Universidad de Granada
Facultad de Farmacia
Programa Oficial de Posgrado en Ciencias Farmacéuticas

FUNDACIÓ HOSPITAL DE l'Esperit Sant

TESIS DOCTORAL

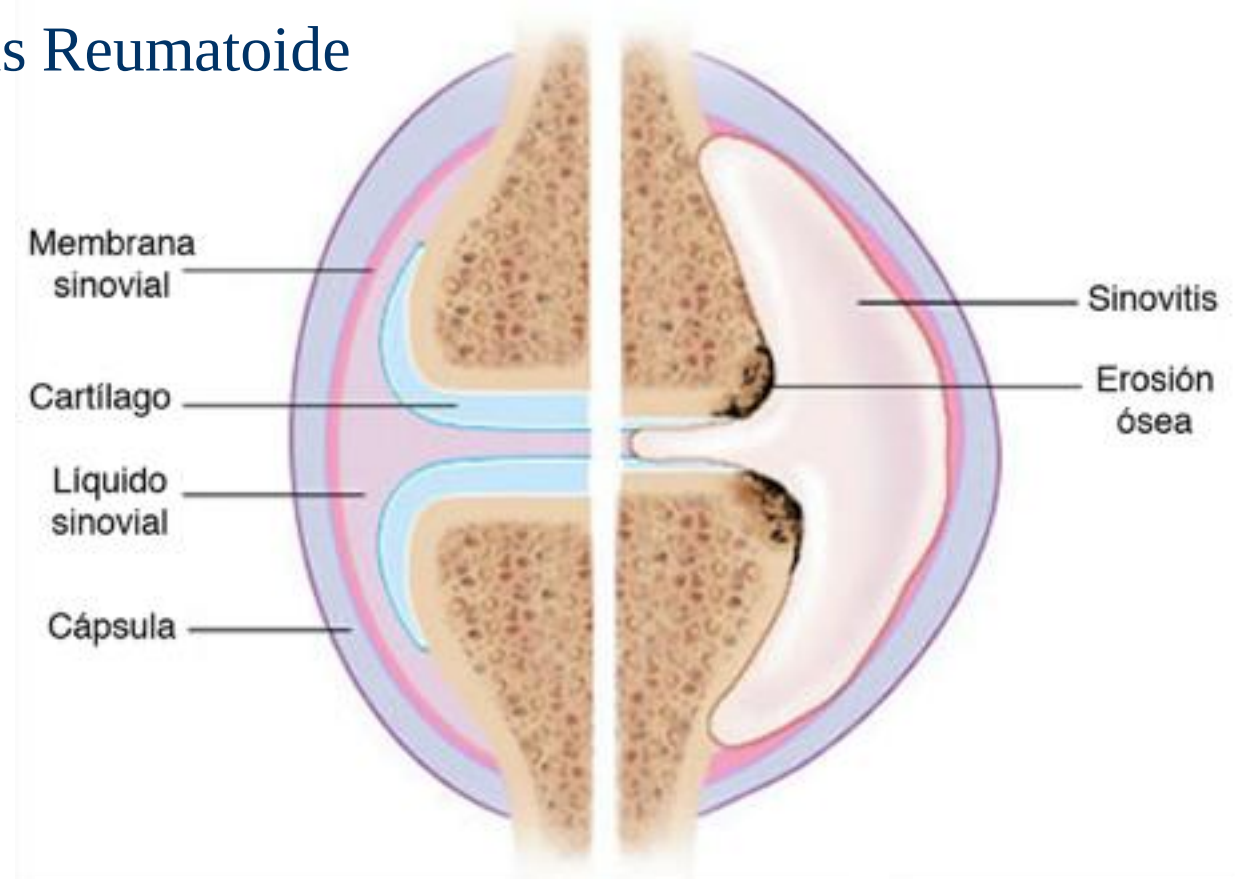
PATRÓN DE SUPERVIVENCIA DE LOS ANTAGONISTAS DEL FACTOR DE NECROSIS TUMORAL EN ARTRITIS REUMATOIDE

Presentada por Dña. Virginia Martínez Santana para optar al Grado de Doctora por la Universidad de Granada

