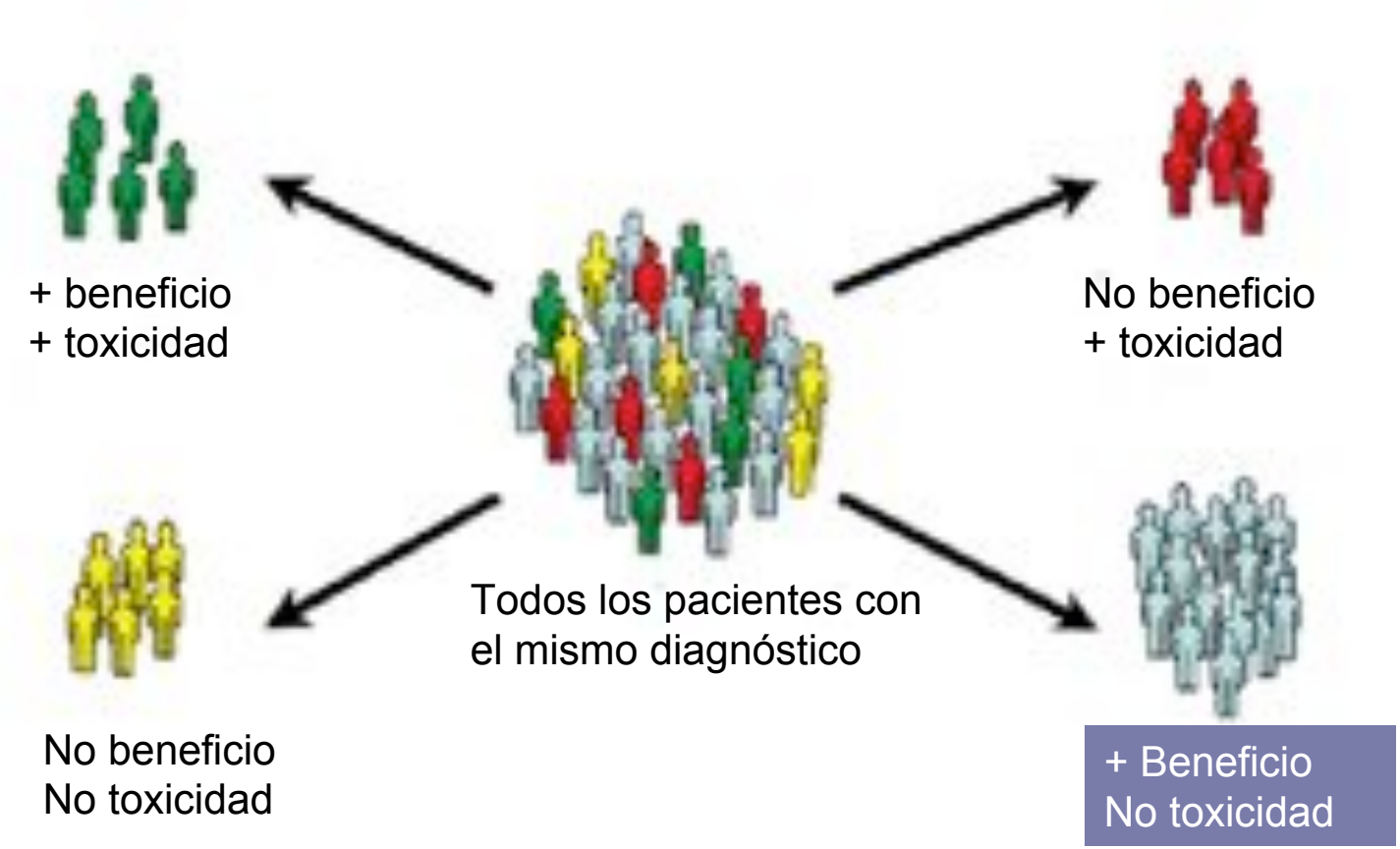
Eficicencia en la mejora de resultados en Salud

Patricio Más Serrano
Unidad de Farmacocinética Clínica
Servicio de Farmacia
Hospital General Universitario de Alicante

