TRASTUZUMAB: NUEVA VÍA DE ADMINISTRACIÓN

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PASADO - PRESENTE

- Dosificación por superficie corporal.
- Dosificación por Kg.
- Vía oral: unas pocas dosis o dosis fijas.

PRESENTE - FUTURO

- Dosificación por Superficie corporal y por Kg.
- Nuevas dianas terapéuticas. ¿Dosificación?.
- Más vía oral.
- «Dose banding».
- Nuevas vías de administración de fármacos conocidos: dosis fijas.
- Dosis fijas por vía IV.

FARMACOCINÉTICA TRASTUZUMAB IV

- Dosis estudiadas 10, 50, 100, 250, 500 mg.
- Fármaco no lineal (al aumentar la dosis disminuye el aclaramiento).
- Vida media: 28-38 días.
- Cl: 0,24 L/día (68kg).
- V_c: 3,02 L V_p: 2,68 L. (fármaco bicompartimental).
- Edad y función renal no afectan significativamente su farmacocinética.

TRASTUZUMAB Sc

- Ventajas vía Sc:
  - Administración más cómoda (vía menos invasiva).
  - Menor tiempo de elaboración para el Servicio de Farmacia.
  - Menor tiempo de administración (2-5 minutos).
  - Más económica.
  - Preferida por los pacientes.

- Inconvenientes vía Sc:
  - Soporta poco volumen de administración (1-2mL).
  - Problemas de biodisponibilidad con fármacos de PM elevado.

- TRASTUZUMAB Sc
  - Tecnología farmacéutica: ¿Es posible una formulación para administración Sc?
  - Es más fácil manejar una dosis única. ¿Es posible fijar una dosis única?
  - Dado el pequeño volumen de distribución es posible en un amplio rango de pesos fijar una dosis única.

TRASTUZUMAB Sc

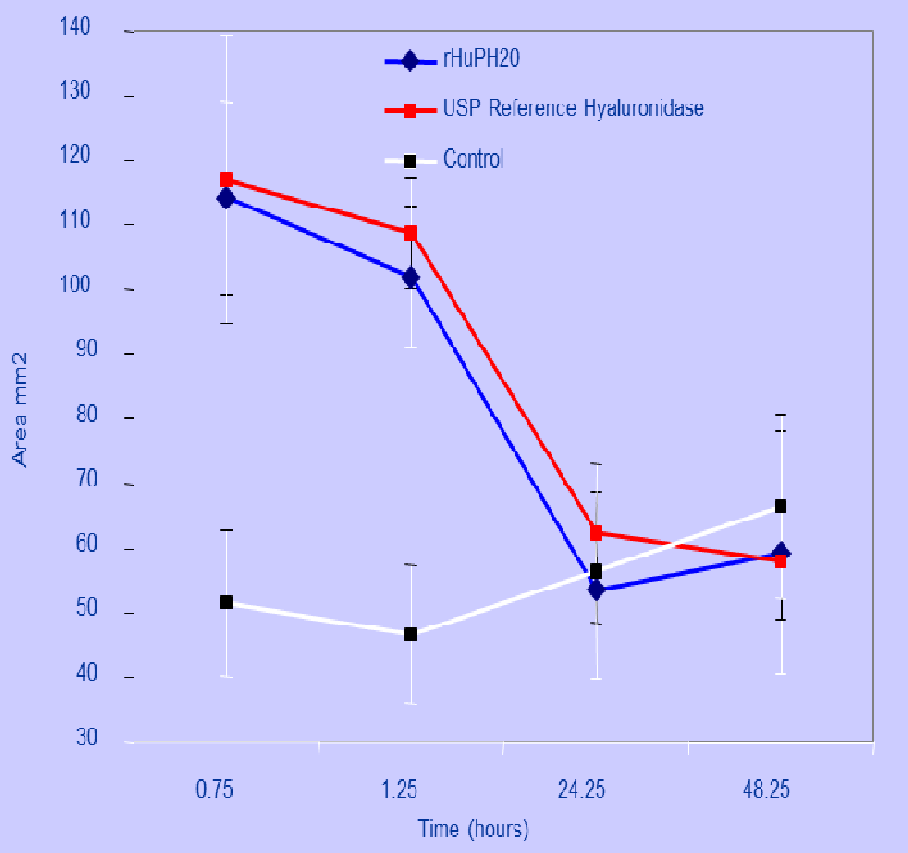
- Volumen de administración 5 mL:
  - **Hialuronidasa recombinante humana (rHuPH20)**
  - L-histidina, L-histidina hidrocloruro monohidrato.
  - a,a-trehalosa dihidrato, L-metionina
  - Polisorbato 20
  - Agua para inyectables

HIALURONIDASA

- Tejido subcutáneo formado por red de fibras de ácido hialurónico y colágeno.
- Para administración subcutánea de 5 ml de trastuzumab se necesita abrir espacios intersticiales.
- La hialuronidasa recombinante humana (rHuPH20) degrada de forma temporal y local el ácido hialurónico respetando las fibras de colágeno.
- Como resultado de ello se aumenta temporalmente el área de dispersión subcutáneo local.
- Tras la administración subcutánea el ácido hialurónico se regenera de forma natural.

Cambios tisulares REVERSIBLES producidos por hialuronidasa recombinante humana

Datos pre-clínicos en modelos animales.

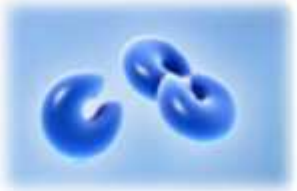


- La permeabilidad intersticial se recupera totalmente a las 24 horas
- No se observaron cambios histológicos despues de 48 horas de observación.

Anticuerpo altamente concentrado

HIALURONIDASA RECOMBINANTE HUMANA (rHuPH20)

+



SOLUCIÓN...

Inyección SC del mAb altamente concentrado

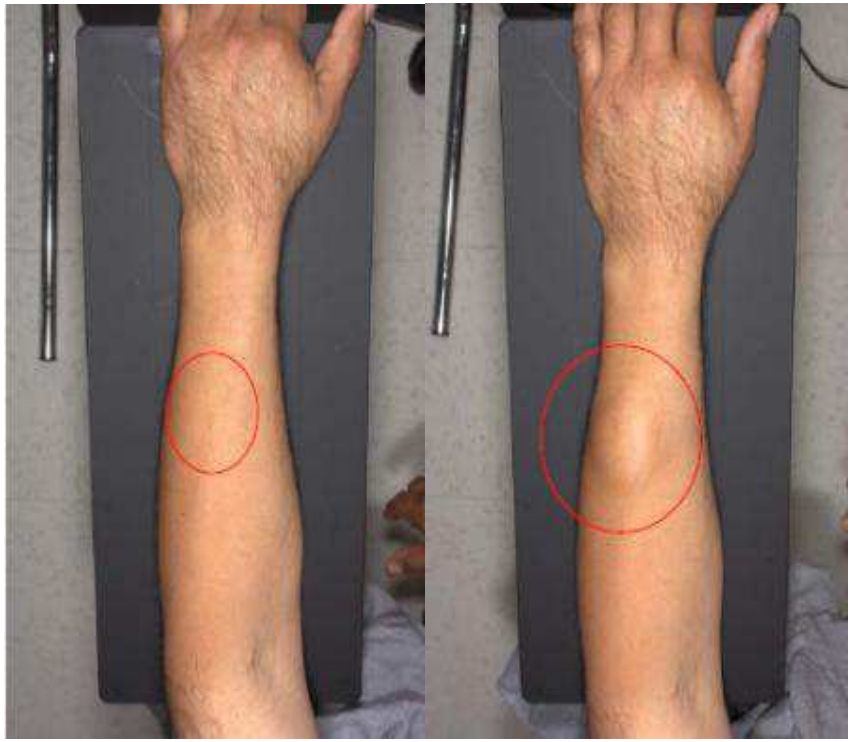
rHuPH20 reduce la viscosidad y aumenta la flexibilidad de la matriz intersticial

