entwicklung wirksamer antiviraler Substanzen zu arbeiten.

Introduction

Cytomegalovirus as a pathogen in the immunocompromised host is commanding increasing attention. Although it may be the cause of severe malformations in the congenitally infected infant and may occasionally cause substantial morbidity when primary infection occurs in either neonates or adults, cytomegalovirus is rarely the cause of serious clinical illness in persons with normal host defenses. In patients with suppression of normal host defenses such as those with leukemia or lymphoma, congenital or acquired immune deficiency syndromes, or in those receiving organ allografts, the situation may be quite different. In these patients, cytomegalovirus infection has been associated with syndromes of fever and leukopenia, hepatitis, arthralgias and arthritis, retinitis, ulcerative disease of the esophagus, stomach and bowel, pneumonia, and encephalitis as well as diffusely disseminated infection. Cytomegalovirus disease appears to be most common and most severe among recipients of organ allografts. Cytomegalovirus pneumonia has been observed in approximately 15% of allogeneic marrow graft recipients (1) and more recently has been reported in a similarly high proportion of renal allograft recipients who are either transplanted from cytomegalovirus-seropositive donors or who receive more intensive immunosuppressive regimens (2). Other important syndromes associated with cytomegalovirus infection among renal and cardiac transplant patients include graft rejection and bacterial, fungal, or protozoan superinfection.

Epidemiology of Cytomegalovirus Infection

After birth, cytomegalovirus infection is acquired primarily through person-to-person exposure to infected body fluids such as urine, saliva, breast milk, or cervical or

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seminal secretions. An additional source in persons with otherwise normal host defenses is exposure to virus-containing blood transfusions, for example during cardiac or trauma surgery; this is the source of the well-known "post-perfusion" mononucleosis syndrome. Although immunosuppressed patients may also acquire infection through exposure to any of these sources, the most common sources in these patients include either infected blood products or, among patients receiving organ allografts, transmission of virus in the transplanted organ. There are ample data confirming blood as a source in both renal and cardiac transplant patients (3–5), and it appears that both the volume of blood transfused and the number of blood donors used are important determinants of the risk of transfusion-acquired cytomegalovirus infection. The fact that individual seropositive blood donors can transmit cytomegalovirus infection is apparent from studies of granulocyte transfusions, which appear to be extremely "efficient" in transmitting cytomegalovirus infection (6).

A final source of cytomegalovirus infection is reactivation of latent virus from the patient. As an illustration of the incidence of cytomegalovirus infection in immunosuppressed patients, Table 1 shows the risk of infection in allogenic marrow transplant patients grouped according to pre-transplant serology and use of granulocyte transfusions (6). In this series, seronegative patients who received no granulocyte transfusions had an incidence of infection of 33%. Most of these infections were presumably acquired from leukocyte-containing platelet transfusions, although seropositive marrow donors may also have contributed to the risk of infection in this group. Seropositive patients who received no granulocyte transfusions had an incidence of infection of 62%, attributable both to reactivation of latent virus as well as to exposure to virus-containing blood products. The use of granulocyte transfusions from seropositive donors, but not from seronegative donors, significantly increased the incidence of cytomegalovirus infection among seronegative patients. The already high incidence of infection among seropositive patients was not influenced further by use of granulocyte transfusions from seropositive donors.
Because of these many different sources of cytomegalovirus infection, it is reasonable to assume that control will require different approaches in different patients.

Treatment of Cytomegalovirus Infection

There are a small number of systemically-administered antiviral agents presently available with suggested or proven activity against human viral infections, most commonly against herpes simplex or varicella-zoster virus infections. These agents include vidarabine, acyclovir, and a variety of human alpha interferons. Although these agents also have *in vitro* activity against human cytomegalovirus, this activity usually requires higher drug concentrations than those needed for herpes simplex or varicella-zoster virus. Although some trials suggest clinical improvement among patients treated for cytomegalovirus infection with acyclovir (7), most trials with interferon (8) vidarabine (9, 10), acyclovir (11) or combinations of these agents (12, 13) indicate little efficacy against clinically manifest cytomegalovirus disease. Effective treatment of cytomegalovirus infection will require the development of additional antiviral agents with increased activity against cytomegalovirus *in vivo*, and it would appear that efforts at prophylaxis may be more fruitful until more effective antiviral agents are available.