Director: Dr. D. Miguel Ángel Calleja Hernández

I. Introducción

Artritis Reumatoide



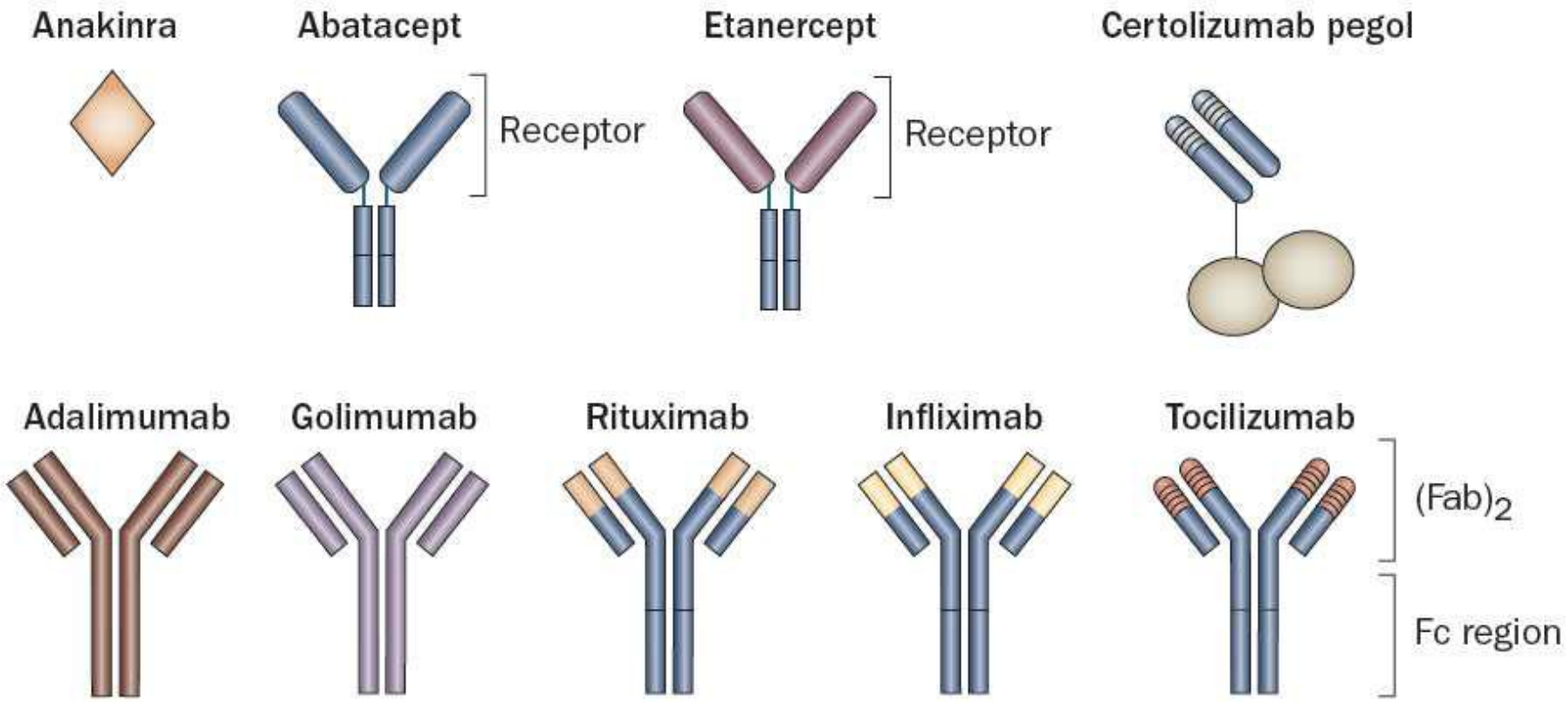
I. Introducción
Epidemiología

- Baja prevalencia (0,5%)
- Alto impacto social
- Predominantemente femenino; relación 3:1
- Inicio de la enfermedad 35-50 años

I. Introducción
Tratamiento

Objetivos: remisión del dolor, la inflamación y evitar la progresión de la enfermedad

1. AINES
2. FAMES → 3. Corticoides
4. BIOLOGICOS


Anakinra
Abatacept
Receptor
Etanercept
Receptor
Certolizumab pegol
Adalimumab
Golimumab
Rituximab
Infliximab
Tocilizumab
(Fab)2
Fc region

II. Justificación

- Enfermedad incapacitante
- Enfermedad compleja y requiere muchos medicamentos
- 50% pacientes no responden o presentan efectos adversos

- La estrategia terapéutica sigue siendo controvertida

III. Objetivos

Objetivos primarios

- **Evaluar** la **supervivencia** de los antagonistas del factor de necrosis tumoral en artritis reumatoide
- **Definir** los **factores predictores de supervivencia**

IV. Material y Métodos

Diseño metodológico

Estudio observacional, longitudinal, retrospectivo.