Absorción directamente en el sistema linfático

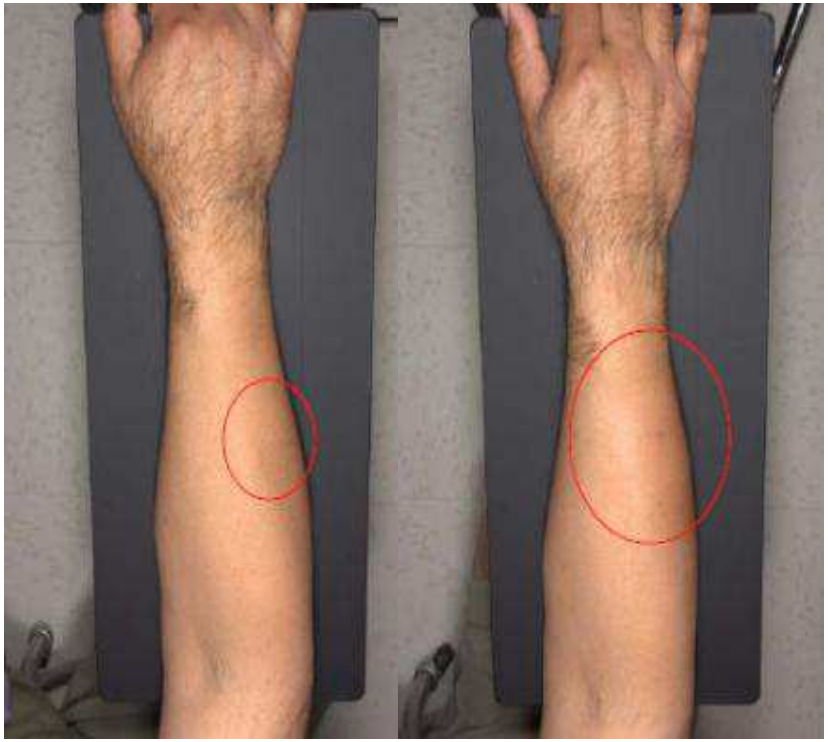
- Volumen mayor
- Aumenta BIODISPONIBILIDAD vía SC

USO DE HIALURONIDASA

Inyección sin rHuPH20



Inyección con rHuPH20 2000 U/mL



BUSQUEDA DOSIS Sc

ACCP

Pharmacokinetics

The Journal of Clinical Pharmacology
53(2) 192–201

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Comparison of Subcutaneous and Intravenous Administration of Trastuzumab: A Phase I/Ib Trial in Healthy Male Volunteers and Patients With HER2-Positive Breast Cancer

Chris Wynne, MB, ChB[1], Vernon Harvey, MD[2], Christian Schwabe, MD[2], Devonie Waaka, MB, ChB[1], Christine McIntyre, PhD[3], and Beate Bittner, PhD3

Abstract

Trastuzumab is a key component of treatment for human epidermal growth factor receptor 2 (HER2)–positive breast cancer in both the early and metastatic settings. It is administered intravenously, with between 17 and 52 infusions in standard regimens over 1 year. Intravenous administration of trastuzumab requires substantial time commitments for patients and health care professionals and can result in patient discomfort. A subcutaneous formulation of trastuzumab, containing recombinant human hyaluronidase to overcome subcutaneous absorption barriers, would reduce the administration duration and remove the need to establish intravenous access, thus improving the overall convenience of trastuzumab administration. This open-label, 2-part, phase I/Ib study (NCT00800436) was undertaken in healthy male volunteers and female patients with HER2-positive early breast cancer to identify the dose of subcutaneous trastuzumab that resulted in exposure comparable with the approved intravenous trastuzumab dose. A subcutaneous trastuzumab dose of 8 mg/kg was found to result in exposure comparable with the intravenous trastuzumab dose of 6 mg/kg. The subcutaneous formulation was well tolerated, with a trend toward fewer adverse events versus intravenous administration; most adverse events were mild in intensity. These results support an ongoing phase III efficacy and safety study comparing a fixed subcutaneous trastuzumab dose with intravenous trastuzumab administration.

Keywords

trastuzumab, subcutaneous, pharmacokinetics, HER2-positive, breast cancer

Approximately 20% to 25% of breast cancers show gene amplification and/or overexpression of the human epidermal growth factor receptor 2 (HER2),[1,2] which is associated with poor prognosis.[3] Trastuzumab, a humanized monoclonal antibody targeted to HER2, has proven survival benefits when added to chemotherapy in patients with HER2-positive breast cancer in both the early[4-6] and metastatic[7,8] settings, as well as in patients with HER2-positive metastatic gastric cancer.[9]

Trastuzumab is administered intravenously on a 3-weekly or weekly schedule, with the first dose administered over 90 minutes and subsequent infusions given over 30 to 90 minutes.[10] Trastuzumab is usually given over 1 year as 17 or 52 infusions. This results in considerable time commitments for patients and health care professionals. A subcutaneous trastuzumab formulation is in development, with an administration time of <5 minutes. Potential benefits include improved convenience, which may result in optimization of medical resource utilization. In addition, subcutaneous administration may be associated with a reduced frequency and/or intensity of infusion-related reactions, due to the slow absorption of trastuzumab from the interstitial tissue, as observed with intravenous and subcutaneous administration of alemtuzumab.[11]

Limiting factors for subcutaneous administration include absorption from the subcutaneous space,[12] required drug volume, and tolerability. The speed of absorption may be reduced by the structure of subcutaneous tissues, which include hyaluronan, a glycosaminoglycan of the extracellular matrix. This viscoelastic polymer has a rapid turnover rate with a half-life of 15 to 20 hours and represents a feasible target for modification.[13] Hyaluronidase is an enzyme that hydrolyzes hyaluronan, thus reducing barriers to bulk fluid flow, temporarily enhancing the dispersion of coinjected drugs.

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www.nature.com/psp

ORIGINAL ARTICLE

Use of a Population Pharmacokinetic Approach for the Clinical Development of a Fixed-Dose Subcutaneous Formulation of Trastuzumab

F Hourcade-Potelleret[1,2], A Lemenuel-Diot[1], C McIntyre[3], M Brewster[3], B Lum[4] and B Bittner[3,5]

A new subcutaneous (s.c.) trastuzumab formulation provides savings in terms of time and is preferred by patients and health care professionals relative to standard intravenous (i.v.) administration due to simpler and more rapid administration (2–5 minutes). Selection of the s.c. dose was based on a pharmacokinetic bridging approach that aimed to achieve noninferior trastuzumab serum trough concentrations (C_{trough}) vs. reference i.v. administration. Using population modeling and simulation, we showed that a fixed 600-mg trastuzumab s.c. dose, administered thrice-weekly (Q3W) without a loading dose, would provide C_{trough} (predose Cycle 8) and area under the time–concentration curve ($AUC_{0\text{-}21\ day}$, Cycle 7) at least as high as Q3W i.v. administration. The model was retrospectively validated using observed pharmacokinetic data from an independent phase III study of (neo) adjuvant trastuzumab (HannaH). These results provide a strong pharmacokinetic rationale for the trastuzumab s.c. 600-mg fixed dose, supported by the noninferior efficacy of this regimen vs. reference i.v. administration.

CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e87; doi:10.1038/psp.2013.63; published online 2 January 2014

Trastuzumab (HERCEPTIN, F. Hoffmann-La Roche, Basel, Switzerland) is the standard of care for human epidermal growth factor receptor 2 (HER2)–positive breast cancer across all disease stages.[1–3] The currently available formulation is administered by intravenous (i.v.) infusion on thrice-weekly (Q3W) or weekly schedules, with body-weight-adjusted dosing and a loading dose in the first cycle.[4] The loading dose should be administered over a period of 90 minutes, and maintenance doses are given over 30 minutes, if the loading dose is well tolerated. A new subcutaneous (s.c.) formulation of trastuzumab has been developed as an alternative to i.v. administration.[5] This formulation contains recombinant human hyaluronidase (rHuPH20), which temporarily degrades hyaluronan at the injection site to facilitate injection of the 5-ml dosing volume.[6] With a total recommended administration time of between 2 and 5 minutes, the s.c. formulation provides substantial time savings in the clinic and is preferred by both patients and health care professionals.[7,8] Administration by the s.c. route is also expected to improve compliance and reduce administration costs.