Prevention of Primary Infection by Screening of Blood Products and Organ Donors

Screening of blood products to eliminate transfusions from seropositive donors has been shown to be effective in the prevention of primary infection in neonates (14) and cardiac transplant patients (5). An alternative approach that has been effective in renal dialysis patients is the use of frozen, deglycerolyzed blood products (15). Whether screening of blood products to eliminate seropositive donors would be logistically possible among marrow transplant patients who receive very large numbers of platelet transfusions remains to be demonstrated. In all situations it would be preferable to eliminate only those products which actually contain cytomegalovirus rather than removing all antibody-positive donors from the donor pool. However, virus can be cultured only rarely from the blood of seropositive persons (or their blood products) who are clinically well, and no methods presently exist to determine precisely which units actually carry cytomegalovirus and thus are capable of transmitting infection. Thus the only practical alternative at this time is elimination of all antibody-positive blood products, a procedure which may have substantial impact on

Table 1: Relationship of cytomegalovirus infection to patient and granulocyte donor CMV antibody status[a].

CMV serology before transplant	No granulocytes	Prophylactic granulocytes		Therapeutic granulocytes	
		GD-negative	GD-positive	GD-negative	GD-positive
Seronegative (< 1:8)	37/113 (33%)	16/46 (35%)	21/28 (75%)	2/11 (18%)	3/3 (100%)
Seronegative (≥ 1:8)	57/92 (62%)	7/13 (54%)	25/44 (57%)	3/4 (75%)	7/9 (78%)

[a]CMV = cytomegalovirus; GD-negative = granulocyte donor seronegative for CMV; GD-positive = granulocyte donor seropositive for CMV. Numbers in parentheses represent percentage of patients affected.
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blood-banking procedures in areas in which a substantial proportion of the donor pool is seropositive.

Use of seronegative organ donors for seronegative recipients should also reduce the occurrence of cytomegalovirus infection, especially after renal transplantation in which the risk associated with seropositive organ donors is best defined and in which a choice of organ donors often exists (4). In cardiac and marrow (and presumably liver) allografting, the opportunities for such a choice are less common, and thus in these patients alternative means of preventing primary infection are desirable. Neither screening of blood products nor selection of organ donors should affect reactivation of cytomegalovirus in seropositive patients, however.

Prevention of Virus Reactivation in Seropositive Patients

Prevention of virus reactivation among seropositive patients may be more difficult than prevention of primary infection among seronegative patients. Seropositive patients presumably harbor their own latent cytomegalovirus and develop active infection when this latent virus reactivates, although molecular evidence proving that reinfection with exogenous strains does not also occur in some patients is lacking at this time. The mechanisms of latency and reactivation are not understood, although animal studies have suggested that graft-versus-host or host-versus-graft reactions may play a role in virus reactivation (16, 17). It is likely that the period of time over which prophylaxis must be effective to prevent reactivation in seropositive patients will be longer than the time needed to prevent primary infections among seronegative patients in whom exposure to exogenous virus may be limited to the time of blood transfusions.

The methods needed to prevent virus reactivation may also be different than those which prevent primary infections. For example, it is already clear that antibody (or cellular mechanisms using antibody) is not effective in preventing virus reactivation; nor does the presence or production of antibody prevent the development of severe cytomegalovirus disease in some patients.

Interferon

One method to prevent virus reactivation may be the use of prophylactic interferon. Interferon was first recognized by its ability to prevent virus replication (18), even though its immunologic and antitumor activities are of equal or greater current interest. There have been only a few demonstrations of the efficacy of interferon as an antiviral agent in humans. Among these is the ability of human alpha interferon to delay or prevent the manifestations of cytomegalovirus infection among renal allograft recipients.

Cheeseman et al. (19) first reported that partially purified Cantell alpha interferon, given at the time of kidney transplant and twice weekly for six weeks after transplant, could delay the onset of cytomegalovirus excretion and decrease cytomegalovirus viremia (Table 2) among patients receiving either cadaveric or living related transplants. This effect on viremia was not seen among patients receiving antithymocyte globulin, nor did interferon change the clinical manifestations of cytomegalovirus infection among patients whether or not they received antithymocyte globulin. Although some patients had reversible leukopenia and thrombocytopenia, these apparent toxicities did not interfere with interferon use in most patients.