Ámbito y duración del estudio

Servicios de Farmacia y Reumatología

Duración: seguimiento retrospectivo

12 años

IV. Material y Métodos

Selección de pacientes

- : artritis reumatoide, mayores de edad, atendidos en HCUV, al menos una dosis de biológico (enero 2011 - enero 2012)
- : diagnóstico erróneo, fallecimiento no relacionado con el tratamiento

IV. Material y Métodos

Análisis de los datos

- Variables cuantitativas: media y desviación típica

  Asociación: test Chi-cuadrado Pearson

- Variables cualitativas: distribución de frecuencias

  Comparación de valores cuantitativos: T de Student

Análisis de supervivencia: Kaplan-Meier

Modelo de regresión de Cox multivariante

SPSS v 20.0 para Windows
p<0,05

V. Resultados

Pacientes y tratamientos administrados

Período de estudio:

91 pacientes – 126 tratamientos

Exclusión
- Diagnóstico erróneo 5
- Exitus 2

Edad en la inclusión: 58 ± 12,3 años (29-85 años)

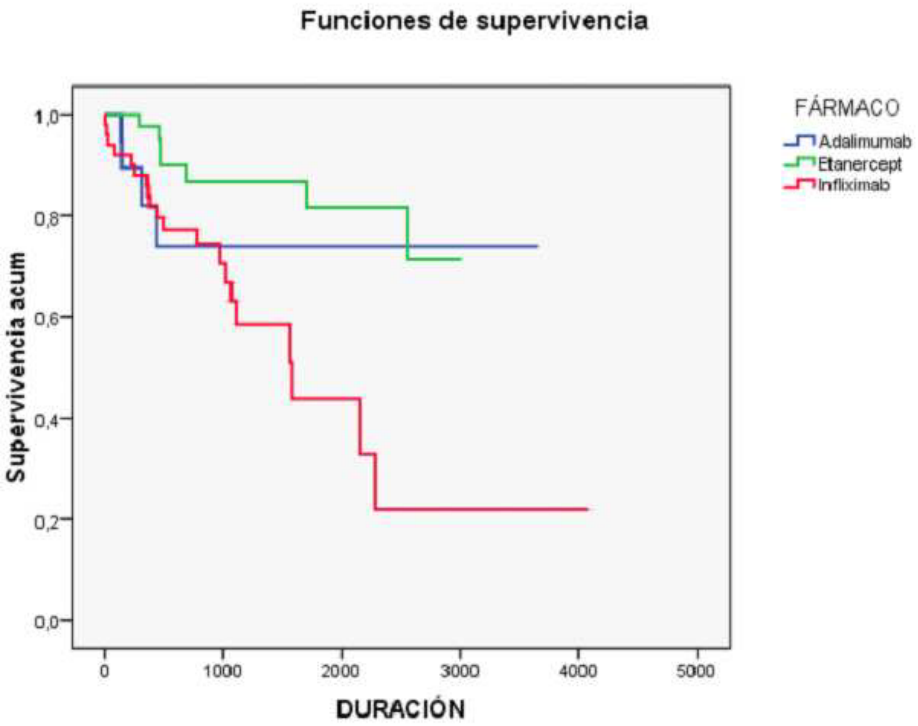
72,5% mujeres (relación 2,6:1)

V. Resultados

Supervivencia de la terapia anti-TNF

A. Análisis general

p=0,0015



V. Resultados

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Supervivencia de la terapia anti-TNF
A. Análisis general