Selection of the s.c. dose was based on a pharmacokinetic bridging strategy, assuming that an s.c. dose that maintains trastuzumab serum trough concentrations (C_{trough}) at least as high as those with i.v. administration would be expected to achieve saturation of target receptors and result in comparable efficacy. Support for this hypothesis is provided by the absence of significant difference in response rate in metastatic breast cancer (MBC) between the approved weekly regimen (4 mg/kg loading dose; 2 mg/kg maintenance doses) and an unapproved weekly regimen (8 mg/kg loading dose; 4 mg/kg maintenance doses), suggesting a plateau in the dose–efficacy relationship.[9] Potentially higher C_{trough} values than those observed with the i.v. regimen were considered acceptable due to the results from a previous phase I/II study in women with HER2-positive MBC. An intensive loading regimen of trastuzumab (6 mg/kg i.v. on days 1, 8, and 15, followed by 6 mg/kg every 3 weeks from day 22) resulted in a median estimated C_{trough} of 119 mg/l, which is higher than the steady-state trough concentrations with a conventional weekly or Q3W regimen (64.9 or 47.3 mg/l, respectively). No new or unexpected adverse events or increased cardiotoxicity were reported during the study. The dosing regimen was well tolerated and had a good efficacy profile.[10]

The appropriateness of the fixed dose of s.c. trastuzumab selected using the above approach has subsequently been confirmed in the phase III HannaH study (BO22227), which used a noninferiority design to compare the pharmacokinetics, efficacy, and safety of fixed s.c. dosing vs. the reference i.v. regimen in the (neo)adjuvant setting.[11]

Pharmacokinetic studies of s.c. trastuzumab have been performed in a two-part, phase I/Ib, dose-finding/dose-confirmation trial.[12] This study used body-weight-adjusted dosing of trastuzumab s.c. to facilitate comparison with reference (i.e., body weight-based) i.v. dosing and to support assessment of the safety of s.c. administration. To avoid potential underdosing of patients with breast cancer, initial s.c. dose finding in part 1 was conducted in healthy male volunteers. Doses of 6, 8, and 10 mg/kg s.c. and 6 mg/kg i.v. regimens were evaluated, and, based on these results, two trastuzumab s.c. doses (8 and 12 mg/kg) were tested in part 2 (dose confirmation) in patients previously treated for HER2-positive early breast cancer (EBC). The 8 mg/kg s.c. dose was expected to result in trastuzumab serum levels in the range of those achieved with the 6 mg/kg i.v. maintenance dose. The

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ESTUDIO BP22023

Estudio abierto, multicéntrico, de búsqueda de dosis y confirmación

Parte 1 (Búsqueda de dosis)

Cohorte	Ruta de administración	Sujetos	Dosis (mg/kg)
1	IV	6 voluntarios sanos	6
2	IV	6 pacientes* (HER2+ CMp)	6
3	Sc	6 voluntarios sanos	6
4	Sc	6 voluntarios sanos	8
5	Sc	6 voluntarios sanos	10

Parte 2 (Confirmación de dosis)

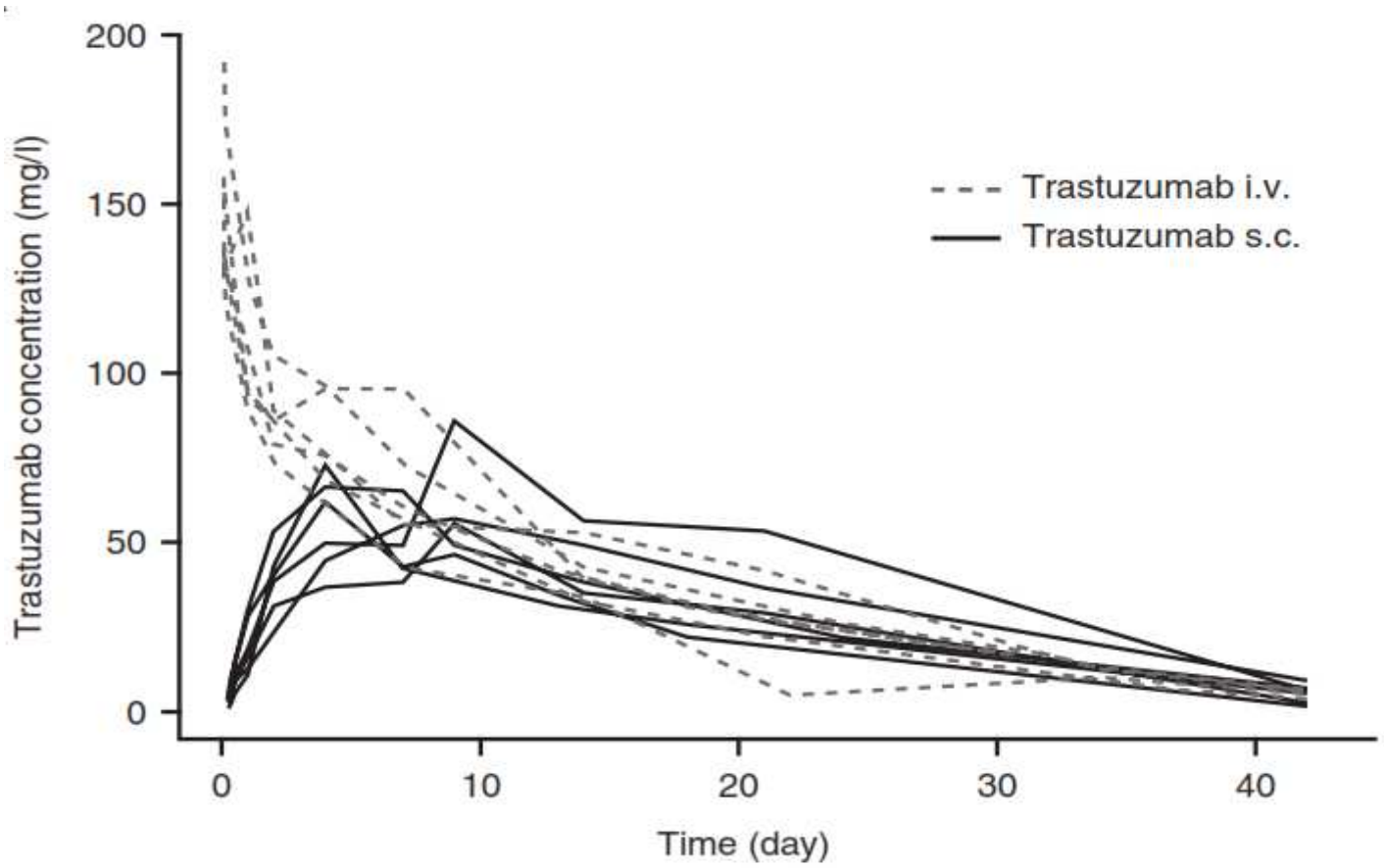
Cohorte	Ruta de administración	Sujetos	Dosis (mg/kg)
A	Sc	20 pacientes* (HER2+ CMp)	8
B	Sc	20 pacientes* (HER2+ CMp)	12