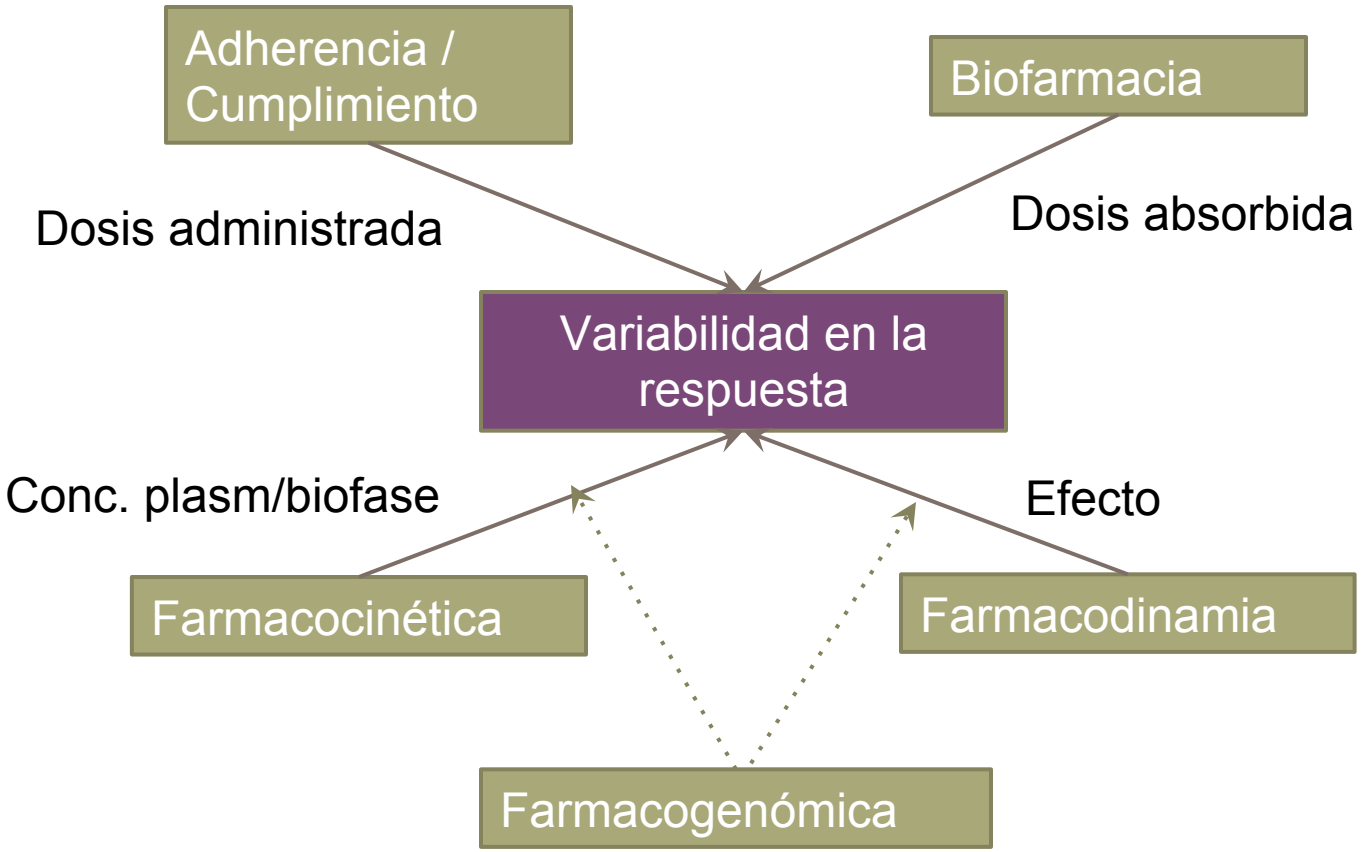
Valencia. 24 de Abril de 2015

Variabilidadrespuesta

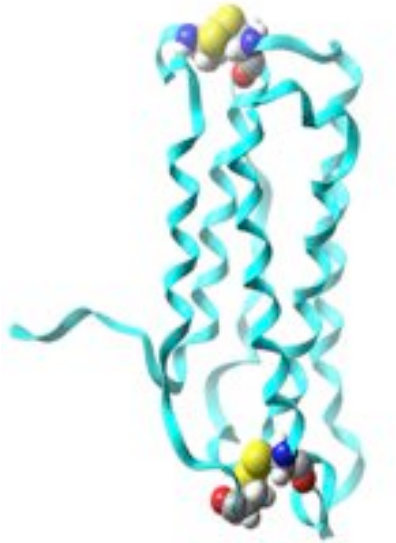


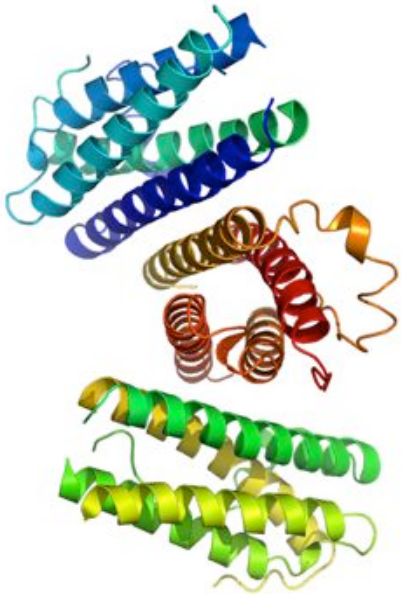
Eficiencia de resultados en salud

Fuentesvariabilidad

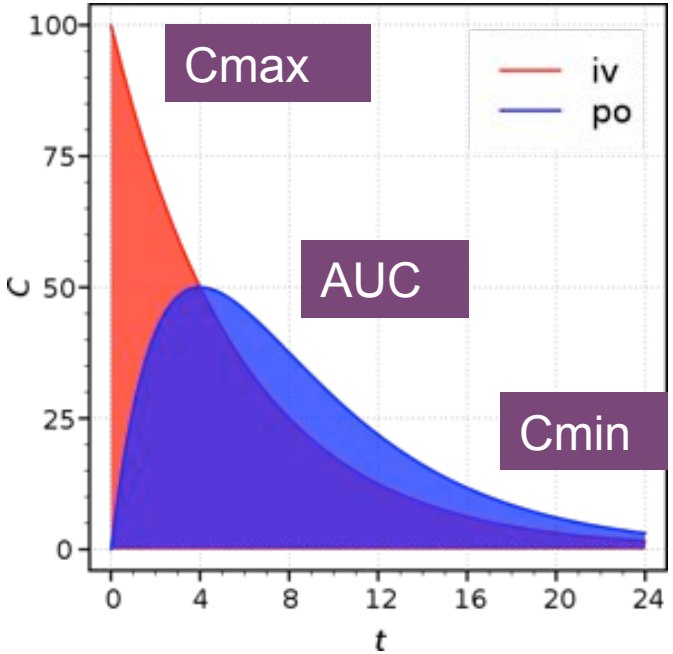


Fármacosbiológicos





Farmacocinética Definición

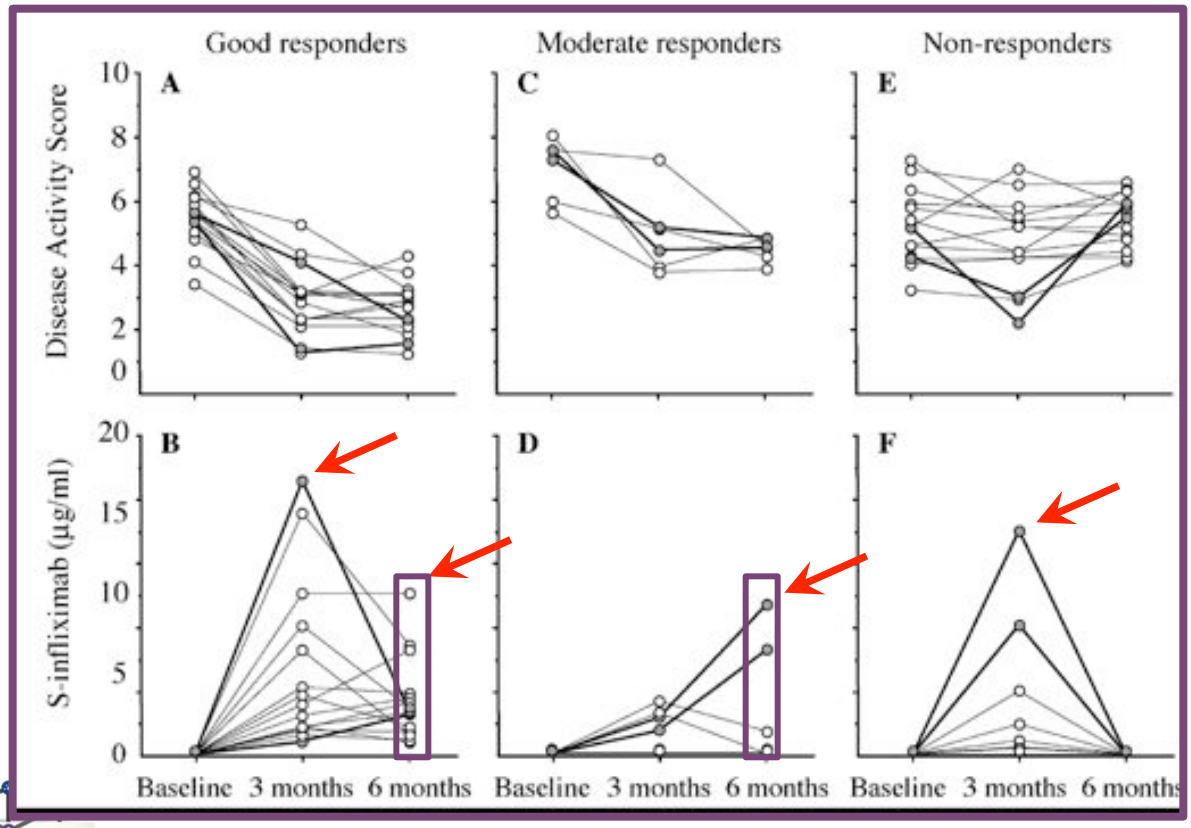


Correlación

ARInfliximabPK/PD

Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis.

Timothy R.D.J. Radstake[1], MD, PhD; Morten Svenson[2], PhD; Agnes M. Eijsbouts[3], MD, PhD; Frank H.J. van den Hoogen[3], MD, PhD; Christian Enevold[2]; Piet L.C.M. van Riel[1], MD, PhD; Klaus Bendtzen[2], MD, DMSc



- Cp valle
- Alta variabilidad Cp
- Solapamiento de Cp valle
- ELISA propio
- n=35

ARInfliximabPK/PD

EXTENDED REPORT

Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis

G J Wolbink, A E Voskuyl, W F Lems, E de Groot, M T Nurmohamed, P P Tak, B A C Dijkmans, L Aarden

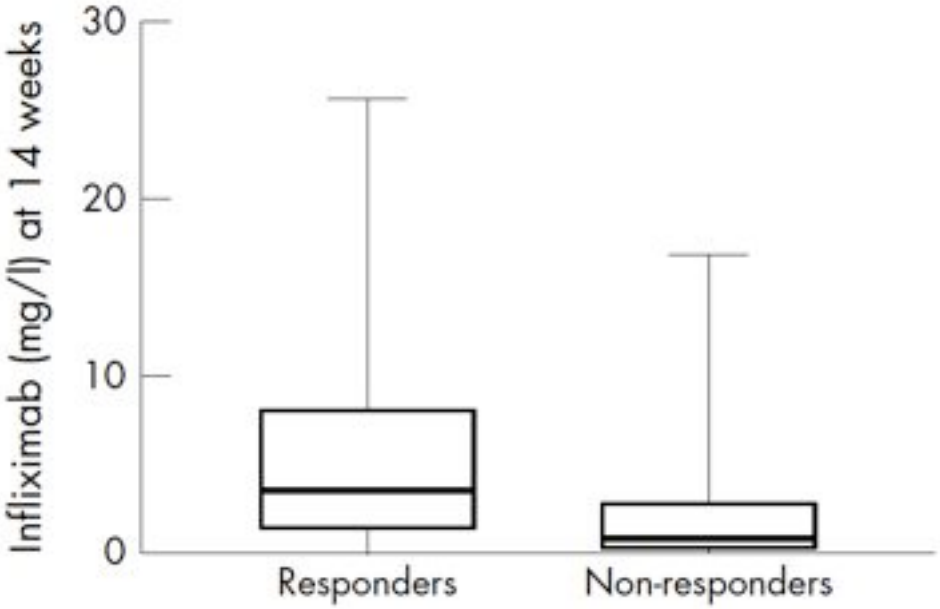


Figure 3 Serum trough infliximab levels in patients with RA treated with infliximab according to clinical response at 14 weeks.

- Cp valle
- Alta variabilidad Cp
- Solapamiento de Cp valle
- ELISA propio
- n=35

ARInfliximabPK/PD

Table 1 Clinical response of patients with low, intermediate, and high serum trough infliximab levels at 14 weeks

Clinical response	Serum trough infliximab levels at 14 weeks			Significance
	Low (0–1.2 mg/l)	Intermediate (1.3–4.7 mg/l)	High (5.0–25.8 mg/l)	
Mean DAS28, t=0	6.4	6.1	5.8	NS
Mean CRP, t=0	49	29	17	*
EULAR responders (%)	50	90	88	*
Mean change in DAS28 between				
0–2 Weeks	−1.3	−1.2	−1.1	NS
2–6 Weeks	−0.4	−0.7	−1.0	NS
6–14 Weeks	0.9	−0.1	−0.2	*
0–14 Weeks	−0.9 (−1.4)	−2.0 (−1.3)	−2.4 (−1.4)	*

*Indicates statistical significance, NS indicates no statistical significance.

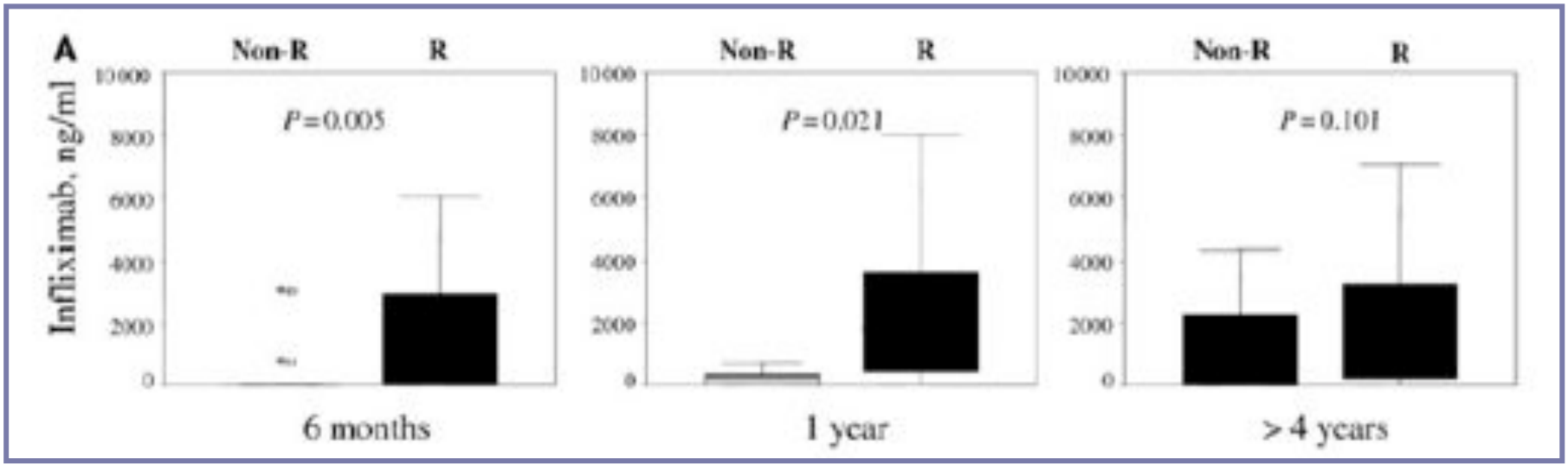
Relación PKPD indepndiente del la variable de eficacia

VI Congreso SVFH 23-25 abril 2015

ARInfliximabPK/PD

Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis

Dora Pascual-Salcedo[1], Chamaida Plasencia[2], Susana Ramiro[1], Laura Nuño[2], Gema Bonilla[2], Daniel Nagore[3], Ainhoa Ruiz del Agua[3], Antonio Martínez[3], Lucien Aarden[4], Emilio Martín-Mola[2] and Alejandro Balsa[2]

