Criteria to define interruption of transmission of human cytomegalovirus from organ donor to recipient

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Summary

In this review article we consider results suggesting that transmission of human cytomegalovirus (HCMV) from a donor of a solid organ to an immunologically naive individual can be reduced. Two randomised controlled trials have been conducted recently, one of active immunisation of recipients pre-transplant and another of passive immunisation with monoclonal antibodies specific for HCMV given at the time of transplant. Although the available data are encouraging – providing evidence of a reduction in the incidence of HCMV viraemia - they fall short of what would be required to prove definitively that transmission has been completely prevented. Here we reflect on these studies and propose a set of five criteria which, if satisfied in the future, could be taken as proof that active and/or passive immunisation against HCMV effectively interrupts transmission of virus from the donor. We suggest that these criteria are considered when designing future randomised controlled trials.

Abbreviations:

AUC- Area Under the Curve

C_{max}- maximum concentration (in serum)

D- Donor

gH- glycoprotein-H

mAbs- monoclonal antibodies

PK- Pharmacokinetics

R- Recipient

SOT- Solid Organ Transplant

$t_{1/2}$- Elimination half-life

T_{max}- Time at which drug concentration is maximal

UL Unique Long -region of HCMV genome

Introduction

Human cytomegalovirus (HCMV) is an important opportunistic pathogen in patients undergoing solid organ transplantation (SOT). The natural history of HCMV infection in these patients is complex (1). Recipients who have HCMV-specific IgG antibodies before transplant (seropositives; R+) are at risk of reactivating virus once they receive immunosuppressive drugs. They are also at risk of reinfection if a different strain of HCMV is transferred from a seropositive donor organ (D+). Recipients who are seronegative (R-) may also acquire primary infection from a seropositive donor organ (1, 2). After transmission, viral replication in the recipient leads to the appearance of HCMV DNA in the blood (viraemia) reflecting an increased potential to disseminate HCMV causing a variety of end-organ diseases which is directly related to higher viral loads (2, 3). The ability of HCMV to reactivate from latency and reinfect seropositive individuals, along with the threat of primary infection means the risk of infection is so high, and the risk of disease so serious, that transplant centres routinely employ one of two strategies to use ganciclovir or its oral prodrug valganciclovir to prevent HCMV end-organ disease (4).

For the strategy of *prophylaxis*, patients are given drug from the time of transplant onwards for a fixed period of time, with clinical trials supporting duration of prophylaxis of 100 days or 200 days (5, 6). This strategy effectively prevents end-organ disease for these periods of time, but patients remain at risk of developing viraemia and late onset disease once prophylaxis

is stopped (7). This is a particular problem in the high risk D+R- subgroup where a recipient without natural immunity receives an organ from a seropositive donor (7). In some cases, late onset disease is caused by strains of HCMV that have developed resistance to ganciclovir which requires the use of increasingly toxic second line therapies (8, 9).

For the strategy of *pre-emptive therapy*, no patient receives prophylaxis and drug is only administered to those where surveillance samples detect viraemia above a threshold value defined by real time polymerase chain reaction (PCR) (2). Pre-emptive therapy is typically stopped when a patient has two consecutive blood samples where HCMV DNA is undetectable (2). Surveillance for infection continues and some patients develop a second episode of viraemia which is again treated until viraemia becomes undetectable. Thus one clear advantage of this approach is the administration of a toxic drug in limited doses to a subset of patients at highest risk of HCMV disease. Occasional patients develop resistant strains of HCMV (10).

These two strategies are equally effective at preventing end-organ disease as shown by a meta-analysis by the Cochrane collaboration of the seven controlled trials that have randomised SOT patients to be managed by either prophylaxis or pre-emptive therapy (11). As a consequence, both strategies are recommended in clinical guidelines as suitable ways of preventing HCMV end-organ disease (4). However, they have different characteristics such that some centres prefer one strategy over the other. For example, prophylaxis may be preferred where patients are discharged from a transplant centre for

continuing care to a small, distant hospital that does not have access to PCR diagnosis.