Wynne C, et al. *The Journal of Clinical Pharmacology* 2012;53(2):192 –201

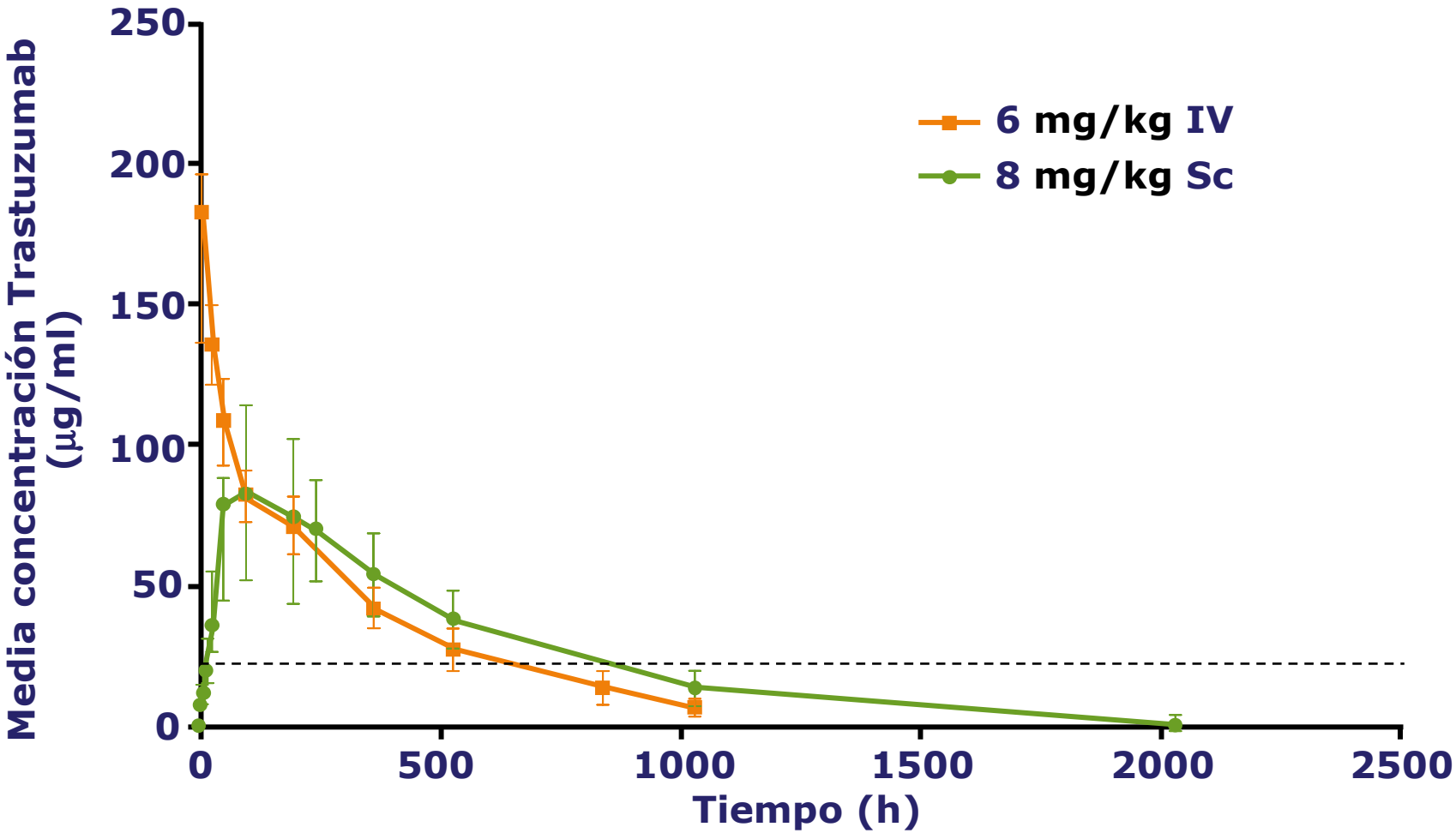
BIODISPONIBILIDAD TRASTUZUMAB Sc

	6 mg/kg IV	6 mg/kg Sc	8 mg/kg Sc	10 mg/kg Sc	12 mg/kg Sc
AUC (Calculado)	1610	1350	1960	2500	
AUC* (Ajustado a Dosis)			1470	1500	
F (%)		84	91	93	
HER2+ CMp					
AUC (Calculado)	1800		2090		3550
AUC* (Ajustado a Dosis)			1568		1775
F (%)			87		99

FARMACOCINÉTICA TRASTUZUMAB



FARMACOCINÉTICA TRASTUZUMAB



TRASTUZUMB Sc

- Dosis fija 600 mg (8mg/kg para un paciente de 75 kg).

- Ajustado por biodisponibilidad corresponde aproximadamente a una dosis de 480-500 mg administrados por vía IV (6mg/kg para un paciente de 80-83 kg).

- Las concentraciones séricas deben de mantenerse por encima de un nivel mínimo (CME) (indica la **saturación del receptor** para mantener la eficacia).

  ✓ **20 µg/ml** identificado por modelos xenográficos preclínicos.

TRASTUZUMAB Sc DOSIS FIJA FRENTE IV mg/Kg

Comparación con el régimen trisemanal

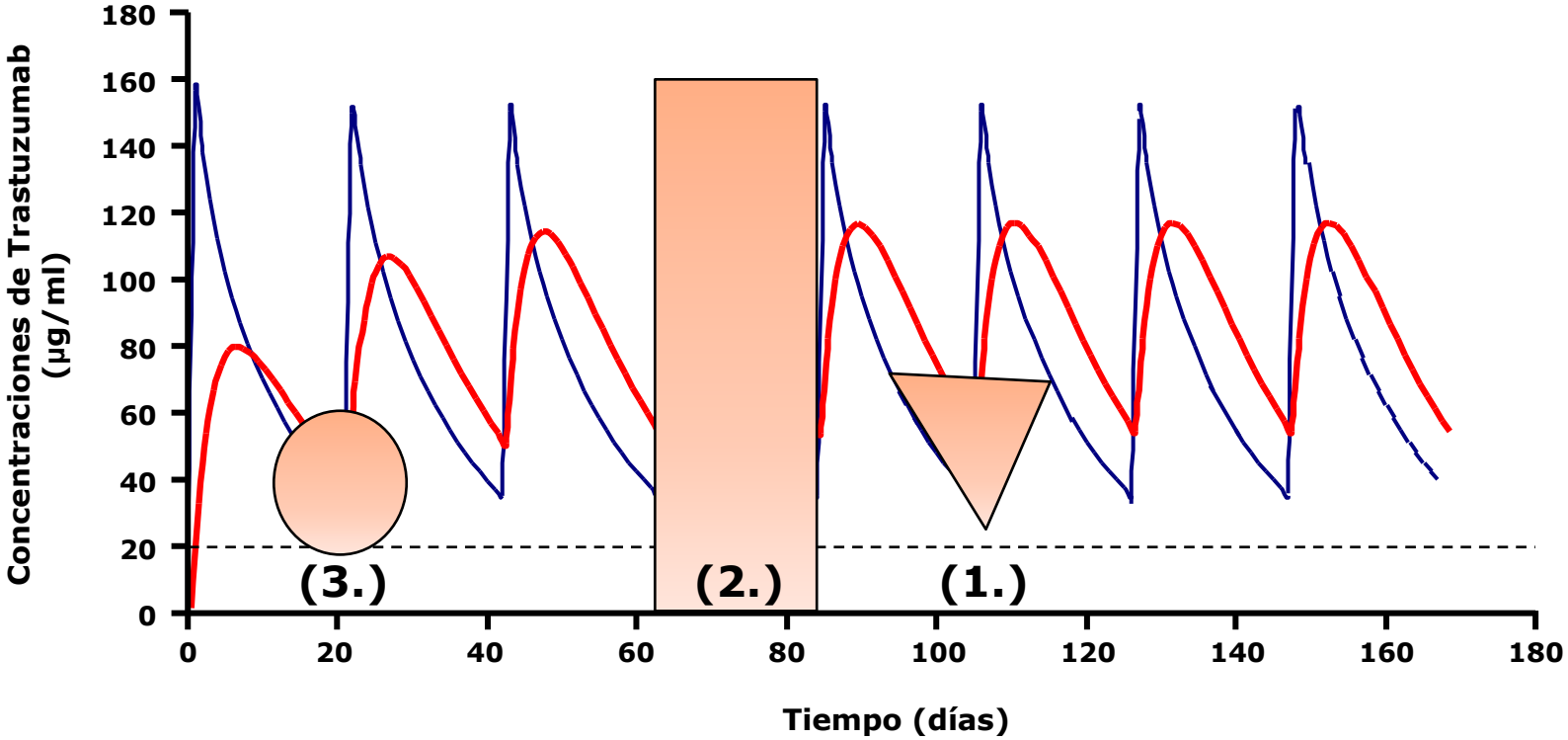
IV: 8 mg/kg carga, 6 mg/kg mantenimiento

SC: 600 mg

(1.) Concentraciones séricas por encima de 20 µg/ml (indica saturación del receptor) · No se compromete seguridad si C_{max} es más baja.

(2.) Similar área bajo la curva (AUC)

(3.) Sin dosis de carga una exposición comparable en el Ciclo 1



ESTUDIO HannaH

Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I–III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial

Gustavo Ismael, Roberto Hegg, Susanne Muehlbauer, Dominik Heinzmann, Bert Lum, Sung-Bae Kim, Tadeusz Pienkowski, Mikhail Lichinitser, Vladimir Semiglazov, Bohuslav Melichar, Christian Jackisch

Summary

Background A subcutaneous formulation of trastuzumab has been developed, offering potential improvements in patient convenience and resource use compared with the standard intravenous infusion of the drug. We compared the pharmacokinetic profile, efficacy, and safety of the subcutaneous and intravenous formulations in patients with HER2-positive early breast cancer.