Table 2: Incidence of viremia in CMV-infected patients after renal transplant.

Treatment	Antithymocyte globulin	No antithymocyte globulin	Combined[a]
Interferon	5/7	0/4[b]	5/11[c]
Placebo	6/6	3/4[b]	9/10[c]
Combined[a]	11/13[d]	3/8[d]	14/21

[a]95% confidence intervals for combined groups were: interferon: 0.20 – 0.75; placebo: 0.65 – 0.99; antithymocyte globulin: 0.57 – 0.97; and non-antithymocyte globulin: 0.11–0.71.
[b]p = 0.07, interferon versus placebo by Fischer's exact test.
[c]p = 0.04, interferon versus placebo.
[d]p = 0.04, antithymocyte globulin versus non-antithymocyte globulin.

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In a more recent study, *Hirsch* et al. (20) gave Cantell interferon to seropositive recipients of cadaveric or living related transplants for a total of 14 weeks. Interferon was given three times a week for the first six weeks and then twice weekly for the remaining eight weeks. Twenty interferon recipients were compared to 22 placebo recipients in a randomized, blinded trial. In contrast to the previous study, timing of cytomegalovirus infection was not affected by interferon use except among patients receiving antithymocyte globulin. However, clinical disease attributed to cytomegalovirus infection was significantly reduced in the interferon group, being observed among seven of 22 placebo recipients, but only one of 20 interferon recipients (p = 0.03) (Table 3). Most syndromes occurred in

Table 3: Incidence of CMV syndromes after renal transplant according to randomization subgroup.

Subgroup	No. with syndrome/No. in subgroup Interferon		Placebo	Total[b]
Antithymocyte globulin	0/9	p = 0.02[a]	5/10	5/19
No antithymocyte globulin	1/11		2/12	3/23
Total[b]	1/20	p = 0.03[a]	7/22	8/42
Cadaver donor	0/12	p = 0.01[a]	7/15	7/27
Living related donor	1/8		0/7	1/15
Total[b]	1/20	p = 0.03[a]	7/22	8/42

[a]Fischer's exact test.
[b]95% confidence intervals: interferon: 0.20 – 0.25; placebo: 0.17 – 0.54; antithymocyte globulin: 0.13 – 0.50; no antithymocyte globulin: 0.05 – 0.34;
cadaver donor: 0.14 – 0.45; living related donor: 0.02 – 0.32.
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patients receiving cadaveric transplants who also received antithymocyte globulin. Interferon was well tolerated and apparent marrow suppression was equivalent in the two groups. Similar trials on the prevention of primary infection in seronegative patients are still underway.

In contrast to these findings in renal transplant patients, preliminary results of a prophylactic trial of Cantell alpha interferon among marrow allograft recipients were not as encouraging (21). Although a slight delay in the onset of cytomegalovirus excretion or seroconversion was observed, there was no apparent effect on the overall incidence or severity of cytomegalovirus infection. An important difference between the trials in renal and marrow allograft recipients is that interferon was started at the time of kidney implantation but not until approximately two and a half weeks after marrow infusion, possibly too late to interfere with the initial stages of either cytomegalovirus reactivation or primary infection. Alternatively, marrow transplant recipients may be too immunosuppressed to benefit from interferon use.

With the present availability of purer interferons produced by recombinant DNA techniques, these trials will be confirmed in renal transplant patients and will hopefully be extended to other allograft recipients as well. Despite the greater purity of these cloned interferons, however, it appears that hematologic (and possibly liver) toxicity will continue to be a limiting factor in the use of interferon in some patients. An important question is whether interferon will be effective only in preventing virus reactivation or whether it can prevent primary infection as well. The mechanism of protection – antiviral or immunologic – also remains to be proven.

Antiviral Agents for Prophylaxis of Cytomegalovirus Infection

Few studies on the prophylactic use of antiviral agents other than interferon have been conducted, in part because of the poor activity of available antiviral agents against cytomegalovirus as described above. Vidarabine, given intermittently for ten day periods at a dose of 5 mg/kg/day after marrow transplant, did not change the occurrence of cytomegalovirus infection (22). Orally-administered acyclovir was reported to prevent cytomegalovirus infection in one study (23), although a subsequent study using higher doses had no effect (24). As noted above, other agents with increased activity against cytomegalovirus *in vitro* and *in vivo* will be needed. Additionally, the additive or synergistic effects of combinations of antiviral agents including interferon against cytomegalovirus may be of relevance for the design of future prophylactic trials (25, 26).