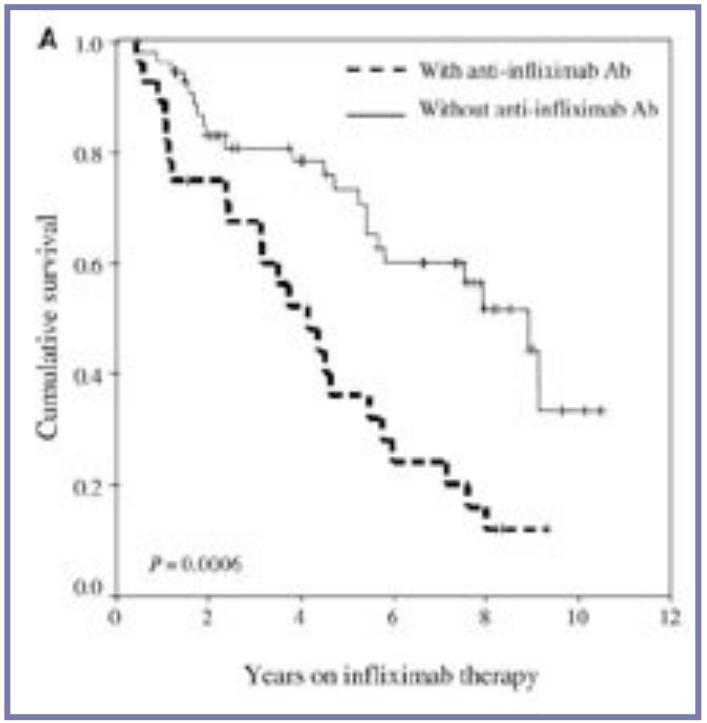


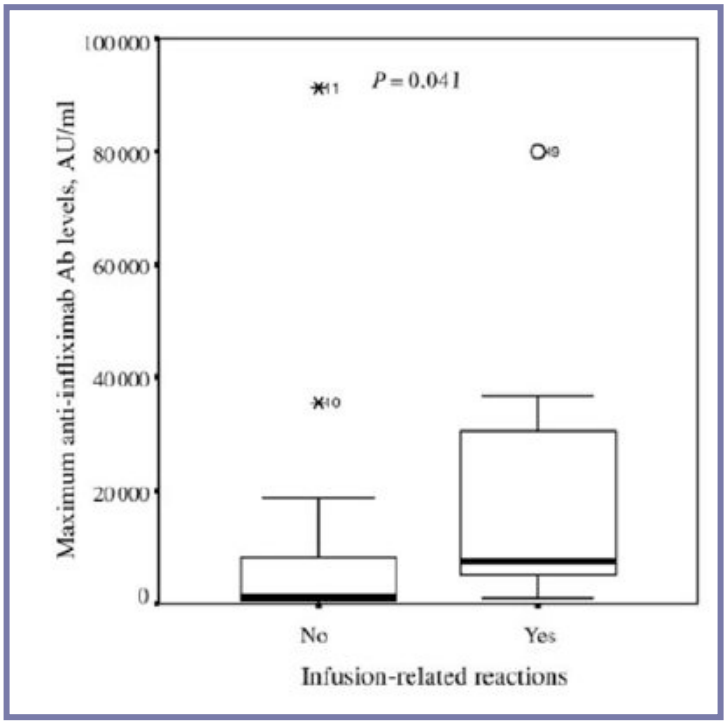
Relación PKPD se mantiene al año

ARInfliximabPK/PD Inmunogenicidad

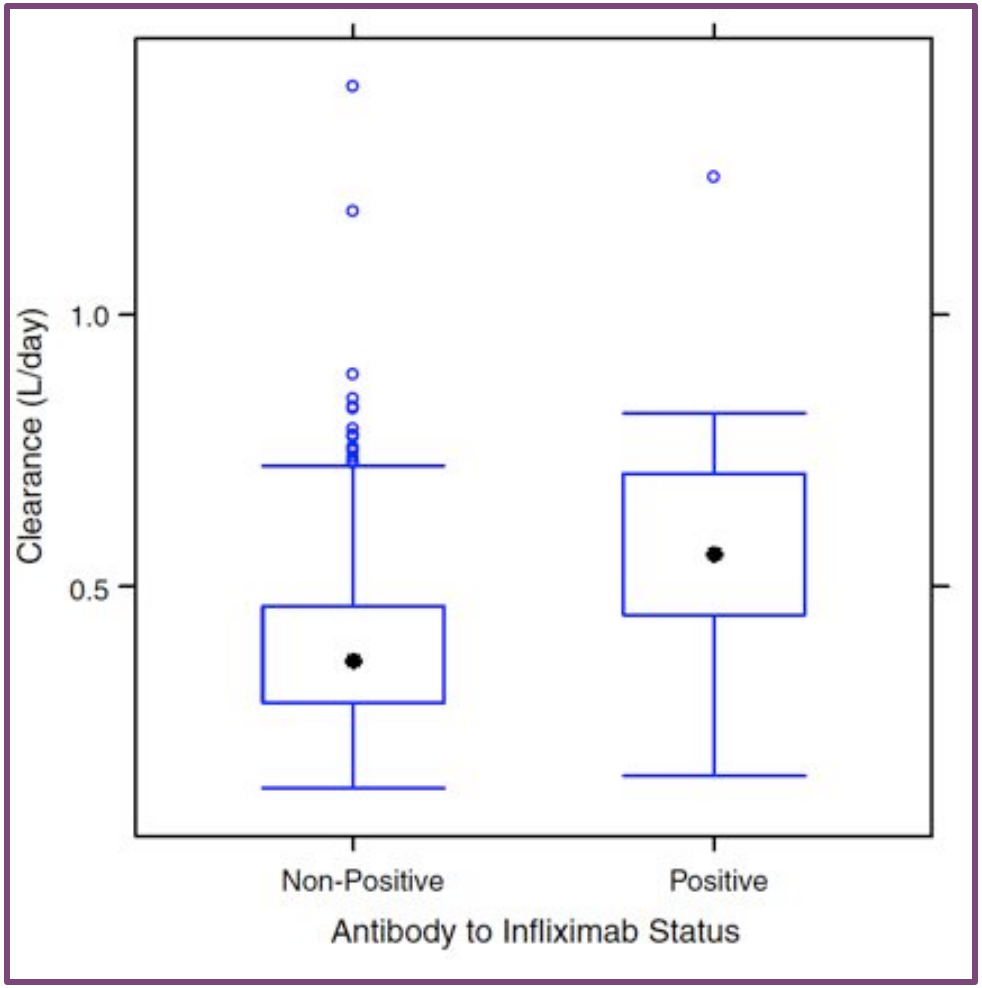
Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis

Dora Pascual-Salcedo[1], Chamaida Plasencia[2], Susana Ramiro[1], Laura Nuño[2], Gema Bonilla[2], Daniel Nagore[3], Ainhoa Ruiz del Agua[3], Antonio Martínez[3], Lucien Aarden[4], Emilio Martín-Mola[2] and Alejandro Balsa[2]





ARInfliximabPK/PD Inmunogenicidad



ARAdalimumabPK/PD

Table 2. Correlation between observed disease activities, DAS28 scores and trough levels of infliximab and adalimumab over time.

	Infliximab (N = 35)			Adalimumab (N = 34)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Number of patients						
Clinical response						
Good	-	11 (31%)	15 (43%)	-	17 (50%)	16 (47%)
Moderate	-	9 (26%)	6 (17%)	-	7 (21%)	8 (24%)
No	-	15 (43%)	14 (40%)	-	10 (29%)	10 (29%)
DAS28						
Good	5.5 ± 0.9	2.9 ± 0.7	2.7 ± 0.8	5.7 ± 0.9	3.0 ± 0.6	2.7 ± 0.6
Moderate	7.0 ± 1.0	4.9 ± 1.3	4.5 ± 1.0	6.0 ± 1.3	3.6 ± 1.1	3.7 ± 0.8
No	5.2 ± 1.2	4.7 ± 1.4	5.4 ± 0.8	5.6 ± 1.0	4.9 ± 1.0	4.9 ± 0.5
Serum trough levels of drug (µg/ml)						
Good	<0.2	3.1 (0.8-17)	2.7 (0.9-10)	<0.2	31 (3-151)	32 (3-150)
Moderate	<0.2	1.9 (0-5)	0.8 (0-9)	<0.2	12 (7-138)	14 (2-41)
No	<0.2	0.2 (0-14)	0 (0-0)	<0.2	2 (0-7)	1 (0-0)

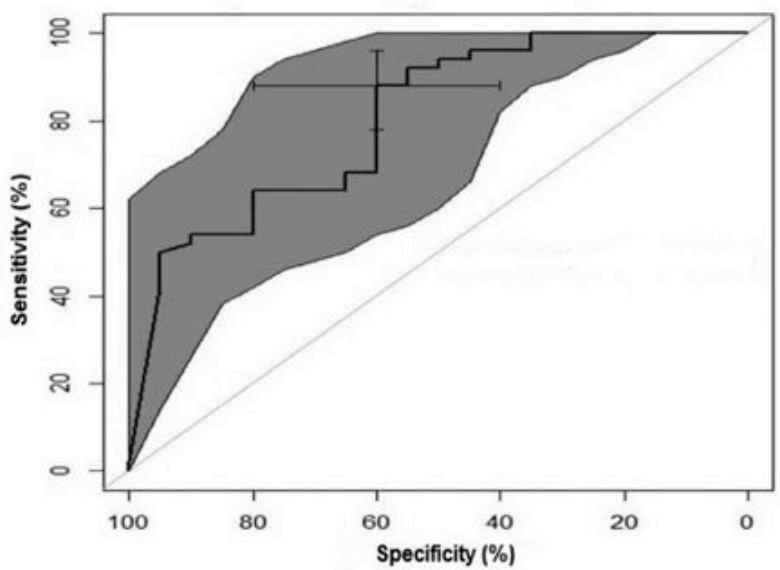
Clinical responses were recorded using the EULAR response criteria. Data are displayed as Means ± SD's.

VI Congreso SVFH 23-25 abril 2015

ARAdalimumabPK/PD

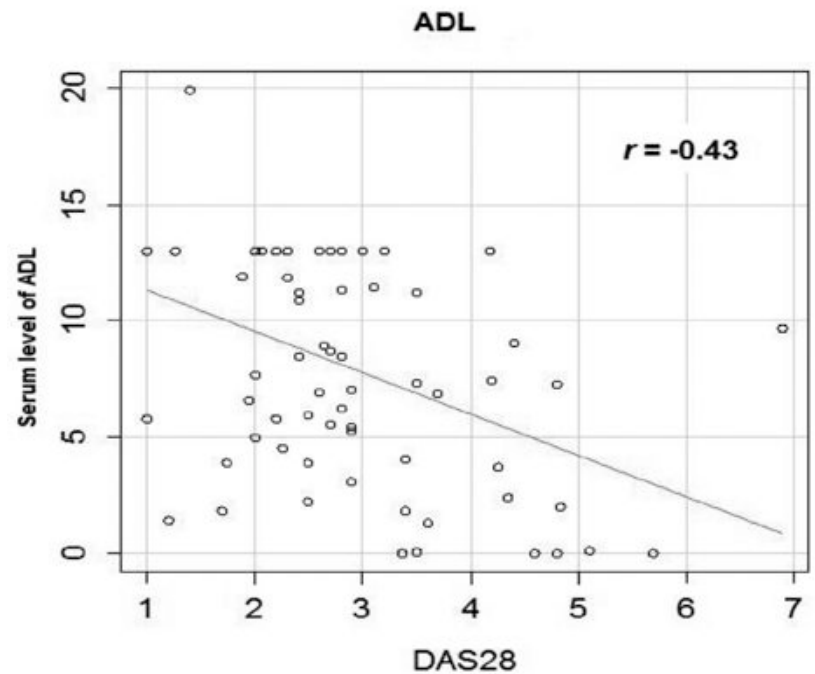
Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice

J. Rosas[1], F. Llinares-Tello[2], I. de la Torre[3], C. Santos-Ramírez[4], J.M. Senabre-Gallego[1], L. Valor[3], X. Barber-Vallés[5], D. Hernández-Flórez[3], G. Santos-Soler[1], E. Salas-Heredia[1], L. Carreño[3], and the AIRE-MB Group



Serum levels of ADL	DAS28 score ≤3.2	DAS28 score >3.2
≤4.3 mg/L	6 (12%)	12 (60%)
>4.3 mg/L	44 (88%)	8 40%)

Fig. 2. ROC curve: cut-off of the serum level of ADL for DAS28 score of low disease activity (≤3.2); ADL: adalimumab.