Methods The HannaH study was a phase 3, randomised, international, open-label, trial in the (neo)adjuvant setting. Patients with HER2-positive, operable, locally advanced or inflammatory breast cancer were randomly assigned to eight cycles of neoadjuvant chemotherapy administered concurrently with trastuzumab every 3 weeks either intravenously (8 mg/kg loading dose, 6 mg/kg maintenance dose) or subcutaneously (fixed dose of 600 mg); 1:1 ratio. Chemotherapy consisted of four cycles of docetaxel (75 mg/m²) followed by four cycles of fluorouracil (500 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (500 mg/m²), every 3 weeks. After surgery, patients continued trastuzumab to complete 1 year of treatment. Coprimary endpoints were serum trough concentration (C_{trough}) at pre-dose cycle 8 before surgery (non-inferiority margin for the ratio between groups of 0·80) and pathological complete response (pCR; non-inferiority margin for the difference between groups of −12·5%), analysed in the per-protocol population. This study is registered with ClinicalTrials.gov, number NCT00950300.

Findings 299 patients were randomly assigned to receive intravenous trastuzumab and 297 to receive subcutaneous trastuzumab. The geometric mean presurgery C_{trough} was 51·8 μg/mL (coefficient of variation 52·5%) in the intravenous group and 69·0 μg/mL (55·8%) in the subcutaneous group. The geometric mean ratio of C_{trough} subcutaneous to C_{trough} intravenous was 1·33 (90% CI 1·24–1·44). 107 (40·7%) of 263 patients in the intravenous group and 118 (45·4%) of 260 in the subcutaneous group achieved a pCR. The difference between groups in pCR was 4·7% (95% CI −4·0 to 13·4). Thus subcutaneous trastuzumab was non-inferior to intravenous trastuzumab for both coprimary endpoints. The incidence of grade 3–5 adverse events was similar between groups. The most common of these adverse events were neutropenia (99 [33·2%] of 298 patients in the intravenous group *vs* 86 [29·0%] of 297 in the subcutaneous group), leucopenia (17 [5·7%] *vs* 12 [4·0%]), and febrile neutropenia (10 [3·4%] *vs* 17 [5·7%]). However, more patients had serious adverse events in the subcutaneous group (62 [21%] of 297 patients) than in the intravenous group (37 [12%] of 298); the difference was mainly attributable to infections and infestations (24 [8·1%] in the subcutaneous group *vs* 13 [4·4%] in the intravenous group). Four adverse events led to death (one in the intravenous group and three in the subcutaneous group), all of which occurred during the neoadjuvant phase. Of these, two—both in the subcutaneous group—were deemed to be treatment related.

Interpretation Subcutaneous trastuzumab, administered over about 5 min, has a pharmacokinetic profile and efficacy non-inferior to standard intravenous administration, with a similar safety profile to intravenous trastuzumab, and therefore offers a valid treatment alternative.

Funding F Hoffmann-La Roche.

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Introduction

Treatment with trastuzumab represents the standard of care for HER2-positive breast cancer.[1–4] This drug is administered every 3 weeks for 1 year in patients with early breast cancer, or until disease progression in patients with metastatic disease.[5] A 90 min intravenous infusion is administered for the first dose and if well tolerated, delivered as a 30 min infusion for subsequent doses, with dosage adjusted according to bodyweight.[5]

A new subcutaneous trastuzumab formulation, containing a fixed dose of 600 mg and recombinant human hyaluronidase PH-20 (rHuPH-20) as an excipient, administered every 3 weeks, has been developed as an alternative to the intravenous regimen. rHuPH-20 is

ESTUDIO HannaH

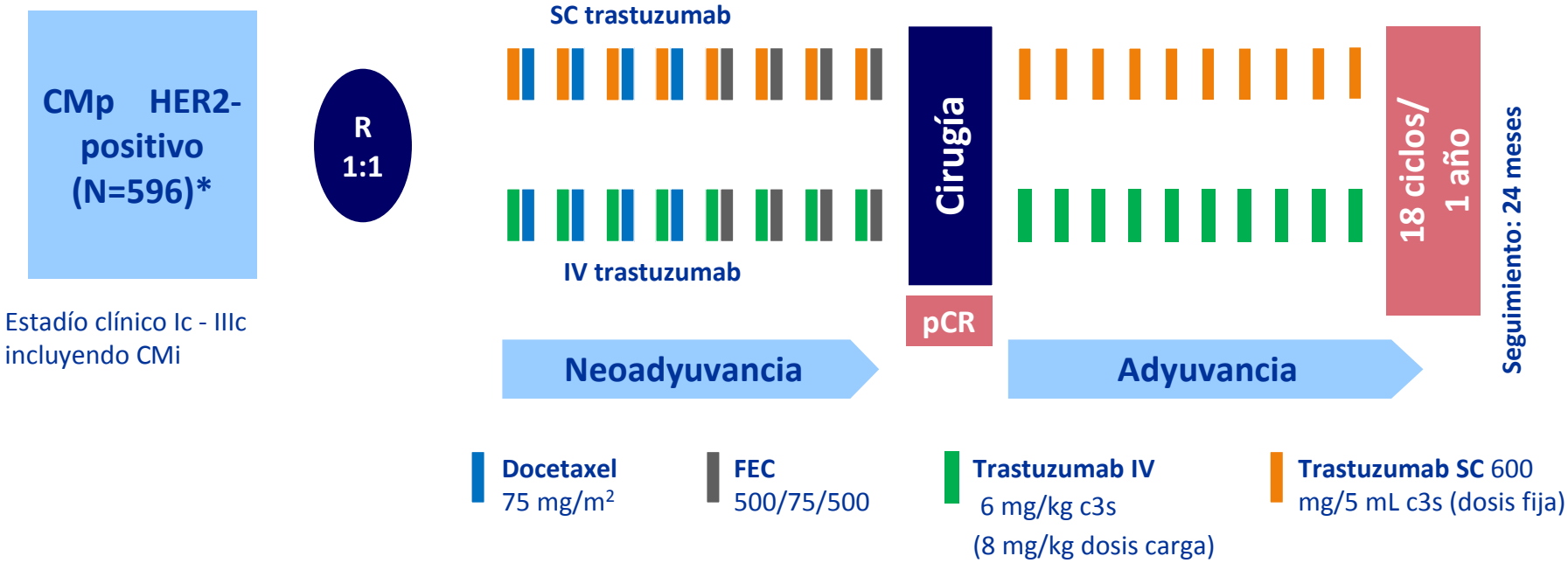
- en**HAN**ced treatment with **N**eo**A**djuvant **H**erceptin®.

- Estudio fase III de no inferioridad (dosis fija 600 mg Sc frente a dosis de 6mg/kg IV con dosis de carga de 8mg/kg cada 3 semanas). Pivotal.

- Objetivos principales:
  - Cmin pre-dosis ciclo 8. Margen de no inferioridad ratio entre grupos 0.8.
  - Respuesta patológica completa (Rpc). Margen de no inferioridad 12,5%. Análisis por protocolo.

- Objetivos secundarios
  - AUC del ciclo 7.
  - Pacientes >20 µg/ml pre-dosis ciclo 8.
  - Rpc en mama y axila.
  - Tasa de respuesta global.
  - Mediana de tiempo hasta respuesta.

DISEÑO ESTUDIO HannaH



Objetivo:

Demostrar no-inferioridad de Sc *vs* IV basado en endpoints co-primarios:

Fc: C_{min} pre-dosis Ciclo 8 (pre-cirugía)

Eficacia: respuesta patológica completa (RpC) en la mama

ESTUDIO HannaH: Resultados farmacocinéticos

	Trastuzumab IV n=235	Trastuzumab Sc n=234
Endpoint primario		
C_{min} observada pre-dosis ciclo 8		
Media geométrica (µg/mL)	**51.8**	**69.0**
Relación de la media geométrica (IC 90%)	1.33 (1.24; 1.44)	
	No-inferioridad de SC vs IV demostrada como límite inferior del IC 90% > margen de no inferioridad pre-especificado de 0.8	
Endpoints secundarios		
Pacientes >20 µg/ml pre-dosis ciclo 8	**232 (98.7%)**	**227 (97.0%)**
AUC en el ciclo 7		
Media geométrica (µg/ml*día)	**1978**	**2108**
Relación de la media geométrica (IC 90%)	1.07 (1.01; 1.12)	

ESTUDIO HannaH: Resultados farmacocinéticos

Brazo de tratamiento	Ciclo	n	Media (µg/mL)	SD (µg/mL)	% CV	Mediana (µg/mL)	Rango (µg/mL)
IV dosis de carga	1	291	34.5	22	30.9	30.9	0–309
SC	1	290	32.7	18.5	56.3	29.3	3–153

Valores de C_{min} en ciclo 1 son similares para Sc e IV; por lo tanto, no se require dosis de carga.