Passive Immunoprophylaxis with Plasma or Globulin

Passive immunization with specific antibody has been used for treatment or prevention of a number of infectious diseases. The closest parallel to prevention of cytomegalovirus infection may be the use of varicella-zoster immune globulin for the prevention of varicella in susceptible immunosuppressed children. However, there are important differences between varicella and cytomegalovirus infection including the limited period of exposure to varicella virus, and the likelihood that cytomegalovirus is transmitted in a latent, nonreplicating, cell-associated form, whether in leukocytes or in the transplanted organ, rather than as cell-free virus as in varicella.

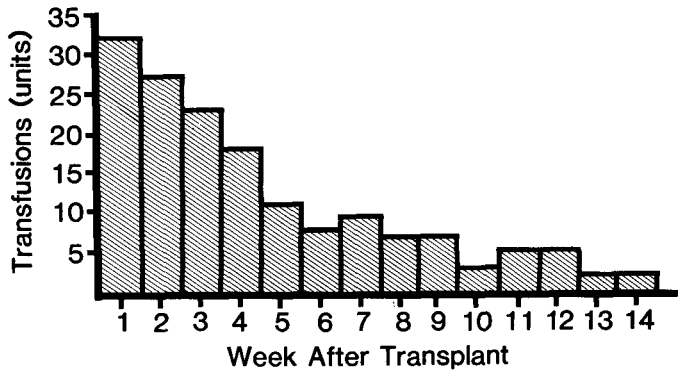

Figure 1: Average number of platelet and red blood cell transfusions by week after allogeneic marrow transplant among 62 patients transplanted for leukemia.

Winston et al. (27) first reported a study of passive immunization for the prevention of cytomegalovirus infection in marrow transplant patients. In this study human plasma with high anti-cytomegalovirus antibody titer was given before and on Day 3 after transplant, then every 15

Table 4: Results of prophylactic trial of CMV immune plasma after marrow transplantation.

	Plasma recipients	Control patients	p
All patients:			
All CMV infection	12/24	15/24	0.56
Symptomatic CMV infection	5/24	12/24	0.07
All interstitial pneumonia	5/24	11/14	0.17
CMV pneumonia	3/24	8/24	0.17
Seronegative patients[a]:			
All CMV infection	not reported[b]	6/15	–
Symptomatic CMV infection	0/13	5/15	0.04
All interstitial pneumonia	1/13	7/15	0.04
CMV pneumonia	0/13	not reported[b]	–
Seropositive patients:			
All CMV infection	not reported[b]	5/5	–
Symptomatic CMV infection	1/4	5/5	0.05
All interstitial pneumonia	0/4	3/5	0.16
CMV pneumonia	0/4	not reported[b]	–

[a]These patients received no granulocyte transfusions.
[b]All CMV infections and CMV pneumonia were not reported in these groups.

Data derived from *Winston* et al. (27) and reprinted from *Meyers* (34) with permission of the publisher.

days between Days 30 and 90 after transplant, with a final transfusion at Day 120 after transplant. Most transfusions were concentrated during the later post-transplant period when cytomegalovirus pneumonia is most common, rather than during the early period when the majority of transfusions are given (Figure 1). Evaluation of this study is complicated by the inclusion of patients with aplastic anemia, who have a significantly lower incidence of cytomegalovirus pneumonia (1, 28), and of patients seropositive for antibody to cytomegalovirus before transplant. In the overall study there was a slightly, but not significantly, lower incidence both of cytomegalovirus infection and cytomegalovirus pneumonia among plasma recipients (Table 4). Among seronegative patients who did not receive granulocyte transfusions, the incidence of symptomatic cytomegalovirus infection and of all interstitial pneumonia was significantly lower among plasma recipients; however, the incidence of all cytomegalovirus infection, and of cytomegalovirus pneumonia specifically, was not reported. A reduction in the incidence of cytomegalovirus infection and of all pneumonia was also reported among patients seropositive for antibody before transplant. The authors concluded that high-titer plasma given prophylactically modified but did not prevent cytomegalovirus infection after marrow transplant.

