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ORIGINAL ARTICLE

Non-specific immunoglobulin titres against cytomegalovirus: An alternative to hyperimmune presentation

D. Campany Herrero,* J.M. Guiu Segura, E. Vallvé Alcón, I. Cardona Pacual, J. Monterde Junyent

Servei de Farmàcia, Hospital Universitari Vall d'Hebron, Barcelona, Spain

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Abstract
Objective: Specific immunoglobulin against cytomegalovirus has demonstrated its effectiveness in preventing and treating infections in solid organ transplantation. Several studies indicate that non-specific immunoglobulin is just as effective.

This study aims to determine anti-cytomegalovirus immunoglobulin titres from one of the non-specific immunoglobulin presentations authorised in Spain.
Method: This was an observational study, in which we analysed the anti-cytomegalovirus antibody titres from different batches of Flebogamma® 5%5g used at the Hospital Universitari Vall d'Hebron during 2008 and 2009.
Results: We analysed 27 batches, which included 18,944 vials of Flebogamma® 5% Depending on the origin, the median concentration of anti-cytomegalovirus immunoglobulin was 28 PEI-U/ml and 22 PEI-U/ml per vial of North American and Spanish origin, respectively (CI 95%for the difference of the medians 5 to 6 PEI-U/ml; P<.001).
Conclusions: The anti-cytomegalovirus antibody concentration of the non-specific immunoglobulin batches analysed was slightly lower than in the specific immunoglobulin preparations. These differences can be compensated by adjusting the dosage.

*Corresponding author.
E-mail address: dcampany@vhebron.net (D. Campany Herrero).

PALABRAS CLAVE
Citomegalovirus;
Inmunoglobulinas;
Trasplante

Titulación de inmunoglobulinas inespecíficas frente a citomegalovirus: alternativa a la presentación hiperinmune

Resumen
Objetivo: La inmunoglobulina específica frente a citomegalovirus ha demostrado su eficacia en la prevención y tratamiento de la infección en el trasplante de órganos sólidos. Distintos estudios indican una eficacia similar respecto a las presentaciones de Ig inespecíficas.

El objetivo de este estudio es determinar la titulación de inmunoglobulina anti-citomegalovirus de una de las presentaciones de inmunoglobulinas inespecíficas autorizadas en España.
Método: Estudio observacional en el que se analizó la titulación de anticuerpos anti-citomegalovirus de distintos lotes de Flebogamma® 5% 5 g utilizados en el Hospital Universitari Vall d'Hebron durante los años 2008 y 2009.
Resultados: Se analizaron 27 lotes, que incluyeron 18.944 viales de Flebogamma® 5% En función del origen, la concentración mediana de inmunoglobulina anti-citomegalovirus fue de 28 UPEI/ml y 22 UPEI/ml para los viales de origen norteamericano y español, respectivamente (IC 95%para la diferencia de las medianas de 5 a 6 UPEI/ml; $p < 0,001$).
Conclusiones: La concentración de anticuerpos anti-citomegalovirus de los lotes de inmunoglobulina inespecífica analizados es ligeramente inferior respecto a las especialidades de inmunoglobulinas específicas. Estas diferencias pueden compensarse mediante un ajuste posológico.

Introduction

Cytomegalovirus (CMV)-specific or hyperimmune immunoglobulin (Ig) combined with other drugs with adequate anti-virus activity, have shown to be effective in preventing and treating CMV infection in solid organ transplant patients, especially those who have greater risk of contracting an illness.[1,2]

Pharmaceutical preparations marketed as CMV-specific Ig contain a purified mixture of human plasma or serum-derived antibodies, with a majority IgG content and standardised anti-virus titres.[3]

There are no monographs on anti-CMV specific Ig in the Spanish Royal Pharmacopoeia or the European Pharmacopoeia.[4,5] We have therefore adapted the characteristics of these products to the monographs published for non-specific human Ig.

Anti-CMV specific Ig preparations ensure that anti-CMV concentration is at least 50PEI-U/ml (PEI-U = Paul-Ehrlich-Institut. Each batch's titration was established using the reference standard proposed by the Paul-Ehrlich-Institut, Langen, Germany).[6-8]

In Spain, there are no anti-CMV specific Ig preparations on the market. This situation is limited with regards availability, and given the urgent nature that its administration could warrant (e.g. immediately before starting a transplant), it is difficult to manage the patients that may need it. It would therefore be interesting to make an alternative anti-CMV specific Ig available. Due to its special characteristics, non-specific Ig preparations could provide this option. For this, we would have to know anti-CMV antibodies titres of these preparations, and, when necessary, establish the adequate dosage adjustment to guarantee that the necessary quantity of anti-virus active antibodies are administered.