FARMACOCINÉTICA TRASTZUMAB IV-Sc (HannaH)

	Trastuzumab IV	Trastuzumab Sc
Cmin (µg/mL)	57,8 (Mediana)	78,7 («»)
Tmax (días)		3 (1-14) («»)
Cmax (µg/mL)	221 («»)	149 («»)
Cl (L/día)		0,22
Vc (L)		2,89

ESTUDIO HannaH: Resultados de eficacia clínica

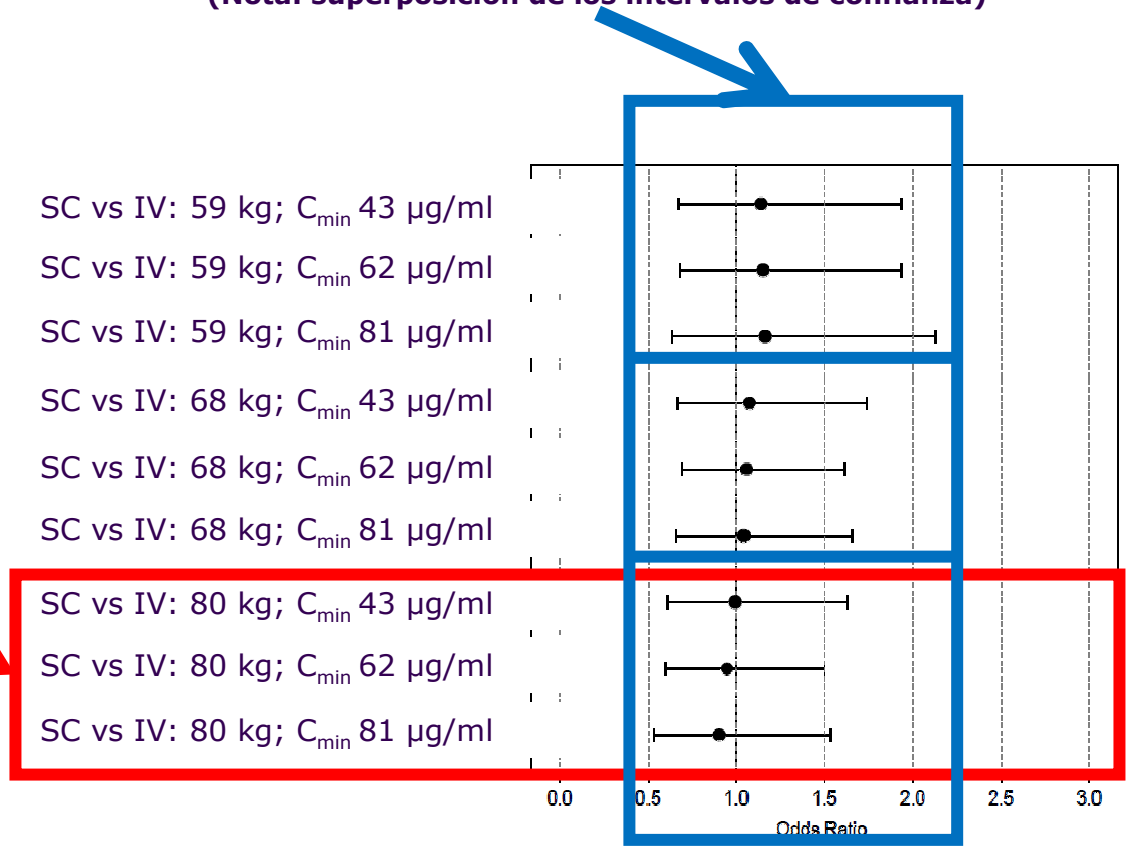
	Trastuzumab IV n=263 n (%)	Trastuzumab Sc n=260 n (%)
Endpoint primario		
RpC en la mama	**107 (40.7%)**	**118 (45.4%)**
Diferencia en tasa de RpC (IC 95%)	4.7% (-4.0%; 13.4%)	
	No-inferioridad de Sc vs IV demostrada como límite inferior del IC 90% > margen de no inferioridad pre-especificado de -12.5%	
Endpoints secundarios		
RpC en mama y axila (tRpC)	**90 (34.2%)**	**102 (39.2%)**
Diferencia en tRpC (IC 95%)	5.0% (-3.5%; 13.5%)	
Tasa de Respuesta Global	**231 (88.8%)**	**225 (87.2%)**
Mediana de tiempo hasta respuesta	**6 semanas**	**6 semanas**

Tasa de RpC *vs* C_{min} y peso

Beneficio comparable para los diferentes grupos según peso

(Nota: superposición de los intervalos de confianza)

En pacientes de 80 kg, no hubo correlación significativa con RpC y el incremento de C_{min}



RpC POR GRUPOS DE PACIENTES

- El peso y los niveles mínimos de trastuzumab pre-dosis Ciclo 8 no impactaron en la tasa de RpC.
  - Peso: Odds ratio 0.99 (95% CI 0.98, 1.01), p = 0.28
  - C_{min}: Odds ratio 1.00 (95% CI 1.00, 1.01), p = 0.45

- El receptor de estrógenos fue el único factor en ambos brazos del estudio con un mayor impacto en la tasa de RpC.
  - Pacientes con RE-negativo tuvieron una mayor oportunidad de RpC Odds ratio 2.68 (95% CI 1.85, 3.87), $p \leq 0.0001$

ESTUDIO HannaH: Resultados de seguridad

	Intravenous trastuzumab (n=298)	Subcutaneous trastuzumab (n=297)
Patients with ≥1 adverse event (any grade)	280 (93·9%)	289 (97·3%)
Patients with ≥1 severe adverse event (grade 3–5)	155 (52·0%)	154 (51·9%)
Patients with ≥1 serious adverse event	37 (12·4%)	62 (20·9%)
Patients with adverse event leading to death	1 (<1%)	3 (1·0%)

Data are number (%).

ESTUDIO HannaH: Resultados de seguridad

	Intravenous trastuzumab		Subcutaneous trastuzumab	
	Adverse events	Serious adverse events	Adverse events	Serious adverse events
Total	4171	50 (1·2%)	4178	90 (2·2%)
Grade 1	2669	3 (0·1%)	2732	3 (0·1%)
Grade 2	1125	6 (0·5%)	1111	17 (1·5%)
Grade 3	273	21 (7·7%)	254	46 (18·1%)
Grade 4	81	19 (23·5%)	73	21 (28·8%)
Grade 5	1	1 (100·0%)	3	3 (100·0%)
Missing	22	0 (<0·1%)	5	0 (<0·1%)
Grade 1–2	3794	9 (0·2%)	3843	20 (0·5%)
Grade ≥3	377	41 (10·9%)	335	70 (20·9%)

Data are number or number (% of adverse events). All events were counted irrespective of multiple occurrences in a patient.