ELISA Progenika®

Cp > 4,3 mg/L

ELISA Progenika®

SpAInfliximabPK/PD

CONCISE REPORT

Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation

Mirjam K de Vries, Gerrit Jan Wolbink, Steven O Stapel, Henk de Vrieze, J Christiaan van Denderen, Ben A C Dijkmans, Lucien A Aarden, Irene E van der Horst-Bruinsma

Ann Rheum Dis 2007;66:1252–1254. doi: 10.1136/ard.2007.072397

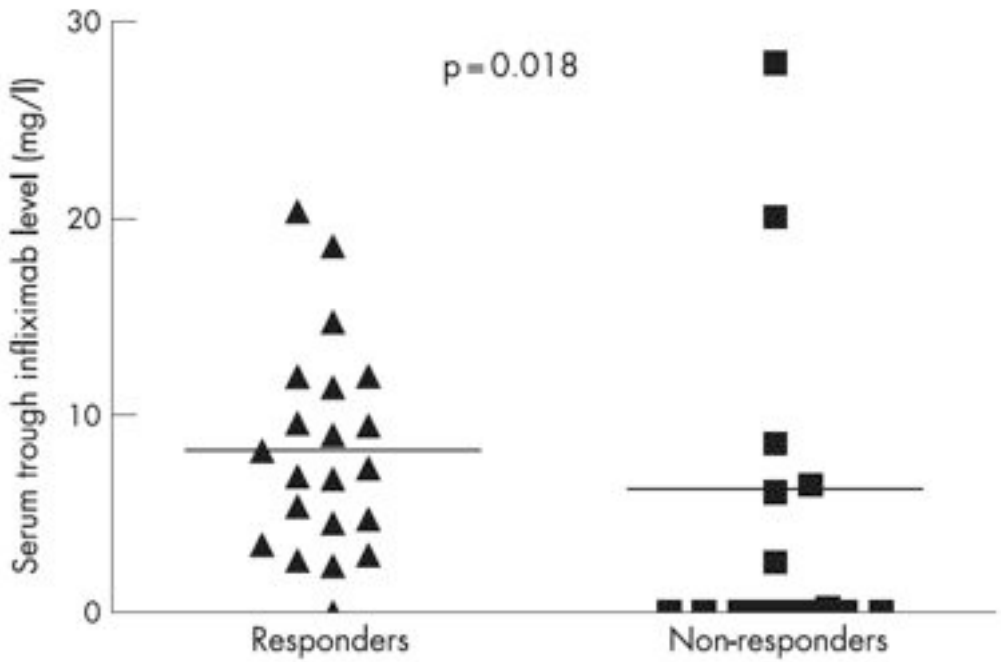


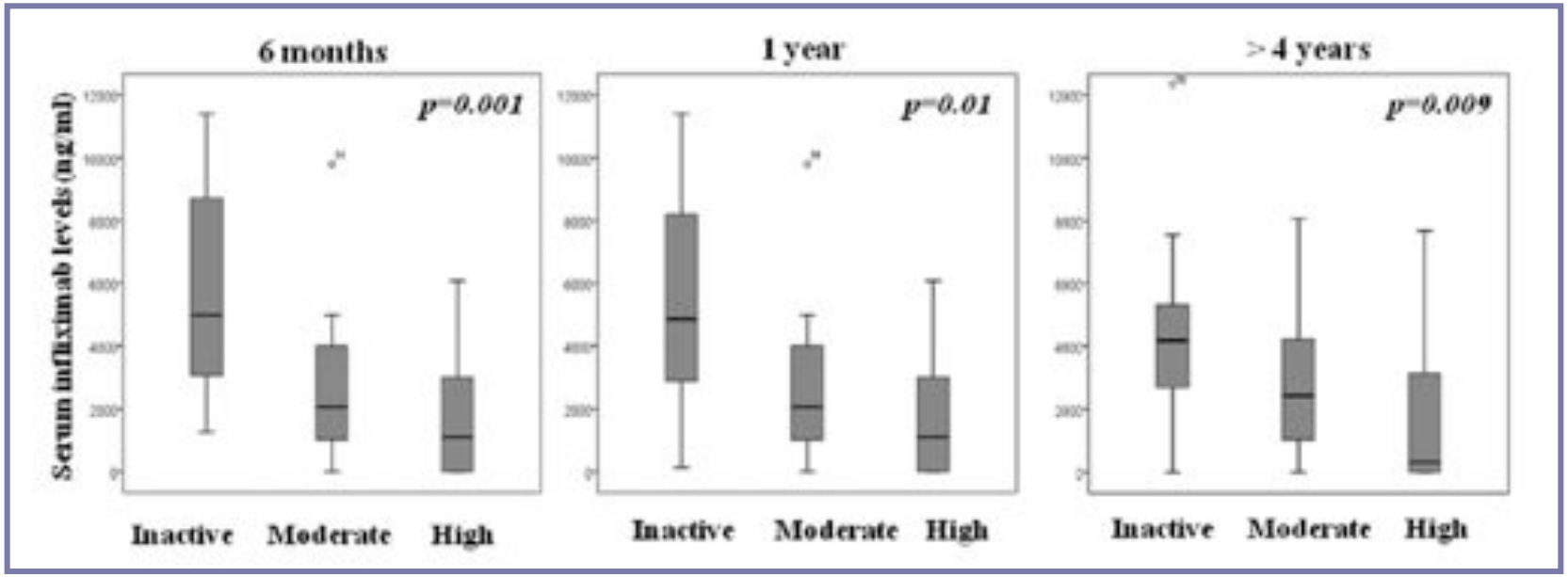
Figure 1 Serum trough infliximab level for responders (n=21; 8.2 mg/l) and non-responders (n=17; 6.3 mg/l) according to the ASAS-20 response criteria, at week 54 (p=0.018).

- Cp valle
- Alta variabilidad Cp
- Solapamiento de Cp valle
- ELISA propio
- n=38

SpAInfliximabPK/PD

Influence of immunogenicity on the efficacy of long-term treatment of spondyloarthritis with infliximab

Chamaida Plasencia,[1] Dora Pascual-Salcedo,[2] Laura Nuño,[1] Gema Bonilla,[1] Alejandro Villalba,[1] Diana Peiteado,[1] Jesús Díez,[3] Daniel Nagore,[4] Ainhoa Ruiz del Agua,[4] Rosario Moral,[2] Emilio Martin-Mola,[1] Alejandro Balsa[1]



Relación PKPD se mantiene al año

SpAInfliximabPK/PD Inmunogenicidad

CONCISE REPORT

Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation

Mirjam K de Vries, Gerrit Jan Wolbink, Steven O Stapel, Henk de Vrieze, J Christiaan van Denderen, Ben A C Dijkmans, Lucien A Aarden, Irene E van der Horst-Bruinsma

Ann Rheum Dis 2007;66:1252–1254. doi: 10.1136/ard.2007.072397

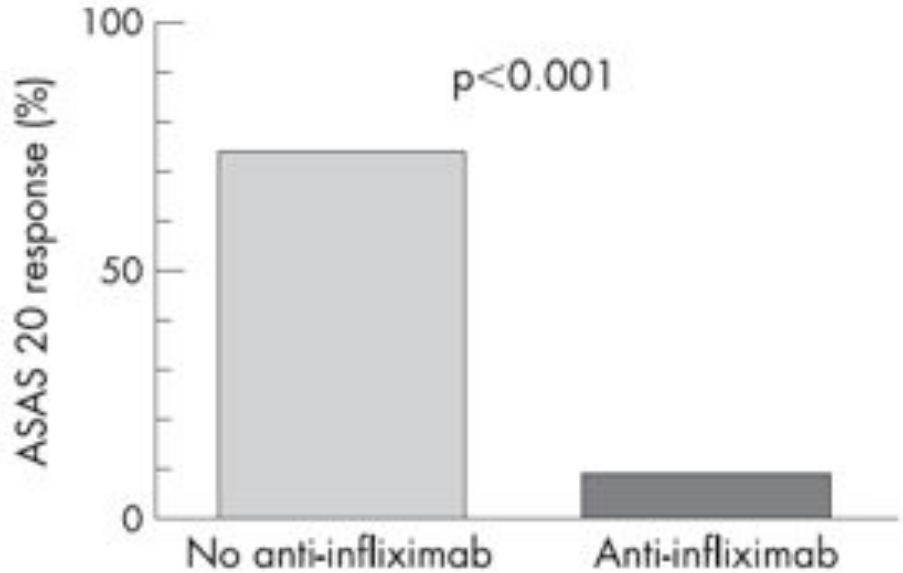


Figure 2 Percentage of patients (n = 38) with (9%) and without (74%) ATI fulfilling ASAS-20 response criteria at week 54 *p<0.001).

SpAInfliximabPK/PD Inmunogenicidad

Influence of immunogenicity on the efficacy of long-term treatment of spondyloarthritis with infliximab

Chamaida Plasencia,[1] Dora Pascual-Salcedo,[2] Laura Nuño,[1] Gema Bonilla,[1] Alejandro Villalba,[1] Diana Peiteado,[1] Jesús Díez,[3] Daniel Nagore,[4] Ainhoa Ruiz del Agua,[4] Rosario Moral,[2] Emilio Martin-Mola,[1] Alejandro Balsa[1]

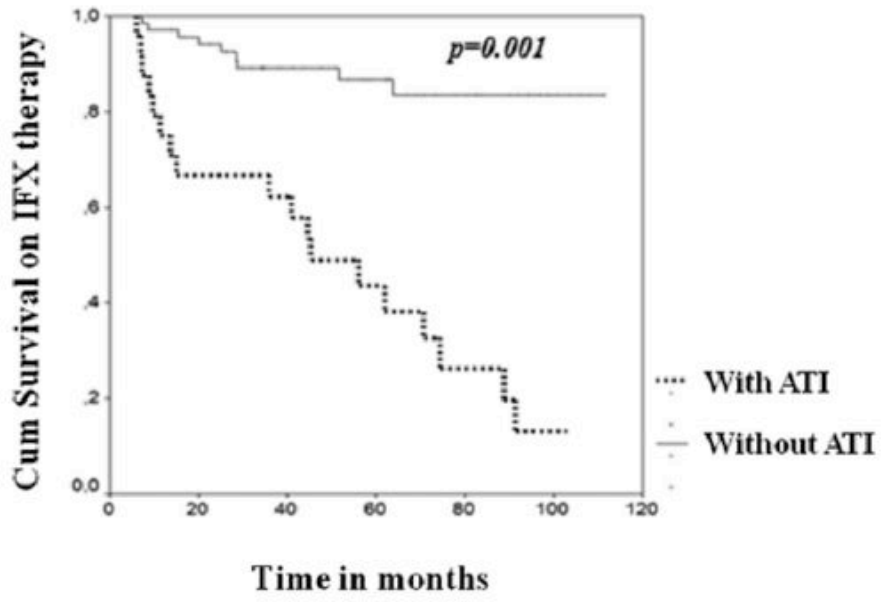


Figure 3 The infliximab survival curve in the patients with spondyloarthritis with/without ATI. Mean drug survival was shorter in the patients with ATI than in those without ATI (4.25 years, 95% CI 3.06 to 5.43 vs 8.19 years, 95% CI 7.54 to 8.85; $p=0.001$).