Pertinent for our own studies, pre-emptive therapy has the considerable advantage that it provides information about the natural history of HCMV infection in individual patients prior to therapeutic intervention. The duration of viraemia, the duration of treatment and the peak viral load represent important biomarkers that can be used to assess the ability of cohorts of patients to control HCMV replication (2). Highest values of all three parameters are found in D+R- patients, intermediate values in D+R+ patients and lowest values in D-R+ patients, paralleling the respective risks for HCMV end-organ disease associated with primary infection, reinfection and/or reactivation and reactivation respectively in solid organ transplant patients (2, 3). The values seen in the 3 patient groups are highly significantly different, but we emphasise that there is substantial overlap so that the viral load results in a single individual cannot distinguish between primary infection, reinfection or reactivation.(2) The availability of these rigorously defined biomarkers allows clinical trials to be designed so that the values can be used as pharmacodynamic assessments of whether or not prototype HCMV immunological interventions given pre-transplant or peri-transplant can control the extent of virus replication post-transplant. Three randomised controlled trials have been conducted to date as reviewed below.

Results from relevant clinical trials

In 1984, a single dose of a live attenuated vaccine based on the Towne strain of HCMV was given to seronegative and seropositive candidates awaiting renal transplantation (12). This vaccine did not reduce the incidence of HCMV infection or the incidence of HCMV end-organ disease after transplant (table 1A). However, it appeared to reduce the severity of disease although the Phase 2 clinical trial was not powered to provide statistical significance in selected subsets of patients (table 1B and figure 1). In light of our current understanding of the pharmacodynamics of HCMV in these patients, we would interpret these results as the vaccine reducing the peak viral load and its associated risk for disease, but PCR, and quantitative measures of HCMV viraemia, were not available at that time. However, it is clear from the study that the vaccination strategy did not interrupt transmission of HCMV, so how did it influence severity of disease? When peak viraemia is plotted against risk of end-organ disease, a sigmoid curve is obtained (13, 14). The fact that both groups developed end-organ disease suggests that they both crossed this threshold value allowing the virus to disseminate to those organs. It is not known if receipt of an even higher dose of virus could increase the severity of disease, but this is one possible explanation for the benefit produced by the Towne vaccine; that is, it reduced the effective inoculum. Alternatively, both groups of patients may have received the same dose of virus, but the recipients of Towne vaccine were better able to control virus replication, because their immune systems had been primed, so limiting the severity of end organ disease.

In 2011, a vaccine comprising soluble recombinant glycoprotein B (gB) together with MF59 adjuvant was given to seronegative and seropositive candidates awaiting transplantation of a kidney or a liver (15). The rationale for this choice of immunogen is that gB is an important structural determinant of virus entry into cells and represents a major target of the humoral response against HCMV in healthy seropositives. Importantly, when compared to placebo recipients, the vaccine appeared to reduce key markers of viral load post-transplant (15). Again, this Phase 2 study was not powered to provide statistical significance in subsets of patients, but the apparent rate of transmission of HCMV from donor to recipient was reduced (table 2). The titre of antibodies induced by the vaccine was reported as a correlate of protection, because it was significantly inversely associated with the duration of viraemia (15). The numbers of patients in subgroups are limited, but the fact that there was no apparent effect on reactivation but the biomakers in those at risk of either reactivation or reinfection were lower, suggested that reinfection was reduced in the D+R+ subgroup (table 2). This potential explanation of reduced exogenous infection was seen even more clearly in the D+R- subgroup at risk of primary infection (table 2). Thus, the gB/MF59 vaccine used in this study may have interrupted transmission of HCMV from the donor to both seronegative and seropositive recipients.