The main objective of this study is to determine anti-CMV titres for one of the non-specific Ig preparations licensed in Spain. The secondary objectives are to calculate which non-specific Ig dosage regimen ensures that an adequate quantity of anti-CMV Ig are administered, and to perform a cost-efficiency analysis comparing non-specific Ig with specific anti-CMV Ig when used in solid organ transplant.

Method

We conducted an observational, retrospective, cross-sectional study, in which we analysed the anti-CMV antibody titres from all Flebogamma® 5%5 g batches used at the Vall d'Hebron University Hospital during 2008 and 2009.

The analysis was performed sequentially in Instituto Grifols, S.A. as each of the batches had been produced. We analysed data using the ELISA technique, by means of the Bioelisa CMV IgG Biokit®.

The main variable for this study was the mean anti-CMV antibody titres of the sample analysed. As secondary variables, we examined the mean anti-CMV antibody titres and plasma origin.

To compare the mean values, we applied the student's t test for normal distribution. When irregular distribution was found, we applied the Mann-Whitney U test. The Kolmogorov-Smirnov test was used to evaluate sample distribution. To evaluate the statistically significant differences, we used a

bilateral value of $P<.05$ and a confidence interval of 95%. Statistical analysis of all data was performed using the statistical software SPSS 12.0.

We used the specific Ig preparation's authorised plan to calculate the anti-CMV non-specific Ig regimen for prophylaxis in solid organ transplantation: first post-transplant dose: 150 mg/kg; week 2, 4, 6 and 8 post-transplant: 150 mg/kg; weeks 12 and 16 post-transplant: 100 mg/kg. For anti-CMV specific Ig titres, the regimen above corresponds to at least 75PEI-U/ml and 50PEI-U/ml, respectively.

The pharmacoeconomic analysis was carried out from a hospital pharmacy point of view, using a cost reduction model, assuming that the 2 therapeutic options were equally efficient and safe. A 75 kg patient was used to calculate the dosage regimen. The cost registered in 2008 to purchase the 2 Ig preparations was: Cytotec® 10%, 10 ml: €130; and Flebogamma® 5%, 100 ml: €265.10. Costs associated with storage, preparation or administration were not taken into consideration, as they are similar for both options. The pharmacoeconomic analysis was performed using the Pharma-Decision software (version Hospital 1.2).

Results

We analysed 27 batches, including 18 944 vials of Flebogamma® 5%. The anti-CMV Ig titres of the vials did not present a normal distribution (Kolmogorov-Smirnov test $P<.001$). The mean concentration of anti-CMV Ig was 22.86 PEI-U/ml (SD±4.05).

The median anti-CMV Ig concentration was 28 PEI-U/ml for plasma from North America and 22 PEI-U/ml from Spain (CI 95% for the difference between medians 5 to 6 PEI-U/ml; $P<.001$), Figure and Table 1.

Considering a dosage regimen of 150 mg/kg, corresponding to the anti-CMV specific Ig preparations, a concentration of 75 PEI/kg was obtained in 35% of the Flebogamma® 5% vials. However, with a dose of 200 mg/kg of Flebogamma® 5%, 99.9% are predicted to reach the 75 PEI-U/kg target. A dose of 220 mg/kg should be recommended to guarantee 100% administration for anti-CMV Ig, given that some batches have non-specific Ig with a concentration of 17 PEI-U/ml.

As such, 147 mg/kg of non-specific Ig is equivalent to 100 mg/kg of the anti-CMV specific preparation, with regards anti-virus titre concentration.

For a patient weighing 75 kg, the anti-CMV specific Ig option cost €9265.60 for the whole treatment. The differential cost of Flebogamma® used in anti-CMV prophylaxis for solid organ transplant was therefore €−3721.90.

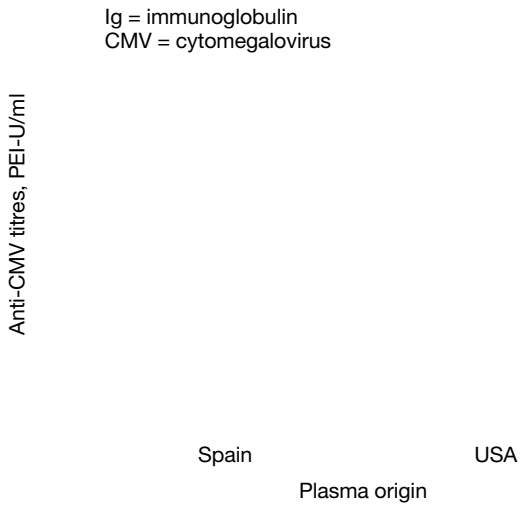

Figure 1 Differences in anti-CMV Ig concentration in accordance with the origin of the batches analysed.