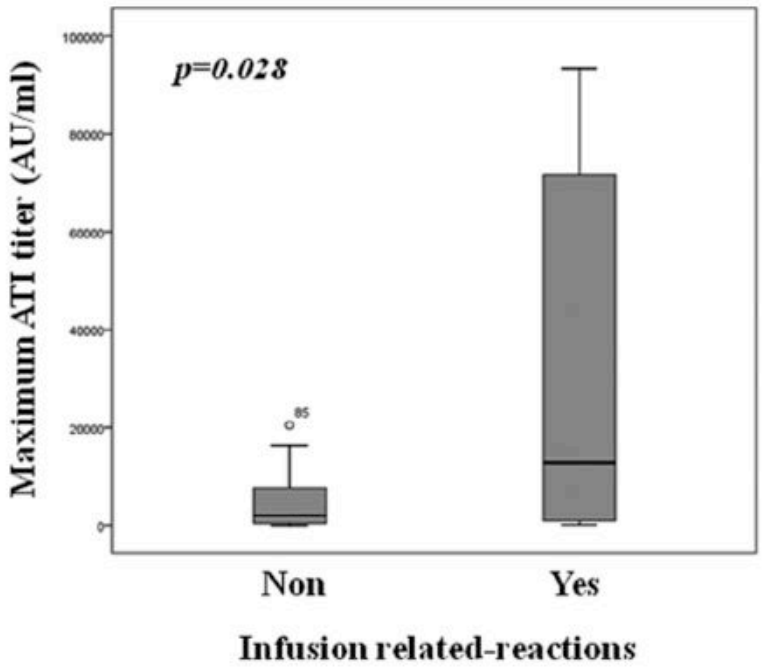


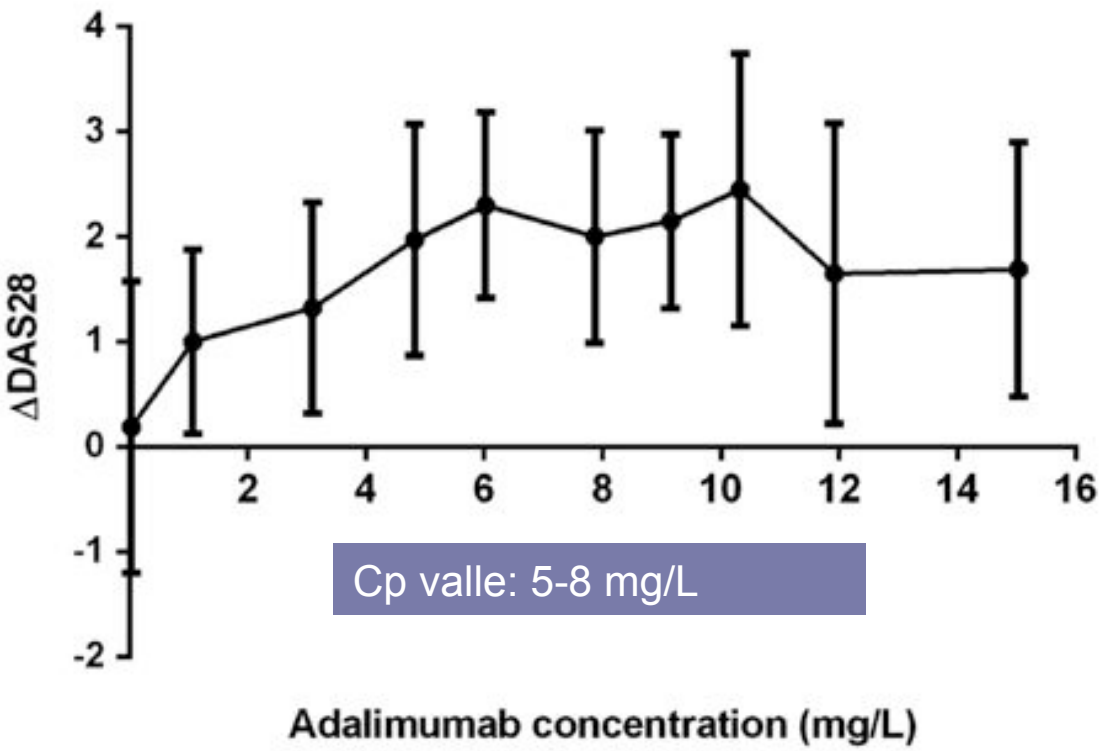
Figure 4 The maximum anti-infliximab antibody (ATI) levels in the patients who developed or did not develop infusion-related reactions. The data are presented as interquartile ranges (75th centile, upper edge of the box; 25th centile, lower edge of the box; 50th centile, midline of the box).

APsAdalimumabPK/PD

CONCISE REPORT

Anti-adalimumab antibodies and adalimumab concentrations in psoriatic arthritis; an association with disease activity at 28 and 52 weeks of follow-up

Erik H Vogelzang,[1] Eva L Kneepkens,[1] Michael T Nurmohamed,[1] Arno W R van Kuijk,[1] Theo Rispens,[2] Gertjan Wolbink,[1,2] Charlotte L M Krieckaert[1]



Cp valle: 5-8 mg/L

Cp valle

Alta variabilidad PKPD

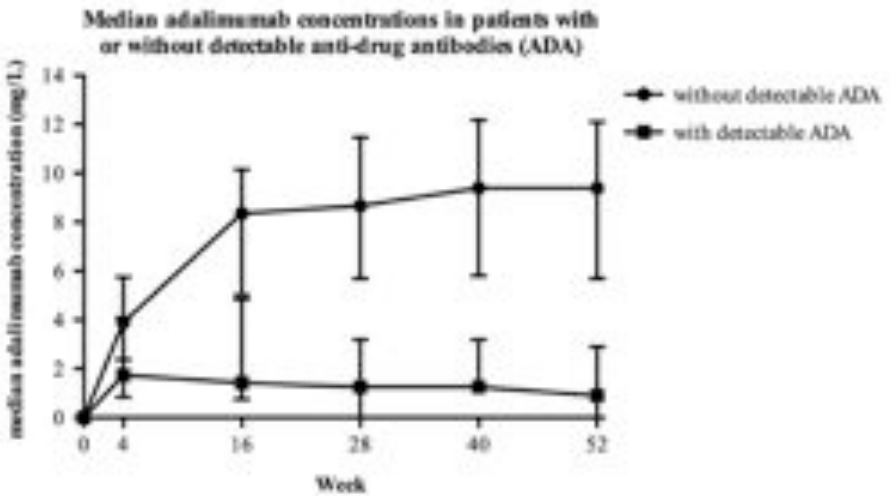
Solapamiento de Cp valle

ELISA Sanquin

n=103

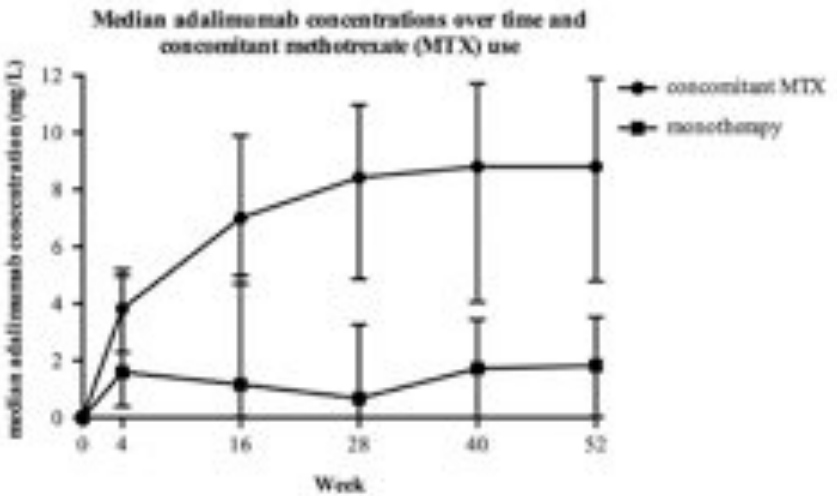
H, *et al*. *Ann Rheum Dis* 2014;**73**:2178–2182.

APsAdalimumabPK/PD Inmunogenicidad



No. patients / week	0	4	16	28	40	52
without detectable ADA	80	80	78	69	66	62
with detectable ADA	23	23	20	18	15	9

C



No. patients / week	0	4	16	28	40	52
concomitant MTX	77	77	75	66	61	55
monotherapy	16	16	14	12	11	8

ADA

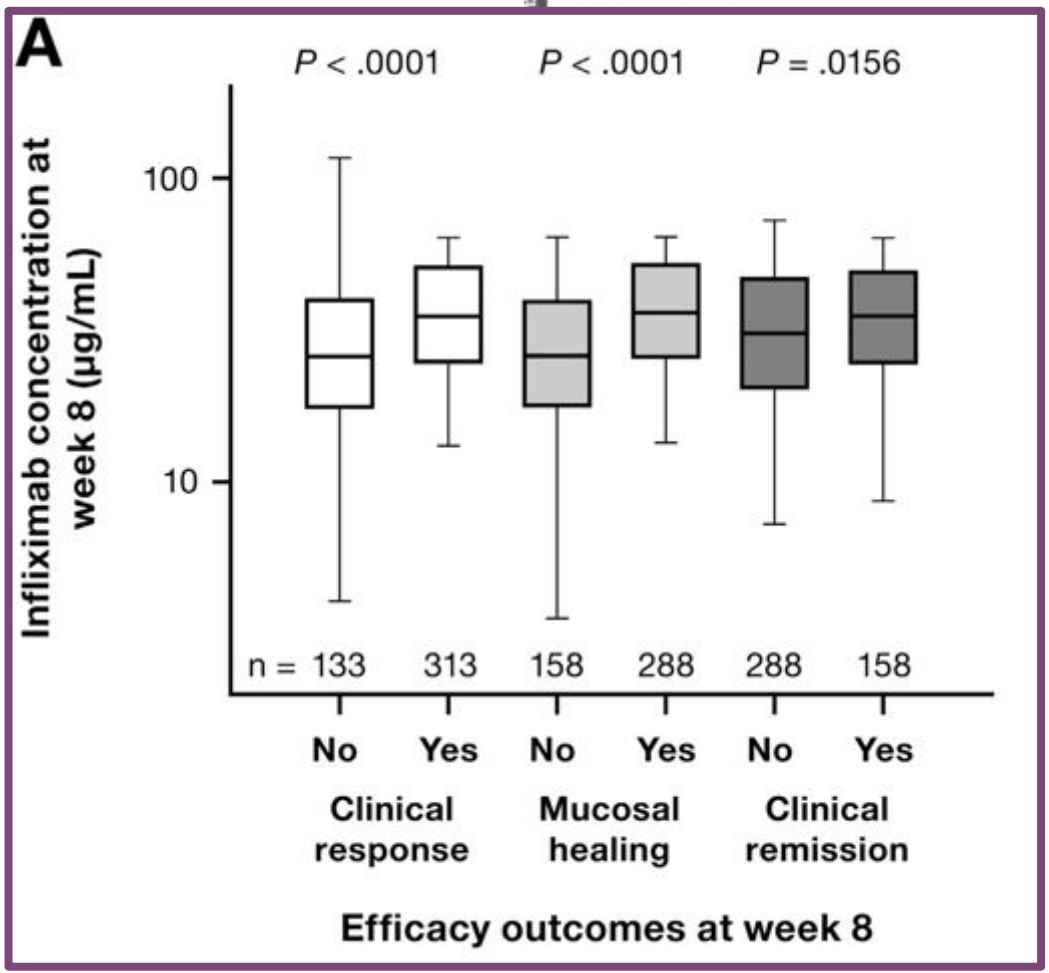
Tto concomitante con MTX

CUInfliximabPK/PD

Gastroenterology 2014;147:1296–1307

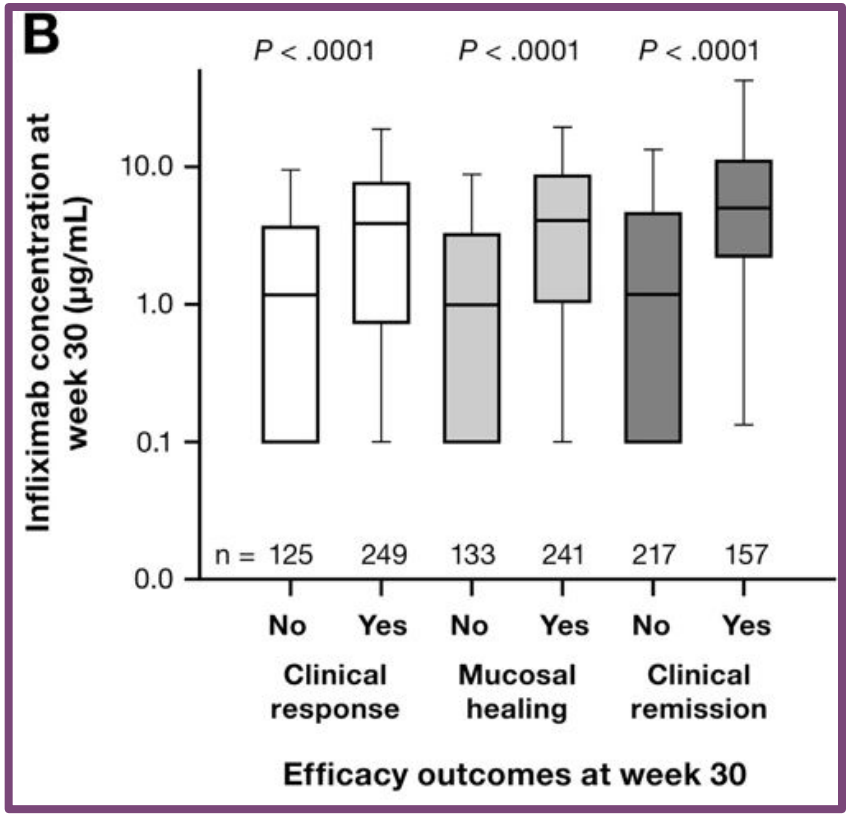
Association Between Serum Concentration of Infliximab and Efficacy in Adult Patients With Ulcerative Colitis