This observation that humoral immune responses against HCMV might be protective in transplant recipients, led one of us (PDG) to propose a clinical trial to Genentech in 2013. The possibility that preformed antibodies present at the time of transplant could reduce transmission of HCMV from the donor

organ could be evaluated in a randomised controlled trial comparing placebo with the infusion of monoclonal antibodies (mAbs) with activity against HCMV. Clinical grade antibodies against gB were not available and so the study was conducted with two different mAbs; one directed against glycoprotein H (gH), another essential protein of the HCMV entry machinery, and one against the protein product of HCMV gene UL131 which is one component of the pentameric complex that is necessary to mediate entry of HCMV into epithelial and endothelial cells (16). Seronegative recipients about to receive kidneys from seropositive donors received either the combination of both mAbs or a matching placebo. Genentech organised and conducted a multicentre, multinational randomised controlled trial to recruit 120 patients and published the results in 2017 (17). These results were consistent with the hypothesis that humoral immunity can prevent transmission of HCMV from the donor organ to cause clinically significant HCMV viraemia in the post-transplant period (table 3). In addition, the study reported significantly reduced CMV syndrome in the recipients of the mAbs (17).

An important conclusion from this application of passive immunity is that measurements of concentrations of mAbs found in recipients inform the target level that active immunisation with the relevant antigen should also aim to achieve. The values are plotted but not reported in the supplementary material of the paper describing the clinical trial but can be inferred from the earlier Phase 1 study that gave the same dose (10mg/Kg each) of the same mAbs to normal volunteers (table 4A and 4B) (17, 18). The half-life was given as 26.9 and 27.4 days in the renal transplant recipients, which is very similar to the values in tables 4A and 4B. Thus, the pharmacokinetic parameters

shown in table 4A and 4B provide direct values of antibody concentrations against gH and UL131 that are associated with protection from acquisition of HCMV. Future Phase 1 clinical studies could use increasing doses of antigens together with a compatible adjuvant to produce a polyclonal response in volunteers that is biologically equivalent to these concentrations of mAbs as a way of prioritising doses to be taken forward into challenge studies in transplant patients. Thus, an iterative cycle of Phase 2 pharmacodynamics of active immunisation in D+R- allograft patients with identification of a humoral correlate of immunity, identification of clinical grade mAbs for placebo-controlled interruption of transmission of donor virus followed by Phase 1 selection of a corresponding immunogen could provide a pathway for development of a protective vaccine candidate to be evaluated in a Phase 3 definitive study.

This study of passive immunity administered the mAbs at the time of transplant and on three occasions post transplant (17). Future studies could compare reduced numbers of administrations to address the question of how long a donated organ remains potentially infectious for a seronegative recipient. We have reported from highly selected anecdotal cases that an organ dwell time of 28 hours is sufficient to transmit CMV from a seropositive donor, but no studies have evaluated how long the risk continues for post-transplant (19).

Suggested criteria to evaluate whether active or passive immunisation can completely or partially interrupt transmission of HCMV from the donor.

It is plausible that these latter two studies interrupted transmission of HCMV, but the data available fall short of what would be required to substantiate this. One problem is that, although the D+R- transplant combination represents a human challenge model, the rate of transmission is less than 100%, with figures of 70% and 88% for renal and liver transplants respectively in our institution and 70% for the renal transplants in the multicentre study of mAbs (2, 17). This aspect introduces an element of uncertainty regarding transmission and introduces a second problem: the number of individuals in a typical Phase 2 clinical trial is small, so limiting robust analyses of subgroups. While these caveats hinder effective retrospective analyses of previous studies there are, currently, a series of HCMV vaccines in various stages of clinical evaluation and some may be studied in the SOT setting (20). We propose that the novel possibility of interrupting transmission of HCMV should be examined in all future studies of active and passive immunisation against HCMV and suggest the following 5 criteria for assessment:

1. **Evidence of HCMV infection in body compartments additional to blood.**

Before PCR became available, surveillance samples of urine and saliva were collected from transplant recipients and tested by conventional cell culture or rapid cell culture confirmation methods to detect HCMV (21). The sensitivity for predicting future HCMV end-organ disease was good, but the positive predictive value was low, because most people with HCMV in the urine or saliva did not develop and-organ disease (21). The same was true when urine and saliva samples were tested by PCR (22). Methods based on PCR were able to detect the lower levels of HCMV found in blood and had a better positive predictive value than either urine or saliva and so replaced these earlier diagnostic methods (2, 22).