Discussion

This study has examined the anti-CMV Ig concentration in a non-specific Ig preparation, which is widely used in our hospital and many other Spanish hospitals. The results show that anti-CMV non-specific Ig titres are slightly lower with respect to the minimum standard titration for anti-CMV specific Ig preparations. (Table 2). This fact is explained because the specific preparations come from donation pools, chosen with minimum anti-CMV antibody content.[3]

The differences observed for anti-CMV antibody concentration between the specific and non-specific preparations can be exceeded by correctly adjusting the non-specific Ig preparation, guaranteeing a similar anti-CMV antibody administration.

Although it was not the purpose of this study, we have found relevant differences with regards anti-CMV antibody content when comparing the plasma origin (plasma was used to purify immunoglobulins). Plasma was donated from Spanish and North American health centres and we have probably not examined enough batches from the USA. In either case, these differences may be explained

Table 1 Anti-CMV antibody titres of the different non-specific Ig batches analysed

	No. vials	Mean (PEI-U/ml) (SD)	Median (PEI-U/ml)	Range (PEI-U/ml)
Spain	15 018	22.06 (3.09)	22.00	17-8
USA	3 926	25.89 (5.78)	28.00	17-33
Total	18 944	22.86 (4.05)	23.00	17-33

CMV indicates cytomegalovirus; PEI-U, Paul Ehrlich Institute Unit.

Table 2 Anti-CMV antibody content for different human immunoglobulin preparations

	Non-specific immunoglobulin	Anti-CMV specific immunoglobulin	
	Flebogamma® 5% 100ml	Cytotect® 10% 50ml	Cytogam® 5% 50ml
Ig concentration, %	5	10	5
Total Ig, g	5	5	2.5
Minimum Ig concentration, %	97	95	na
Anti-CMV Ig concentration, PEI-U/ml	22.89[a]	50[b]	25[b]
Total anti-CMV Ig, PEI-U	2289[a]	2500[b]	1250[b]

CMV indicates cytomegalovirus; Ig, immunoglobulin; na, not available.
[a]According to data found in this study.
[b]Minimum concentration ensured for each batch.

by 2 points: 1) variation of prevalence of anti-CMV seropositivity and, therefore, differences between the anti-CMV antibody titre in the donor populations; and 2) due to variations in the purification and elaboration methods used.[9] This study has analysed the titres of only one non-specific Ig preparation. As a result, differences in the elaboration method can be ruled out, and therefore, it is likely that the differences in anti-CMV concentration titres is a result of the different immunisation levels of the donor populations. Nonetheless, it is difficult to be able to ensure where these differences originate, given the numerous factors that could affect the donor population's anti-CMV seroprevalence (age, sex, socio-economic level).[10-12] Furthermore, some previously published data are the contrary to those obtained in this study.[13,14]

The pharmacoeconomic analysis has been performed using a cost minimisation model. This option can be justified because it considers both therapeutic possibilities.[15,16] The most efficient option is the non-specific Ig, significantly reducing the cost of prophylaxis. The differences in cost for the 2 Ig preparations is probably greater than that documented in this study, as some hospitals have a contract in which the company that purifies and fractions the excess plasma from the blood bank delivers, free of charge, part of their non-specific Ig production to the hospital. This significantly reduces Flebogamma® 5%purchasing cost.

The dosage regimen proposed, based on the anti-CMV antibody content, should be considered safe, as it does not exceed recommendations for many other non-specific Ig therapeutic indications.[17] In either case, clinical efficacy and dose safety proposed for anti-CMV non-specific Ig in solid organ transplant patients would have to be confirmed. However, it would be difficult to conduct this type of clinical trial due to the complications involved with it.

To conclude, this study shows that there is a possible alternative for a pharmaceutical preparation that is not marketed in Spain. The analysis reasoning is based on the fact the both specific and non-specific Ig preparations had the same origin, manufacturing process and pharmacopoeia specifications.

Conflict of interest

The authors affirm that they have no conflict of interest.

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