ESTUDIO HannaH: Resultados de seguridad

	Intravenous trastuzumab (n=298)	Subcutaneous trastuzumab (n=297)
Patients with serious adverse events by system organ class		
Haematological toxicity	19 (6·4%)	21 (7·1%)
Infections and infestations	13 (4·4%)	24 (8·1%)
Injury, poisoning, and procedural complications	4 (1·3%)	3 (1·0%)
Cardiac disorders	2 (<1%)	4 (1·3%)
Gastrointestinal disorders	4 (1·3%)	2 (0·7%)
General disorders and administration site disorders	0	4 (1·3%)
Respiratory, thoracic, and mediastinal disorders	0	4 (1·3%)
Vascular disorders	1 (<1%)	3 (1·0%)
Nervous system disorders	0	3 (1·0%)
Serious adverse events occurring in ≥2 patients		
Febrile neutropenia	10 (3·4%)	13 (4·4%)
Neutropenia	9 (3·0%)	7 (2·4%)
Bronchopneumonia	2 (<1%)	1 (<1%)
Pneumonia	2 (<1%)	1 (<1%)
Tonsillitis	0	3 (1·0%)
Cellulitis	0	2 (<1%)
Postoperative wound infection	0	2 (<1%)
Pleural effusion	0	2 (<1%)
Pulmonary embolism	0	2 (<1%)

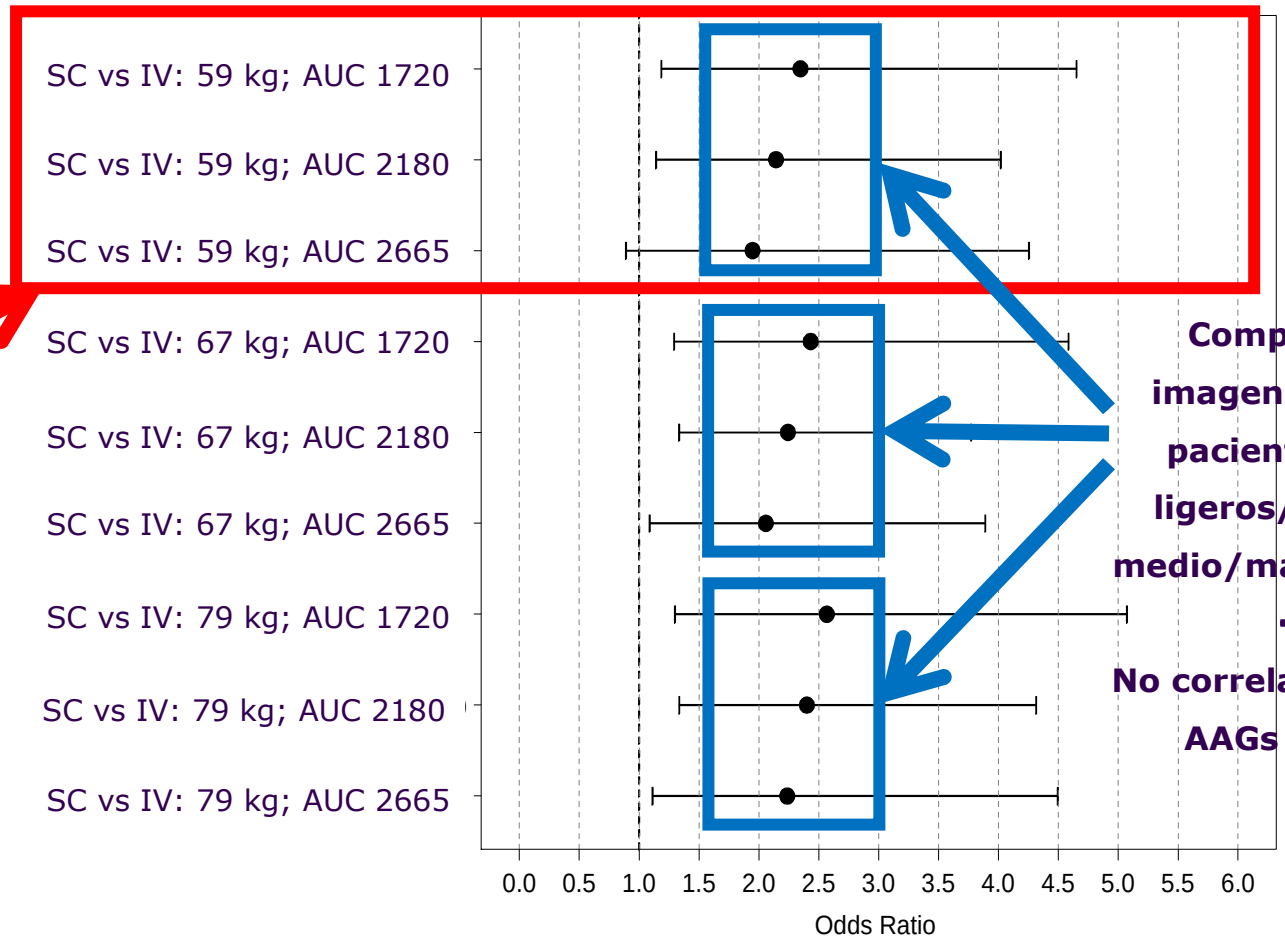
ESTUDIO HannaH: Resultados de seguridad

	Trastuzumab IV n=298 (%)	Trastuzumab Sc n=297 (%)
Total pacientes con al menos un AA	**280 (94)**	**289 (97)**
AA - grado ≥ 3	**155 (52)**	**154 (52)**
AAs graves (AAGs)	**37 (12)**	**62 (21)**
Muertes debidas a AAs	**1 (< 1)**	**3 (1)**
Seguridad cardiaca		
Descenso asintomático de FEVI*	**6 (2.0)**	**7 (2.4)**
FCC sintomático, NYHA clase II	**0**	**2 (0.7)**
AAs cardiacos ≥ grado 3	**3 (1.0)**	**5 (1.7)**

El perfil de seguridad de trastuzumab Sc e IV es comparable.

No correlación entre peso y AAGs

Odds ratios para acontecimientos adversos graves por cuartiles de peso y AUC[1]



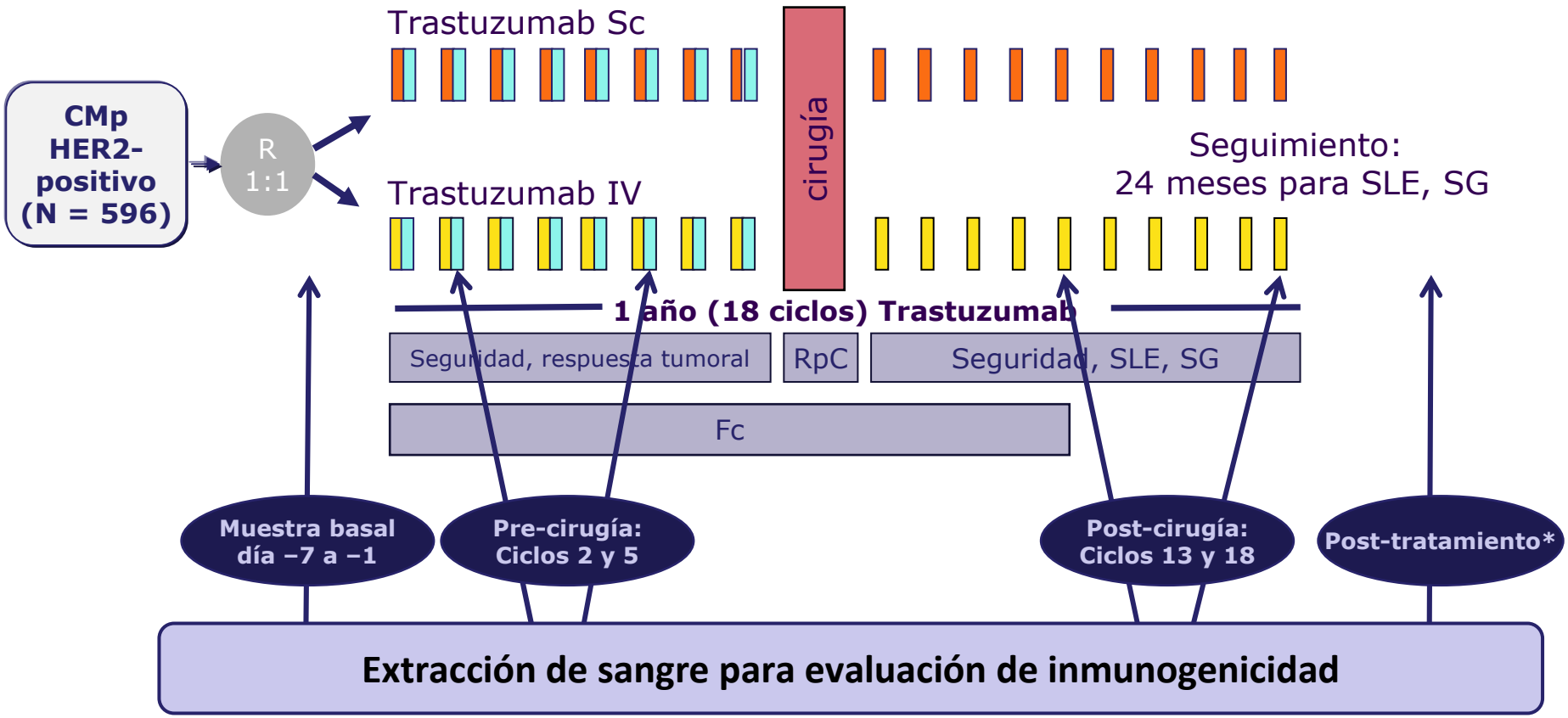
En pacientes más delgados, no hubo correlación significativa con AAGs y AUC