However, in the modern era, detection of HCMV in saliva and urine could be used as sensitive methods of identifying active infection in the salivary glands and kidneys respectively. The observation of serial negative PCR results from saliva and urine in an individual patient would then support the conclusion that HCMV had not been transmitted from the donor.

In our hands, the results of following hundreds of D-R- transplant patients for evidence of viraemia consistently show an absence of infection (2). Thus, serial negative PCR tests from D-R- transplants show a very low probability of recipients acquiring HCMV infection unrelated to their transplant. Nevertheless, the power of sequencing could be harnessed to address the potential confounder that a community acquired primary infection could occur long after transplant (rather than from the donor organ). A sequencing approach would facilitate a direct comparison of the recipient strains of HCMV with those found in the donor (where available).

2. Serological responses to antigens not contained in the vaccine being evaluated.

Patients given active or passive immunisation would be expected to have detectable levels of antibodies reactive with the antigen used in the vaccine or the antigen reactive with any mAbs given passively. However, patients would only be expected to possess antibodies against other HCMV antigens if they had become actively infected.

There are several ways in which antibodies can be detected against HCMV antigens and differentiated from those present in the vaccine. For example, Pass et al absorbed sera with gB before performing standard enzyme immunoassay for IgG when evaluating the gB/MF59 vaccine in seronegative women (23). Alternatively, derivations of western blot assays could be used to detect antibodies of defined antigenic specificity and a number of commercial kits apply this to diagnostic tests for HCMV infection – including the identification of different isotype responses. In the same way, enzyme immunoassays could be developed to detect HCMV individual antigens not present in a particular vaccine.

Clearly, this approach would not be applicable for vaccines based on whole HCMV, such as live attenuated strains. However, manufacturers should consider deleting one or more genes from HCMV that are neither essential for replication nor for protective immunity as a way of facilitating serological evaluation of recipients.

3. Evidence of T cell responses to antigens not contained in the vaccine being evaluated.

Following natural infection, all proteins of HCMV are recognised by the cellular arm of the immune system. A herculean analysis by Sylwester et al demonstrated that the T cell response is large and varied against multiple antigens (24). Thus the detection of T cell responses specific for HCMV in patients given a vaccine that induces humoral immunity alone, or given infusions of mAbs, would show that recipients have immunological experience of antigens independent of those contained in the vaccine.

If the vaccine was designed or known to induce T cell responses, then assays with specificity for antigens not present in the vaccine would have to be used; again this would require manufacturers of attenuated vaccines to delete non-essential genes.

4. Evidence of HCMV latency in recipients.

A key biological characteristic of HCMV is the establishment of latency and would represent a clear marker of transmission from a donor to a seonegative recipient. Long term follow up of patients post-transplant could include an analysis for viral latency in individuals without viraemia. Isolation of monocytes from peripheral blood would allow a simple analysis for the presence of viral DNA and also a viral transcript landscape consistent with latent infection (25, 26).

True latency is defined by the capacity of the virus to reactivate which can be done using *in vitro* stimulation of monocytes, although this would represent an attractive additional analysis rather than a mandatory one (25, 27). Again the power of sequencing could be harnessed whereby a clear demonstration that the recipient strain matched that of the donor would strongly support transmission from a seropositive donor.

Conversely, repeatedly negative samples from a recipient would be consistent with the possibility that transmission of donor virus had been successfully prevented.

5. Evidence of effects on long term NK cell repertoire.

Another aspect would utilise the apparent immunological imprinting associated with HCMV infection. Classically, NK cells were considered to be a part of the innate immune system, some recent publications demonstrate that NK cells undergo preferential clonal expansion following HCMV infection.(28, 29) Therefore, NK cells from HCMV infected individuals possess different subsets of memory-like NK cells. This clonal-like expansion of NK cells in response to HCMV infection shapes and alters the NK cell receptor repertoire in multiple ways: i) expanding an NK cell subset expressing the activating CD94/NKG2C receptor (29) ii) causing stable imprints in the human KIR repertoire which is skewed towards a bias for self-specific inhibitory KIRs(30); iii) driving the expression of the immune evasion genes of HCMV, many of which affect display of HLA class I molecules (31). The memory-like NK cell repertoire is presumably modulated and maintained by mechanisms that rely on both epigenetic modification of gene expression and antibody-dependent