The use of an intravenous globulin prepared from a high-titer plasma has been described by *O'Reilly* et al. (29). In this study globulin with an ELISA antibody titer of 1:3200 was given at a dose of 200 mg/kg body weight on Days 25, 50 and 75 after marrow transplant, with no globulin given during the early period of most transfusions (Figure 1). A randomized comparison group received globulin with no antibody activity against cytomegalovirus and a third nonrandomized group received neither globulin. Evaluation of this study is also complicated by the inclusion of both seropositive and seronegative patients. In addition, at least two patients who received high-titer globulin shed cytomegalovirus before the beginning of globulin prophylaxis. Six of 18 recipients of "cytomegalovirus-antibody-deficient" plasma developed cytomegalovirus infection during prophylaxis compared with none of 17 high-titer globulin recipients; this difference is significant at $p = 0.02$ (Table 5). One of three recipients of cytomegalovirus-antibody-deficient globulin who developed pneumonia had cytomegalovirus pneumonia. In the concurrent nonrandomized comparison group who received no globulin, both cytomegalovirus infection and cytomegalovirus pneumonia occurred at the expected high rates. These data also suggest that antibody can modify the manifestations of cytomegalovirus infection even when given after the period of presumed exposure to infected blood products.

Finally, an immune globulin produced from a plasma pool with an even higher titer of antibody to cytomegalovirus (globulin titer = 1:16,000 by ELISA) was given intramuscularly to marrow allograft recipients beginning before transplant and continuing through Day 77 after transplant (30). Only seronegative patients were included in this study, with stratification both for use of prophylactic granulocyte transfusions and for marrow donor serology. Among patients who did not receive granulocyte transfusions, recipients of globulin developed significantly fewer cytomegalovirus infections than control patients (Table 6, Figure 2). No beneficial effect was seen among patients who received granulocytes from seropositive donors, while the number of patients receiving granulocytes from seronegative donors was too small for firm conclusions. Curiously, among patients who received no granulocytes, a protective effect was seen only among those with seronegative marrow donors (Table 7), perhaps suggesting a dose-response effect. Among the eight control patients who received no granulocytes and who developed cyto-

Table 5: Incidence of CMV infection and interstitial pneumonia after marrow transplant.

Globulin	Total patients	Interstitial pneumonia[a]	Culture or serologic evidence of CMV infection
CMV hyperimmune	17	0	0
		$p = 0.23$	$p = 0.019$[b]
CMV antibody-deficient	18	3(1)	6
		$p = 0.022$[b]	$p = 0.01$[b]
None	20	6(4)	10

[a]Numbers in parentheses indicate number of cases of cytomegalovirus pneumonia.
[b]Fisher's exact test. Comparisons are with patients receiving the CMV hyperimmune globulin.
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Table 6: Incidence of CMV infection among seronegative globulin recipients and control patients by use of prophylactic granulocyte transfusions.

Granulocyte use	Globulin recipients	Control patients
Seropositive granulocytes[a]	7/8[b]	6/7
Seronegative granulocytes[a]	1/5	0/6
No granulocytes	2/17 (12%)[c]	8/19 (42%)[c]

[a]Seropositive and seronegative granulocytes refers to the serologic status of the granulocyte donor.
[b]Number infected/total number in group.
[c]Difference significant at $p = 0.05$ by one-sided Fisher's exact test and $p = 0.03$ by Mantel-Cox test.
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Table 7: CMV infection rates in non-granulocyte recipients by serology of marrow donor.