Comparable imagen para los pacientes más ligeros/de peso medio/más pesados

➔

No correlación entre AAGs y peso

Estudio HannaH: Valoraciones de los anticuerpos



Estudio HannaH: Anticuerpos (ADAs) *baja tasa sin relevancia clínica*

	Trastuzumab IV	Trastuzumab Sc	
	Anti-Trastuzumab	Anti-trastuzumab	Anti-rHuPH20
Pts positivo para ADA ("Tasa de immunogenicidad")	**(10) 3.4%**	**(20) 6.8%**	**(34) 11.2%**

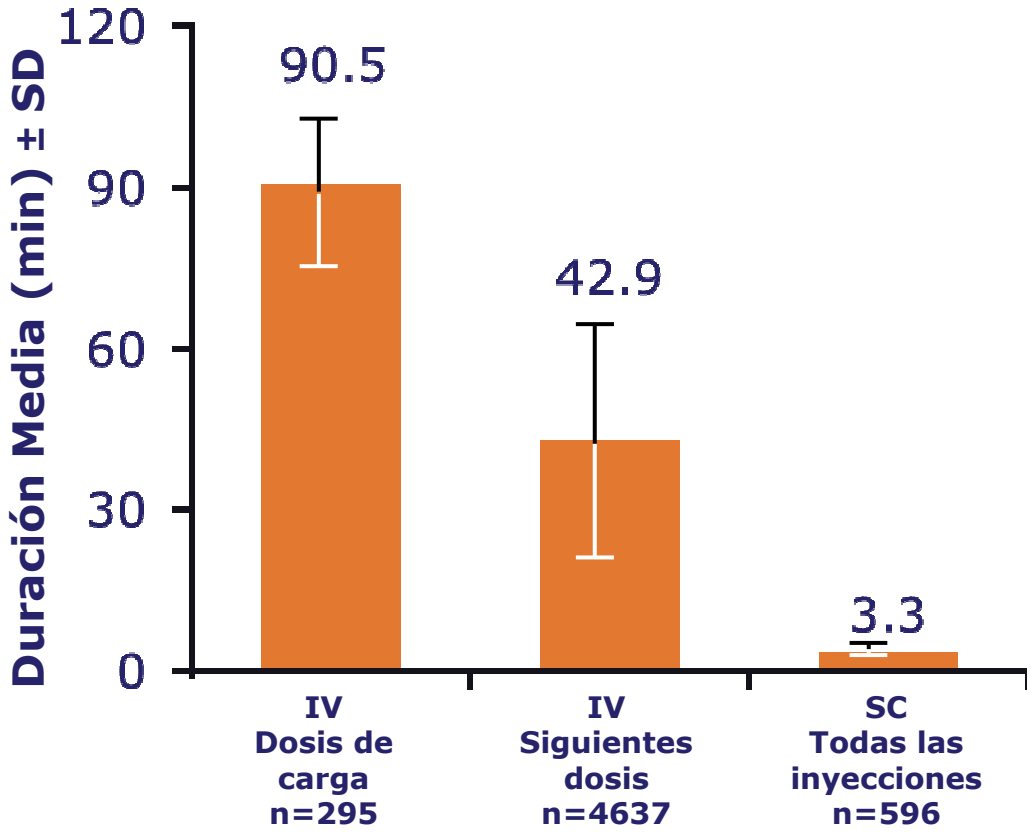
No impacto de ADAs a Trastuzumab o rHuPH20 en:

- **Farmacocinética** (C_{min} predosis ciclo 8)
- **Eficacia** (RpC)
- **Seguridad** (incidencia de reacciones relacionadas con la infusión)

Immunogenicidad de Trastuzumab Sc fué monitorizada a través del estudio y los hallazgos fueron bajos y no afectaron a la farmacocinética, eficacia y seguridad

Estudio HannaH: tiempo de administración

La administración IV de tratuzumab es 14 veces más larga que la inyección SC



TRASTUZUMAB IV vs TRASTUZUMAB Sc

Trastuzumab administrado por vía Sc

Cambios

- Solución ***lista para usar*** (5 ml)
- Administración ***Sc***
- Nuevo excipiente ***hialuronidasa recombinante humana***
- Dosis ***fija*** (600 mg)
- ***NO*** dosis de carga
- Administración en ***5 minutos***

- Trastuzumab Sc a dosis fija (600 mg c/3 semanas) es equiparable a trastuzumab IV (dosis de carga 8 mg/kg seguido de 6 mg/kg c/3 semanas) en términos de eficacia y seguridad en pacientes con CMp HER-2 positivo.
    - ¿Para todos los pacientes?.

- Peso (kg) IV 66,0 (44,4-137,1) – Sc 68,0 (43,0-136,0)
- Pacientes con peso corporal < 51 kg: la media de AUC en el estado de equilibrio fue un 80% mayor después del tratamiento Sc frente al IV.
  - ¿Seguridad?
- Pacientes con peso corporal > 90 kg: la media de AUC en el estado de equilibrio fue un 20% menor después del tratamiento Sc frente al IV.
  - ¿Eficacia?

TRASTUZUMAB IV

- Cáncer de mama metastásico / Cáncer de mama precoz HER-2 positivo.
  - 8mg/kg seguido de 6mg/kg c/3 semanas.
  - 4mg/kg seguido de 2mg/kg semanal.
    - Menor índice de fluctuación, C_{media} en s.s. similar.
- Cáncer gástrico metastásico HER-2 positivo.
  - 8mg/kg seguido de 6mg/kg c/3 semanas.

FARMACOCINÉTICA TRASTUZUMAB IV

En S.S.	C.M.M. (6mg/Kg) c/21 días	C.M.M. (2mg/Kg) c/7 días	C.M.P. (6mg/Kg) c/21 días	C.G.M. (6mg/Kg) c/21 días
E.C.	BO15935	H0648 g	BO16348 HERA	ToGA
AUC (mg.día/L)	1.793	1677*	2206	1213
$C_{max.}$ (µg/mL)	189	104	225	132
$C_{min.}$ (µg/mL)	47,3	64,9	68,9	27,6

FARMACOCINÉTICA TRASTUZUMAB C.G.M.

Cancer Chemother Pharmacol (2014) 73:737–747
DOI 10.1007/s00280-014-2400-5

ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer

Valérie F. Cosson · Vivian W. Ng · Michaela Lehle · Bert L. Lum

Received: 14 November 2013 / Accepted: 24 January 2014 / Published online: 12 February 2014

FARMACOCINÉTICA TRASTUZUMAB C.G.M.

- Análisis farmacocinético del estudio ToGA (Fase III) -2012 (Trastuzumab + quimioterapia frente quimioterapia). Cisplatino + capecitabina o 5-fluorouracilo c/3 semanas.
- 266 pacientes (77,8% varones).
- Variables estudiadas: Peso, gastrectomía previa, albúmina, fosfatasa alcalina y origen étnico.
  - Peso elevado y niveles bajos de albúmina se relacionaron con un mayor aclaramiento.
  - Gastrectomía previa se correlacionó con un menor aclaramiento.
- Pacientes con menor Cmin tuvieron mayor ratio de progresión y menor supervivencia global.
  - HELOISE study (NCT01450696), a phase IIIb study in patients with Her2-positive metastatic gastric or GEJ cancer. 8mg/kg seguido de 6mg/kg c/3 semanas frente 8mg/kg seguido de 10mg/kg c/3 semanas con Cisplatino + capecitabina c/3 semanas en ambos grupos.

¡ Muchas Gracias !