expansion.(30, 32, 33) The presence of so called “memory-like” NK cells in the infected individuals argues that immunological responsiveness of these cells could be different to the NK cells from uninfected subjects. If this change in NK phenotype were seen in transplant recipients, it would provide evidence that HCMV infection was established in the recipient and so implicate transmission of virus from the donor. In contrast, if no such changes in NK phenotype were seen, it would add further support for the conclusion that the recipient had resisted transmission of HCMV from the donor. A single recent publication reports that significant changes in NK phenotype can be seen from 6 months post transplant in patients with primary CMV infection.(34).

Practical considerations for study design

It is clear that there are several practical implications if these concepts are to be incorporated into the design of the next set of studies of active and passive immunisation against HCMV. These include:

- Donor samples should be collected where possible pre-transplant, e.g. in live-related organ transplant to allow a genetic characterisation of this virus
- Urine and saliva as well as blood should be collected at every post-transplant visit to allow for monitoring of infection in different body compartments.
- A follow-up component of the study should be incorporated, perhaps as a sub-study, to examine in detail those D+R- patients who do not have viraemia post-transplant. They should be followed to see if they seroconverted and have the tests discussed above applied. As a way of controlling costs, samples could be stored prospectively and only tested if likely to be informative.

Why is this subject important?

While the development of a vaccine that prevents overt disease in a number of clinical settings is paramount, it is highly desirable that any HCMV vaccine also interrupts transmission of virus. If administered to the general population, such a vaccine would have dramatic implications for young women of child

bearing age given the devastating consequences associated with congenital HCMV infection (35).

The results have inherent scientific value as they will help to differentiate between complete interruption of transmission or merely reduction in the effective inoculum. A more complete understanding of the process that leads to transmission can only help the design of future studies that aim to inhibit it. Our current working hypothesis is that cells in the donor organ harbouring latent HCMV are stimulated by inflammation and cytokine storm at the time of transplantation to reactivate HCMV (D+) (36). Starting from only a small number of cells, HCMV infection proceeds to infect other cells, to spread from the local site of replication and then to cause viraemia (37, 38). The immune system may be able to contain this process at the site of transplant by attacking individual virions or infected cells before virions are released. We propose that the latter target is a more plausible way of explaining how pre-formed antibodies could prevent transmission of infection from the donor to the recipient. The immunological mechanism responsible may therefore include processes like antibody dependent cellular cytotoxicity in addition to the more conventionally studied virus neutralisation if cell associated virus is to be targeted by the humoral antibody response plus innate NK immunity.

The results may also reveal new correlates of protection and/or mechanistic correlates of protection (39). For example, the inverse relationship between the duration of viraemia and the titre of antibodies against gB identified these antibodies as a correlate of protection (15). However, the mechanistic

correlate might have been, for example, CD4 cells specific for HCMV with their contribution to T-help for B-cells explaining the correlation with protection seen for antibody titre. That said, the complementary randomised controlled trial of infusion of mAbs demonstrates that humoral immunity can be protective and likely elevates the titre of gB antibodies into the category of a mechanistic correlate of protection (17, 39). More direct support for gB antibody responses will require studies directly infusing mAbs against gB into recipients -the mAbs infused in the Genetech trial were not specific for gB but for components of two major complexes on the surface of the virion (gH and UL131) (17). We thus propose that any mAbs that recognise HCMV proteins displayed on the surface of infected cells should be considered candidates for clinical evaluation (40).

The follow up studies proposed could also prove important to give advice to recipients who received an experimental vaccine and now require a second transplant. Do they have any long-term immunity against HCMV? Do they harbour latent HCMV and thus will they reactivate HCMV once given high-dose immunosuppressive drugs like basiliximab that they are not currently receiving as maintenance immunosuppression? Will any immunity be sufficient to resist HCMV present in a new donor organ? Should they be given booster doses of the vaccine (if it is still available)? Answers to these questions would help transplant clinicians give accurate information and guidance to their patients.