	Globulin recipients	Controls
Seropositive marrow donor	2/6	3/7
Seronegative marrow donor	0/11[a]	5/12 (42%)[a]

[a]$p = 0.02$ by one-sided Fisher's exact test.
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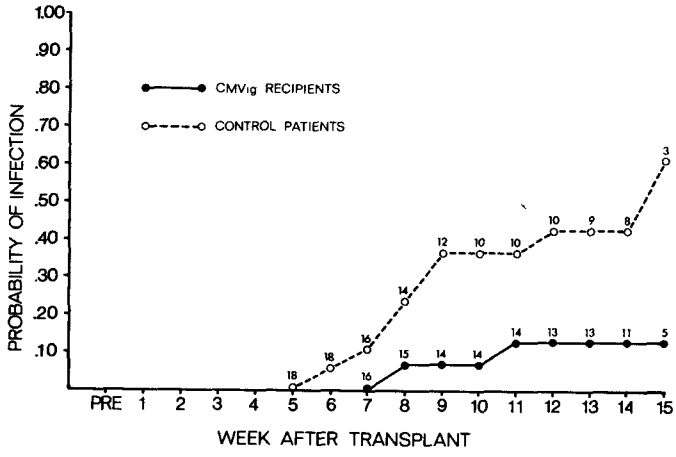

Figure 2: Probability of acquiring cytomegalovirus infection by week after transplantation among globulin recipients (closed circles) and control patients (open circles) who did not receive prophylactic granulocyte transfusions. The numbers indicate the number of patients still at risk of infection at the beginning of each interval. The risk is different at p = 0.03 by the Mantel-Cox test. Reprinted from (30) with permission of the publisher.

megalovirus infection, one each had pneumonia, esophagitis, and viremia compared to no such occurrences among the two infected globulin recipients.

Although the study protocols as well as the antibody preparations differed between these three studies, the conglomerate experience suggests that primary cytomegalovirus infection can indeed be modified – and in some cases prevented entirely – by passive immunization. The mechanism of protection is unknown. In the study by *Meyers* et al. (30), cytomegalovirus infection among patients who received granulocyte transfusions from seropositive donors or among patients with seropositive marrow donors was not prevented, nor can antibody prevent reactivation of virus among patients seropositive before transplant as noted above. Additional studies on the mechanism of protection are warranted and may suggest methods to increase the efficacy of passive immunoprophylaxis.

Other globulin preparations are also available and are under testing. Commercial "unscreened" globulins (that is, fractionated from plasma pools not specifically selected for high antibody titers to cytomegalovirus) which can be given intravenously are being tested at higher doses than those described above (31) and preliminary data indicate effectiveness in the prevention of severe cytomegalovirus disease (e.g. pneumonia), though cytomegalovirus infection is not prevented entirely (32). High-titer intravenous globulins are also being tested in renal and marrow transplant patients and neonates (33) and initial data indicate that high circulating antibody titers can be maintained with this particular preparation. Table 8 shows the relative antibody titers against cytomegalovirus of the intramuscular globulin used by *Meyers* et al. (30), of the high-titer intravenous globulin presently being tested (33), and of unscreened intravenous globulins available from two

Table 8: Comparison of intramuscular and intravenous lots of cytomegalovirus immune globulin.

Globulin type	Cytomegalovirus antibody titer CF	IHA	ELISA	Protein content (g/%)
CMVig, Intramuscular*	1,024	16,000	14,000	16.5
CMVig, Intravenous*	256	8,192	8,000	5.0
Sandoz IV Globulin	–	–	400/800	6.0
Cutter Gamimmune	–	1,280	–	5.0

* Produced by Massachussetts Public Health Biologic Laboratories, State Laboratory Institute, The Commonwealth of Massachussetts, Boston.

manufacturers. The optimal dose or preparation of globulin is not yet determined. The use of intravenous globulin would seem desirable, especially among patients such as marrow graft recipients who are often severely thrombocytopenic. The ability to use commercially-available unscreened globulins with their increased availability must be balanced against the increased expense of the higher globulin doses needed to produce equivalent circulating antibody titers. It may be that the use of globulin for relatively short periods of time to interrupt the initial course of virus infection during periods of most intensive immunosuppression may be adequate to prevent severe cytomegalovirus disease, although not preventing cytomegalovirus infection entirely. Indeed, it may be beneficial to allow a later specific immune response to cytomegalovirus among patients who have a defined period of profound immunosuppression.

Passive immunoprophylaxis with immune globulins should be effective in all seronegative patients at risk of primary infection, including not only allograft recipients but also neonates and persons undergoing cardiac or trauma surgery requiring large quantities of leukocyte-containing blood products. Avoidance of the need to prescreen blood donors or blood products for antibody to cytomegalovirus would decrease the burden on blood-banking facilities. However, cytomegalovirus infection derived from some blood products may not be preventable, as shown by the experience with granulocyte transfusions and seropositive marrow donors (30), and both screening of blood products and passive immunoprophylaxis may be needed to prevent primary infection in some situations.