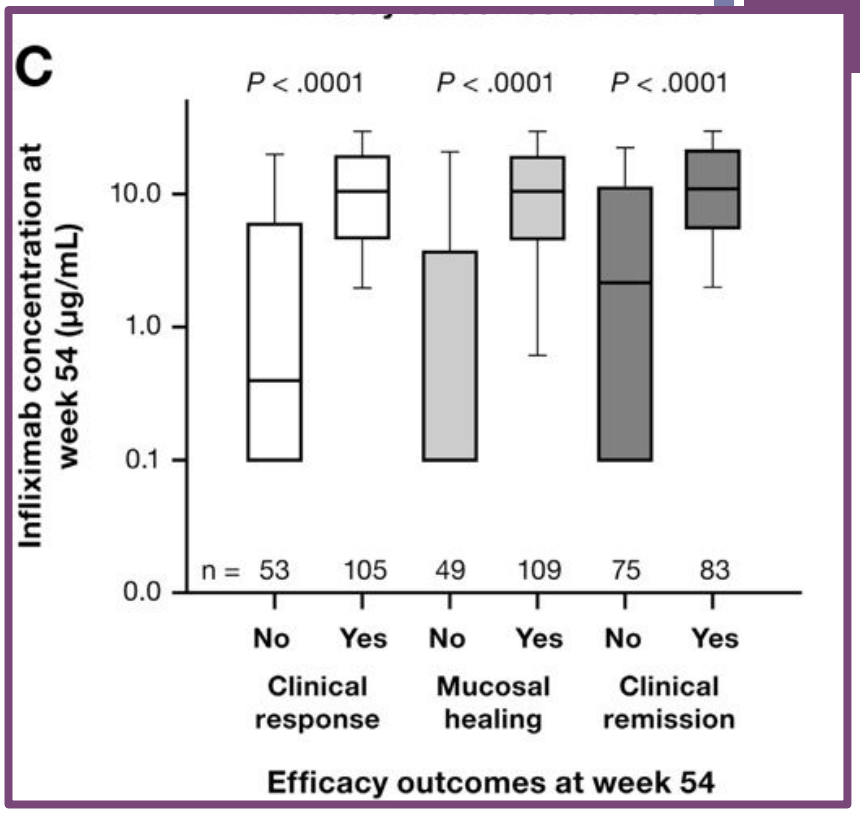
Omoniyi J. Adedokun,[1] William J. Sandborn,[2] Brian G. Feagan,[3] Paul Rutgeerts,[4] Zhenhua Xu,[1] Colleen W. Marano,[1] Jewel Johanns,[1] Honghui Zhou,[1] Hugh M. Davis,[1] Freddy Cornillie,[5] and Walter Reinisch[6,7]



- Cp valle
- Alta variabilidad PKPD
- Solapamiento de Cp valle
- ELISA puente propio
- n=728
- Cp valle 8 sem: 41 mg/L
- Cp valle ss: 3,7 mg/L

CUInfliximabPK/PD



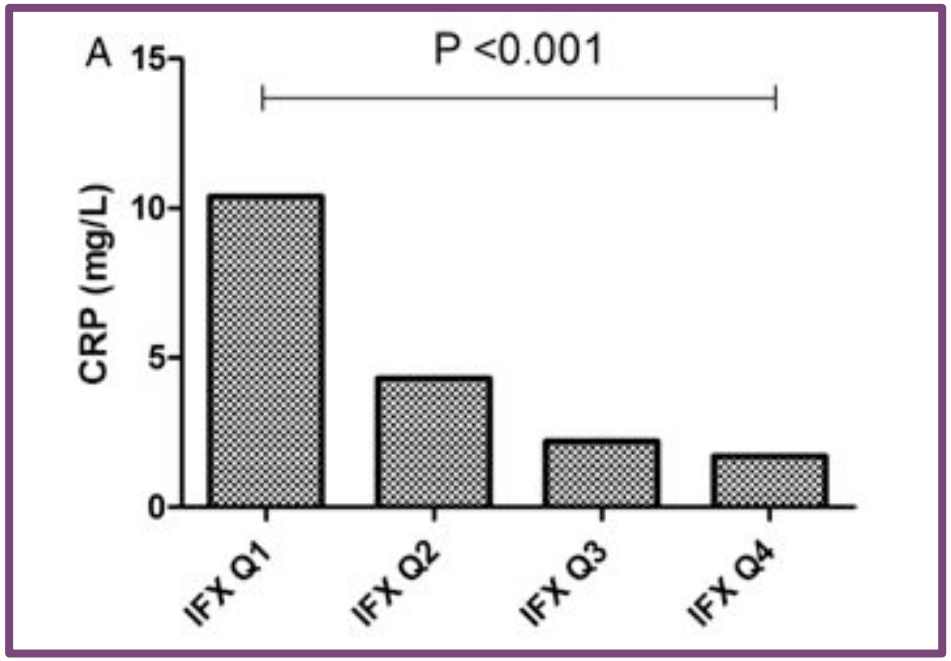


CrohnInfliximabPK/PD

ORIGINAL ARTICLE

The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease

Niels Vande Casteele,[1,2,3] Reena Khanna,[3] Barrett G Levesque,[2,3] Larry Stitt,[3] G Y Zou,[3] Sharat Singh,[4] Steve Lockton,[4] Scott Hauenstein,[4] Linda Ohrmund,[4] Gordon R Greenberg,[5] Paul J Rutgeerts,[6] Ann Gils,[1] William J Sandborn,[2] Séverine Vermeire,[6] Brian G Feagan[3]



ELISA Prometheus

n=483

Variable eficacia: PCR

Remisión: Cp valle > 2,8

CrohnInfliximabPK/PD
Inmunogenicidad

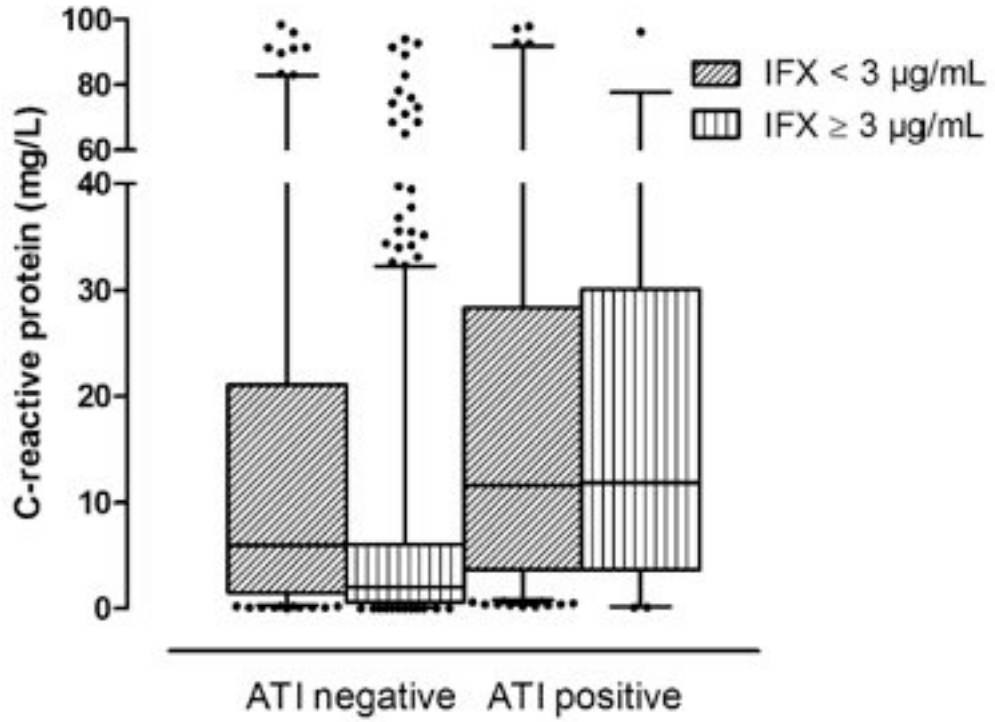


Figure 4 Whiskers boxplot (5th–95th centile) representing the C-reactive protein concentration (mg/L) in samples with an infliximab (IFX) trough concentration above or below the threshold of 3 µg/mL, both for antibody to IFX (ATI) negative (<3.13 U/mL) and ATI positive (≥3.13 U/mL) samples.

Remisión

Cp valle > 2,7 mg/L

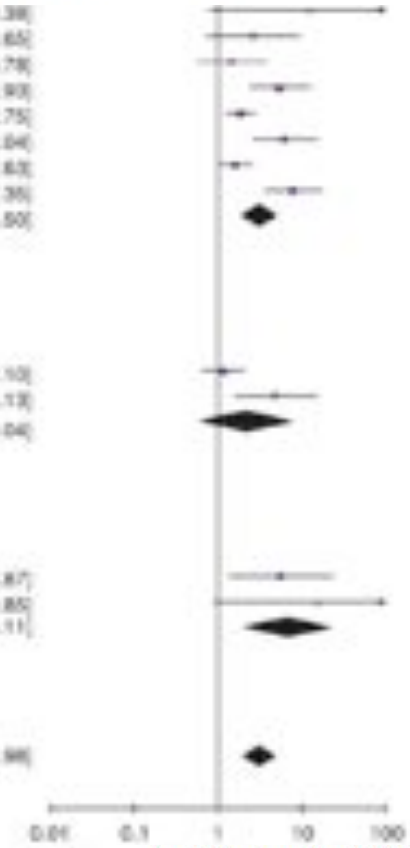
ATI < 3 mg/L (-)

CrohnInfliximabPK/PD Inmunogenicidad

Impact of Antibodies to Infliximab on Clinical Outcomes and Serum Infliximab Levels in Patients With Inflammatory Bowel Disease (IBD): A Meta-Analysis

Kavinderjit S. Nanda, MD[1], Adam S. Cheifetz, MD[1], and Alan C. Moss, MD, FACG[1]
[1]Center for Inflammatory Bowel Disease, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA

Study or subgroup	ATI+ Events	ATI+ Total	ATI− Events	ATI− Total	Weight	Risk ratio M-H, Random
1.1.1 Crohn's disease						
Ainsworth (2008)	8	18	0	13	2.3%	12.53 [0.79, 199.38]
Candon (2006)	6	9	2	8	5.7%	2.67 [0.74, 9.65]
Colombel (2010)	6	14	5	17	8.8%	1.46 [0.56, 3.78]
Farrell (2003)	11	11	4	25	9.6%	5.54 [2.37, 12.93]
Hanauer (2004)	16	20	58	105	13.0%	1.85 [1.25, 2.75]
Imaeda (2012)	12	16	5	42	9.5%	6.30 [2.64, 15.04]
Kopylov (2011)	17	22	13	28	12.6%	1.66 [1.05, 2.63]
Steenholdt (2011)	21	26	6	59	13.1%	7.94 [3.64, 17.35]
Subtotal (95% CI)		145		387	72.7%	3.22 [1.89, 5.50]
Total events	97		93			
Heterogeneity: $\tau^2 = 0.37$; $\chi^2 = 26.11$, df = 7 ($P = 0.005$); $I^2 = 73\%$						
Test for overall effect: $Z = 4.29$ ($P < 0.0001$)						
1.1.2 Ulcerative colitis						
Seow (2010)	21	44	9	22	11.8%	1.17 [0.65, 2.10]
Steenholdt (2011)	8	8	2	12	7.7%	4.91 [1.59, 15.13]
Subtotal (95% CI)		52		34	19.3%	2.21 [0.54, 9.04]
Total events	29		11			
Heterogeneity: $\tau^2 = 0.84$; $\chi^2 = 4.99$, df = 1 ($P = 0.03$); $I^2 = 80\%$						
Test for overall effect: $Z = 1.13$ ($P = 0.27$)						
1.1.3 Mixed inflammatory bowel disease						
Ben-Horin (2011)	10	29	2	33	5.9%	5.69 [1.36, 23.87]
Pariente (2011)	2	6	0	21	2.1%	15.71 [0.85, 289.85]
Subtotal (95% CI)		35		54	8.0%	6.94 [1.92, 25.11]
Total events	12		2			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.38$, df = 1 ($P = 0.54$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.95$ ($P = 0.003$)						
Total (95% CI)		232		475	100.0%	3.16 [2.30, 4.98]
Total events	138		106			
Heterogeneity: $\tau^2 = 0.37$; $\chi^2 = 36.78$, df = 11 ($P = 0.0001$); $I^2 = 70\%$						
Test for overall effect: $Z = 4.95$ ($P < 0.00001$)						
Test for subgroup differences: $\chi^2 = 1.58$, df = 2 ($P = 0.45$); $I^2 = 0\%$						



Am J Gastroenterol. 2013 January ; 108(1): 40–47.

VI Congreso SVFH 23-25 abril 2015

PsoriasisInfliximabPK/PD

Serum Infliximab Concentrations in Psoriatic Patients Treated with Infliximab: A Systematic Review

Carole DANNEPOND[1,2], Annabel MARUANI[1-3], Laurent MACHET[1-3], David TERNANT[1,4], Gilles PAINTAUD[1,4] and Mahtab SAMIMI[1,2,5]
[1]University Hospital of Tours, University François Rabelais, [2]Dermatology Department, Hospital of Tours, [3]Inserm, Imagerie et Cerveau UMR U930, [4]CNRS, GICC UMR 7292, Laboratory of Pharmacology Toxicology, Hospital of Tours, and [5]Laboratory of Molecular Virology and Immunology, ISP 1282 INRA-University François Rabelais, Tours, France

Table II. *Pharmacokinetics of infliximab: evolution of trough serum infliximab over time*

First author, year	Dosage (mg/kg)	Trough serum infliximab (mg/l), in median (ranges)[a]				
		W2[b]	W14	W22	W30	W46
Gottlieb, et al., 2003 (26)	5.0	30.0 (6.0–60.0)	0.7 (NA–5.0)	Not available	Not available	Not available
	10.0	60.0 (15.0–130.0)	7.1 (4.0–20.0)	Not available	Not available	Not available
Reich, et al., 2005 (3)	5.0	Not available	Not available	Concentration of IFX stabilised from W22 to W46 2.8–3.7		
Menter, et al., 2007 (27)	3.0	Not available	Not available	<0.1	<0.1	<0.1
	5.0					2.1
Zhu, et al., 2006 (33)	*3.0*					*<0.1*
	5.0			*2.6*	*1.6*	*2.1*
Torii & Nakagawa 2010 (28)	5.0					2.2
Torii, et al., 2011 (29)	5.0	20.0	2.6–4.0	0.0–2.6	0.7–2.6	0.1–2.0
Torii, et al., 2012 (34)	*5.0*					*1.5*
Takahashi, et al., 2012 (30)	Mean = 4.6 Ranges = 4.1–5.2	Not available	Not available	Not available	Not available	Not available
Gottlieb, et al., 2012 (31)	5.0					Not available
Meyer, et al., 2012 (32)	Median = 5.1 Ranges = 4.6–6.5	Not available	Not available	Not available	Not available	Not available

[a]Serum infliximab concentrations are reported as expressed in the studies, i.e in median (with ranges), median with no ranges, or ranges of medians (« between … and… »).
W: week. (In italic: duplicate publications).

n=733 (10 estudios)

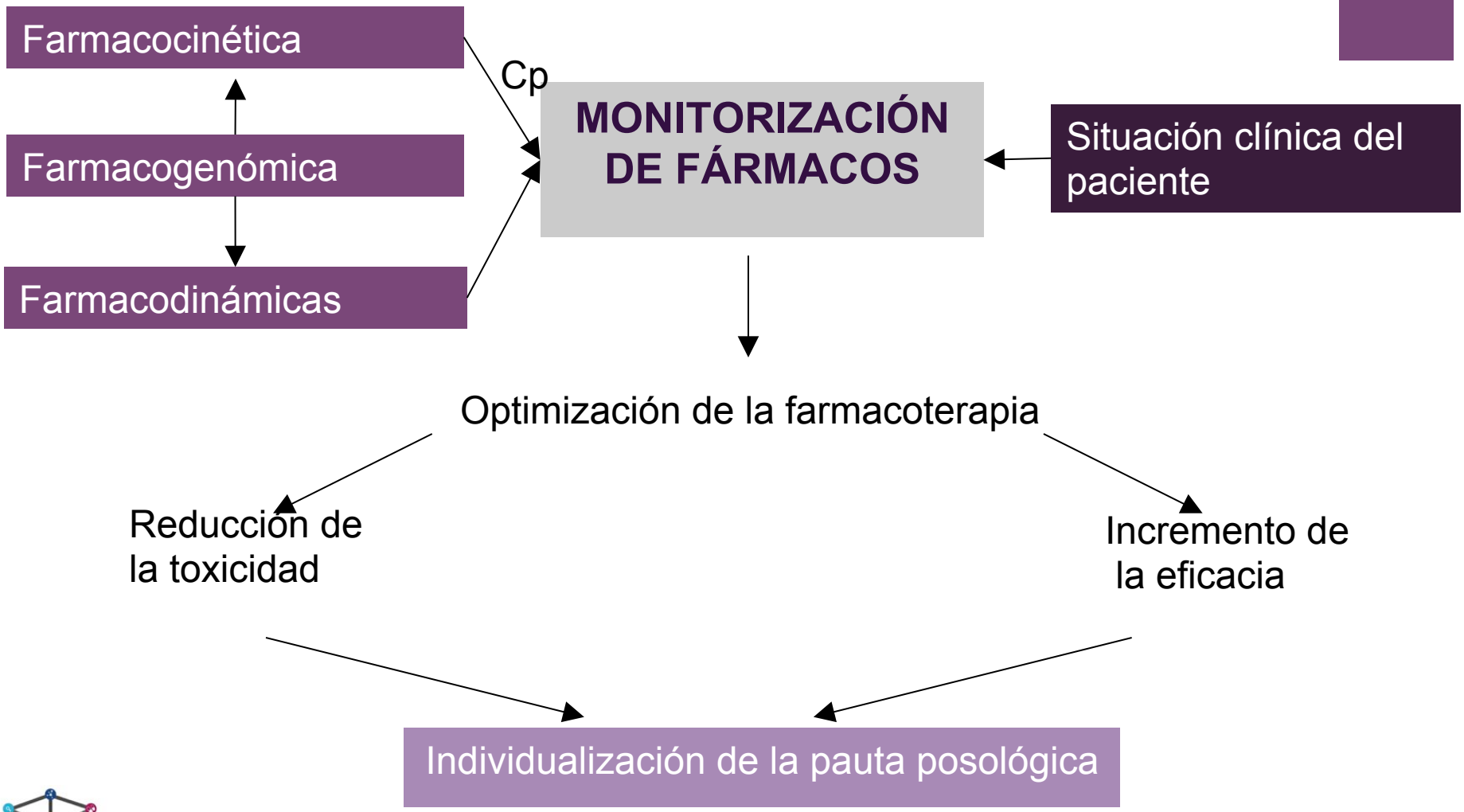
ELISA y RIA

Variable eficacia: PASI

Respuesta mantenida: Cp >0,1 – 1-2 mg/L

Acta Derm Venereol 2015; 95: 401–406

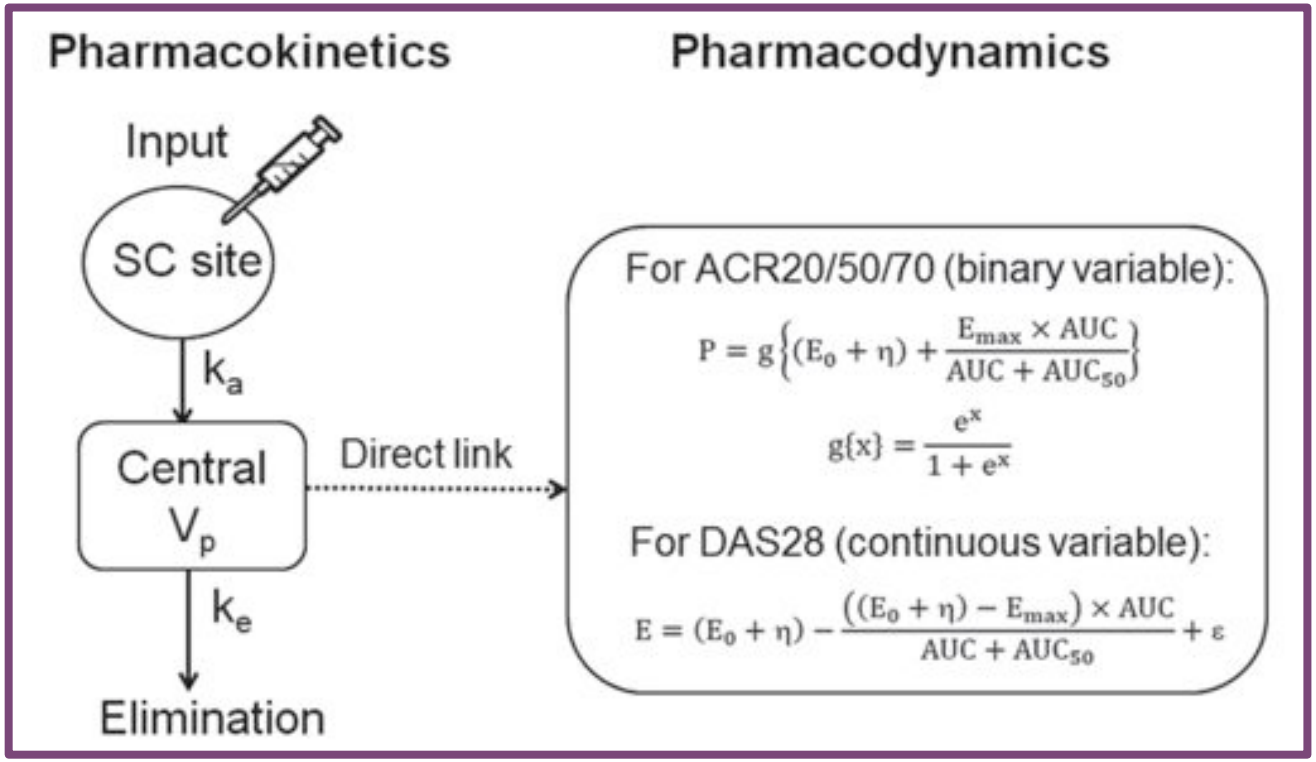
Individualización Farmacoterapia



AnálisisIndicesPK/PD

Evaluation of etanercept dose reduction in patients with rheumatoid arthritis using pharmacokinetic/pharmacodynamic modeling and simulation