It is important to determine if patients who resisted HCMV challenge from an organ donor and subsequently have some evidence of HCMV (*e.g*. T cell responses) but, possibly, no evidence of latent infection, should be considered along with other "seropositives" in terms of assessing life expectancy. Studies to date report an approximate one year lowered median life expectancy from being HCMV seropositive with a relative hazard of approximately 1.2 for overall mortality after controlling for risk factors of diabetes, smoking and obesity (41, 42). It is currently unclear whether this effect is found in individuals with latent infection or whether reactivation(s) and/or reinfections are required in addition. If immunisation can be shown to maintain individuals in the low-risk "seronegative" category, then this would improve cost benefit analyses of vaccine strategies and candidates.

Finally, an extension of these analyses will provide another parameter to allow pre-emptive therapy to be compared with prophylaxis. For example, we are not aware of any studies showing that prophylaxis prevents transmission of virus from the organ donor. Certainly, some recipients get viraemia when prophylaxis is stopped, so arguing that these individuals have been infected (7). However, if prophylaxis did impact on transmission then that could be assessed as a potential benefit.

In conclusion, maximising our understanding from the clinical trials performed with current vaccine candidates has the potential to provide novel insight into the natural history of this virus alongside the clear implications for iterative improvements to the vaccines themselves.

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Table 1. Results from randomised; double blind, placebo controlled clinical trial with Towne strain human cytomegalovirus vaccine study.

A) CMV illness and infection in 91 patients followed ≥6 months after transplant.

B) Grouping of clinical scores in recipient-seronegative donor-seropositive group. D(+)- donor HCMV seropositive, D(-)- donor HCMV seronegative, R(+)- recipient HCMV seropositive, R(-)- recipient HCMV seronegative.

Assessment of severity of disease associated with CMV infection was made with an arbitrary scoring system: fever scored: 1-3 points, leukopenia: 1 point, thrombocytopenia: 1, hepatitis: 1-3, pneumonia: 1-3, central nervous system changes: 1-3, glomerulonephritis: 1-3, arthritis: 2, muscle wasting: 2, bacterial superinfection: 3, gastrointestinal haemorrhage: 3, and death: 4. To be scored, a febrile illness had to occur concomitantly with laboratory evidence of CMV infection (virus excretion or rise in antibody titre).

Figure 1. Clinical scores in recipient-seronegative donor-seropositive vaccine and placebo groups.

The median values of clinical score for vaccine and placebo groups are represented by horizontal lines. Statistical difference- two-tailed p-value (0.0583) was obtained from the Mann-Whitney U test.

Table 2. Results from a randomized; double blind, placebo controlled clinical trial of recombinant soluble glycoprotein-B vaccine with MF-59 adjuvant in solid organ transplant patients.

Serial blood samples were tested for cytomegalovirus DNA by real-time quantitative PCR (rtqPCR). Viraemia was defined as a blood sample that was PCR positive (cutoff 200 genomes per mL whole blood). Any patient with one blood sample containing more than 3000 cytomegalovirus genomes per mL received ganciclovir until two consecutive undetectable cytomegalovirus DNA measurements.

*Total number of person-days during which any participant had viraemia higher than 200 genomes per mL or received treatment divided by total number of days of follow-up for all participants who underwent a transplantation. The proportion of days of post-transplantation follow-up spent with viraemia (or receiving treatment) was calculated for each individual. These values were then compared between vaccine and placebo with a Mann-Whitney *U* test. Comparison of proportion of days of viraemia in (all) vaccine versus (all) placebo p=0·99.

Table 3. Results from a randomized, double-blind, placebo-controlled trial of RG7667.

RG7667 is a combination of two monoclonal antibodies, one reactive with glycoprotein H and the second reactive with the protein from UL131. The proportion of patients with CMV viremia (viral load of ≥150 copies/ml) measured by quantitative PCR and the proportion of patients with CMV syndrome is shown for the follow-up period of 24 weeks post-transplant.