Conclusions

Prevention of cytomegalovirus infection has been demonstrated in at least one subgroup of patients, namely seronegative patients at risk of primary infection, by two methods: Screening of blood products given to neonates and cardiac transplant patients or use of frozen, deglycerolyzed blood products for renal dialysis patients has been effective in decreasing exposure to virus, whereas passive immunoprophylaxis with either plasma or globulin has been effective in preventing or modifying the manifestations of primary infection in marrow transplant patients.

These efforts should be extended to other patients at risk of severe primary infection. The minimum duration of prophylaxis and the optimal antibody regimen has yet to be determined. Prevention of virus reactivation is not yet at hand, although prophylactic interferon has shown some benefit in renal transplant patients. These studies must also be extended. It appears, however, that the effective control of virus reactivation as well as effective treatment of established infection will require the development of antiviral agents with better activity against human cytomegalovirus. Better understanding of the immunologic correlates of severe infection and manipulation of immunosuppressive regimens to reduce the likelihood of severe manifestations of infection should also reduce the impact of cytomegalovirus infection in the compromised host.

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Discussion

Dr. Siegel: In your first study, the group most protected seemed to be those who received marrow from seronegative donors and no granulocytes or granulocytes from seronegative donors only. In the control group of that population, i.e. those who did not get immune globulin, what do you think the source of CMV was? Where did they get their infection from if not from granulocyte transfusion?

Dr. Meyers: They probably acquired their CMV from blood transfusions, although not from granulocyte transfusions. Platelet transfusions also contain a large number of leukocytes. In the control patients, we analyzed the transfusion requirements in order to show that those who did get infected received more blood. And indeed, they did get more transfusions. However, the range of numbers of transfusions was so broad that there was no statistical difference between infected and uninfected patients. Nevertheless, we do not know of another source of infection in these patients. It is presumably a quantitative phenomenon: There is too much virus in granulocyte transfusions for the amount of antibody we were using to overcome. However, since we do not know the site of latency or the mechanism of virus reactivation it is not possible to carry the hypothesis too much further.

Dr. Ullmann: Do you have any information on the rate of CMV infections when recipients were treated prophylactically with acyclovir?

Dr. Meyers: There are several studies using oral or intravenous acyclovir for the prophylaxis of herpes simplex virus infection after marrow transplant in which the occurrence of cytomegalovirus infection was also analyzed. In a study performed in our center using acyclovir at a dose of 400 mg given five times daily, we found no difference in the occurrence or severity of all CMV infections or CMV pneumonia between patients receiving acyclovir or placebo. This is in contrast to the data of *E. Gluckman* in which a possible effect on CMV infection was reported despite using an acyclovir dose of only 200 mg. There is a study beginning now in three centers in the U.S. using intravenous acyclovir prophylactically for CMV to prove or disprove that acyclovir can affect CMV infection. The feeling is that if the intravenous drug fails, then the data of *E. Gluckman* using oral drug, which provides much lower plasma levels, must have been an artifact of small numbers.

Dr. Wahn: What criteria do you use to establish the diagnosis of CMV infections following bone marrow transplantation?

Dr. Meyers: We use both excretion of virus or recovery in tissue specimens and seroconversion. If we take all the patients who are infected by those criteria, 85% have the virus recovered and only 15% seroconvert without any virus recovery. I think that we would all agree that virus recovery is a reasonably reliable criterion. In our studies, it has been either seroconversion or virus recovery, however.

Dr. Lagast: You showed quite nicely that seropositive patients with seropositive donors are at a higher risk of CMV infection. Don't you think that these patients also need higher doses of immunoglobulin?

Dr. Meyers: Yes, they may. Seronegative patients who get more blood transfusions may simply need more antibody than we can provide by passive immunoprophylaxis. I think in that context we really need some other approach to the prevention of CMV reactivation among seropositive patients.

Dr. Lagast: Did you try higher doses of CMV immunoglobulin?

Dr. Meyers: We are trying higher doses in our present intravenous study, but it has only just begun. But we do not give it to seropositive people, just to the seronegative patients.