Li-feng Hsu and Jin-ding Huang



AR

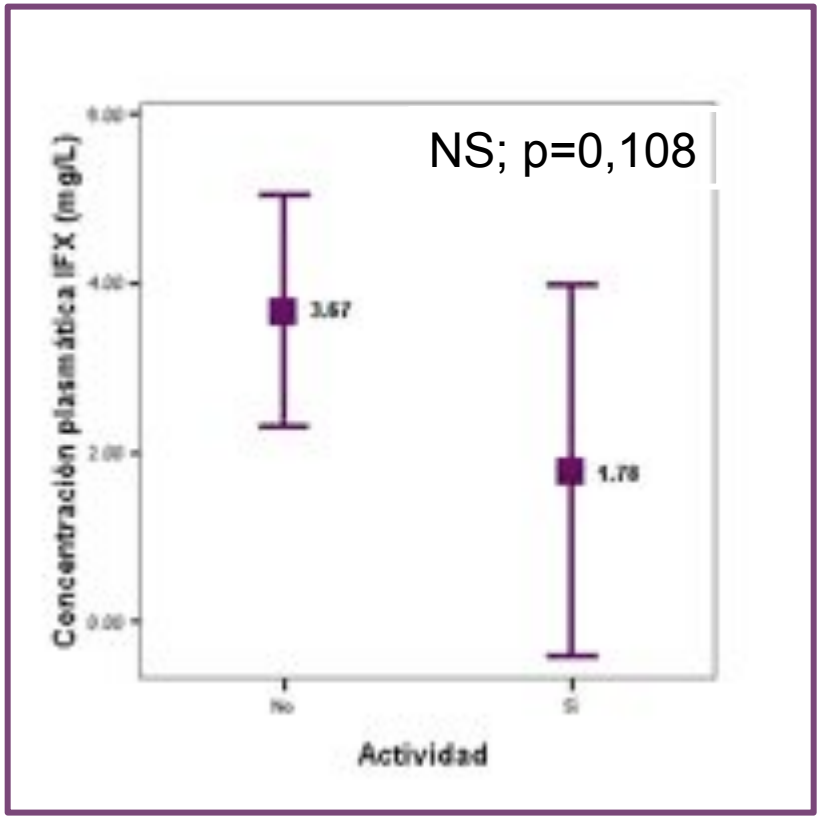
Etanecept

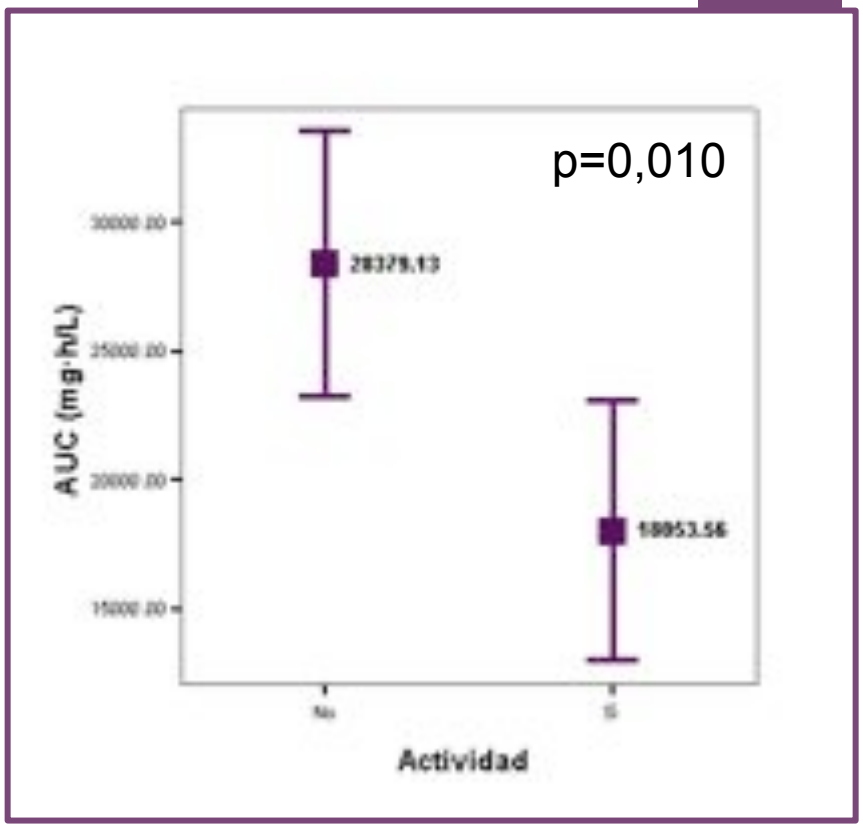
MC - Emax

AUC acumulado

International Journal of Clinical Pharmacology and Therapeutics, Vol. 52 – No. 9/2014 (776-786)

AnálisisIndicesPK/PD





EII

Variable: Actividad clínica

N=30

Infliximab

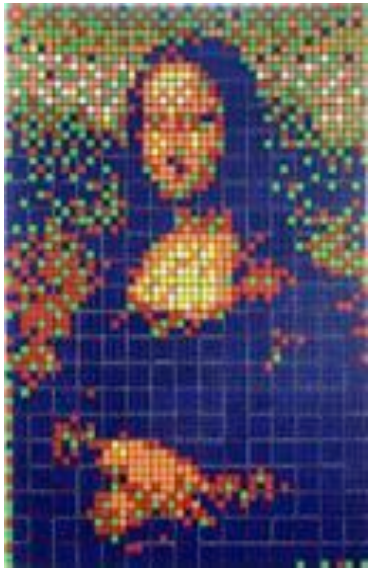
ELISA TheraDiag®

AUCss

Más Serrano y col. 59 Congreso SEFH. Valladolid

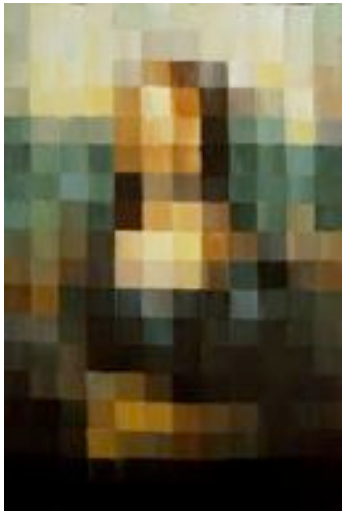
ModeloPoblacional PK

Simplificación de la realidad



ParámetrosPKEstimación Bayesiana

+



=

$$\sum_{i=1}^{N} \frac{(y_i - \bar{y}_i)^2}{\sigma^2} + \sum_{k=1}^{P} \frac{(p_k - \bar{p}_k)^2}{\omega_k^2} =$$

Modelo PK individual

ModelosPopPK

Patient Factors That Increase Infliximab Clearance and Shorten Half-life in Inflammatory Bowel Disease: A Population Pharmacokinetic Study

Iris Dotan, MD,[*,†] Yulia Ron, MD,[*,†] Henit Yanai, MD,[*,†] Stuart Becker, MD,[*,†] Sigal Fishman, MD,[*,†] Lior Yahav, BSc,[*,†] Merav Ben Yehoyada, PhD,[*,†] and Diane R. Mould, PhD[‡]

$$CL = \left(Population\ Mean\ CL \times \left(\frac{Weight(kg)}{70}\right)^{Effect\ of\ Weight} \times \left(\frac{ALB(\frac{g}{dL})}{4}\right)^{Effect\ of\ Albumin} \times (1 + Effect\ of\ ATI \times ATI\ Status) \right) \times \exp(\eta_1),$$

$$Vc = Population\ Mean\ Vc \times \left(\frac{Weight(kg)}{70}\right)^{Effect\ of\ Weight} \times \exp(\eta_2),$$

$$Q = \left(Population\ Mean\ Q \times \left(\frac{Weight(kg)}{70}\right)^{Effect\ of\ Weight} \right) \times \exp(\eta_3),$$

$$Vp = \left(Population\ Mean\ Vp \times \left(\frac{Weight(kg)}{70}\right)^{Effect\ of\ Weight} \right) \times \exp(\eta_4),$$

Infliximab

EII

Albúmina

Peso

Anti-IFX

VI Congreso SVFH 23-25 abril 2015

Modelos PopPK

Eur J Clin Pharmacol (2009) 65:1211–1228
DOI 10.1007/s00228-009-0718-4

PHARMACOKINETICS AND DISPOSITION

Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis

Adedigbo A. Fasanmade · Omoniyi J. Adedokun · Joyce Ford · Danika Hernandez · Jewel Johanns · Chuanpu Hu · Hugh M. Davis · Honghui Zhou

$$CL = 0.407 * \left(\frac{ALB}{4.1}\right)^{-1.54} * (1.471)^{ATI} * (0.764)^{SEX}$$

$$V_1 = 3.29 * \left(\frac{WGT}{77}\right)^{0.538} * (0.863)^{SEX}$$

$$Q = 7.14$$

$$V_2 = 4.13$$

Infliximab

Colitis Ulcerosa

Albúmina

Sexo

Peso

Anti-IFX

Modelos PopPK

Pharmacokinetic Properties of Infliximab in Children and Adults with Crohn's Disease: A Retrospective Analysis of Data from 2 Phase III Clinical Trials

Adedigbo A. Fasanmade, PhD; Omoniyi J. Adedokun, MS; Marion Blank, PhD; Honghui Zhou, PhD; and Hugh M. Davis, PhD

Centocor Research and Development, Inc, Malvern, Pennsylvania

$$CL = 5.42 \cdot (WGT/65)^{-0.313} \cdot (ALB/4.1)^{-0.855} \cdot (1.292)^{ATI} \cdot (0.863)^{IMM}$$

$$V_1 = 52.4 \cdot (WGT/65)^{-0.233},$$

$$V_2 = 19.6 \cdot (WGT/65)^{-0.588}, \text{ and}$$

$$Q = 2.26,$$

Infliximab

Crohn

Albúmina

Inmunosupresor

Peso

Anti-IFX

Clinical Therapeutics/Volume 33, Number 7, 2011

ModelosPopPK

Pharmacokinetics and Exposure–Efficacy Relationship of Adalimumab in Pediatric Patients with Moderate to Severe Crohn's Disease: Results from a Randomized, Multicenter, Phase-3 Study

Shringi Sharma, PhD, Doerthe Eckert, MS,† Jeffrey S. Hyams, MD,‡ Sven Mensing, PhD,† Roopal B. Thakkar, MD,* Anne M. Robinson, PharmD,* Joel R. Rosh, MD,§ Frank M. Ruemmele, MD, PhD,‖ and Walid M. Awni, PhD**

Adalimumab

Crohn

$$CL/F = 0.281 \times (1 + 1.08 \times \mathrm{AAA}) \times \left(\frac{\text{Baseline Body weight}}{\text{Median (Baseline Body weight)}}\right)^{0.48} \times \exp(\eta_1) \quad (1)$$

$$V/F = 4.75 \times \left(\frac{\text{Baseline Body weight}}{\text{Median (Baseline Body weight)}}\right)^{0.904} \quad (2)$$

Peso

Anti-IFX

Inflamm Bowel Dis • Volume 21, Number 4, April 2015

Conclusiones

- Corelación PK/PD
- La presencia de ATI se correlaciona con pérdida de respuesta
- Gran heterogeneicidad en los estudios
- Necesidad de modelos poblacionales

VI Congreso
SVFH
23-25 abril
2015