CMV syndrome was defined as the presence of CMV in the blood and at least one of the following: fever, new or increased malaise, leukopenia, atypical lymphocytosis, or thrombocytopenia. End Organ CMV disease was defined as presence of CMV in the blood and at least one of the following: localized CMV infection confirmed in a biopsy or other specimen and relevant symptoms or signs of organ dysfunction unlikely to be due to other causes

Table 4. Pharmacokinetic parameters of passive immunisation study of RG7667 in normal healthy volunteers.

RG7667 is the code name for two monoclonal antibodies MCMV5322A (a human, affinity-matured version of MSL-109 that recognizes CMV glycoprotein H (gH) and MCMV3068A (a humanized mouse monoclonal antibody that recognizes the protein encoded by UL131). A) Pharmacokinetic parameters of MCMV5322A (mAb gH); B) Pharmacokinetic parameters of MCMV3068A (mAb UL131). Pharmacokinetic parameters were measured at different occasions: 29 and 58 days following the administration of the drug.

Table 1A.

Sub-groups		No.	Received	Infected (%)	Ill (%)
D-	R-	32	**Placebo(12)**	1/12 (8)	1/12 (8)
			Vaccine (20)	0/20 (0)	0/20 (0)
D-	R+	14	**Placebo (5)**	2/5 (40)	0/5 (0)
			Vaccine (9)	3/9 (33)	1/9 (11)
D+	R+	15	**Placebo (7)**	6/7 (86)	2/7 (29)
			Vaccine (8)	6/7 (86)	2/8 (25)
D+	R-	30	**Placebo (14)**	11/14 (79)	10/14 (70)
			Vaccine (16)	15/16 (94)	9/16 (56)

Re-drawn from: Plotkin. Lancet, 1984. 323(8376): p.528-530.

Table 1B.

D+R-	Number with score		
	0	**1-6**	**≥7**
Vaccine	7	9	1
Placebo	4	4	7

Re-drawn from: Plotkin. Lancet, 1984. 323(8376): p.528-530

Table 2.

Sub-groups		No.	Received	Viraemia (>200 genomes/ml)	No. Treated	Proportion of:	
						Days PCR Positive (%)*	Days Treated (%)*
D-	R-	22	Placebo(10)	0	0	0/915 (0)	0/915 (0)
			Vaccine (12)	0	0	0/1204 (0)	0/1204 (0)
D-	R+	18	Placebo (7)	2	0	2/696 (0.3)	0/696 (0)
			Vaccine (11)	4	0	21/1209 (1.7)	0/1209 (0)
D+	R+	22	Placebo (15)	6	3	119/1489 (8.0)	135/1489 (9.1)
			Vaccine (7)	4	0	6/803 (0.7)	0/803 (0)
D+	R-	16	Placebo (5)	5	4	339/599 (56.6)	415/599 (69.3)
			Vaccine (11)	6	5	128/1069 (12.0)	142/1069 (13.3)

Re-drawn from: Griffiths. Lancet, 2011. 377(9773): p. 1256-63.

Table 3.

Parameter	placebo	MAb	p value
Viraemia	40/57 (70%)	30/59 (50.8%)	0.04
Median days to viraemia	46	139	0.01
CMV syndrome	16%	3%	0.03
End-organ disease	4	0	n/a

Re-drawn from: Ishida, Antimicrbo Agents Chemother, 61, e01794–16, 2017

Table 4A.

Selected PK of mAB gH at 10mg/kg in normals				
		Single dose	**d29**	**d57**
AUC	µg.day/ml	3707	3865	4553
C_{max}	µg /ml	277	253	340
T_{max}	day	0.064	0.188	0.125
$t_{½}$	day	ND	ND	23.7

Ishida. Antimicrbo Agents Chemother, 59, 4919-4929, 2015.

Table 4B.

Selected PK of mAB UL131 at 10mg/kg in normals				
		Single dose	**d29**	**d57**
AUC	µg.day/ml	5018	4838	4914
C_{max}	µg /ml	351	441	356
T_{max}	day	0.063	0.063	0.188
$t_{½}$	day	28.2	ND	29.0

Ishida. Antimicrbo Agents Chemother, 59, 4919-4929, 2015