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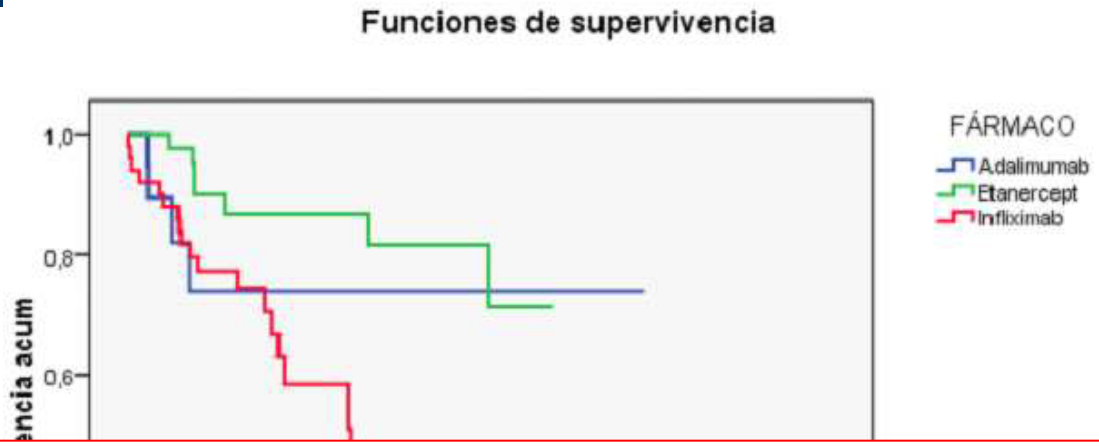

Tiempo medio hasta el cambio:

Adalimumab: 2.769,074 ± 389,452 días

Etanercept: 2.561,082 ± 152,307 días

Infliximab: 1.853,52 ± 306,88 días

Global: 2.713,058 ± 202,126 días

V. Resultados

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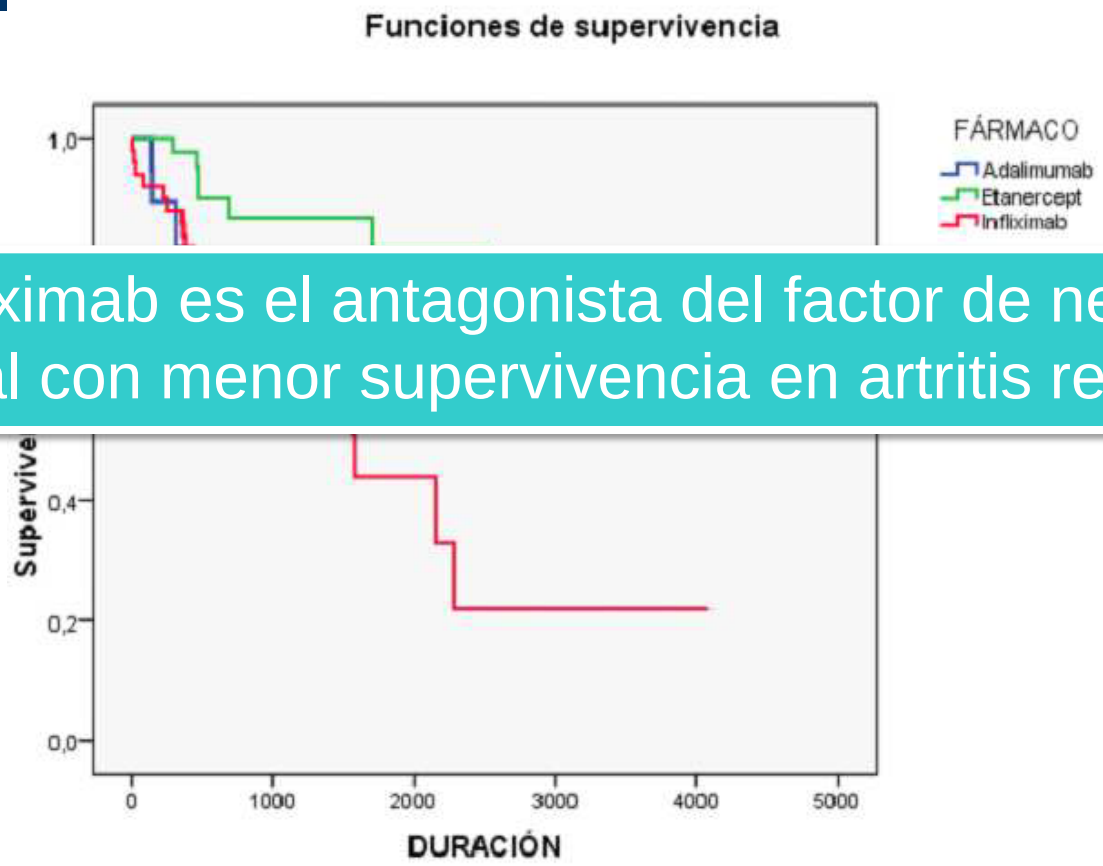
Supervivencia de la terapia anti-TNF
A. Análisis general

p=0,0015



Infliximab es el antagonista del factor de necrosis tumoral con menor supervivencia en artritis reumatoide

V. Resultados

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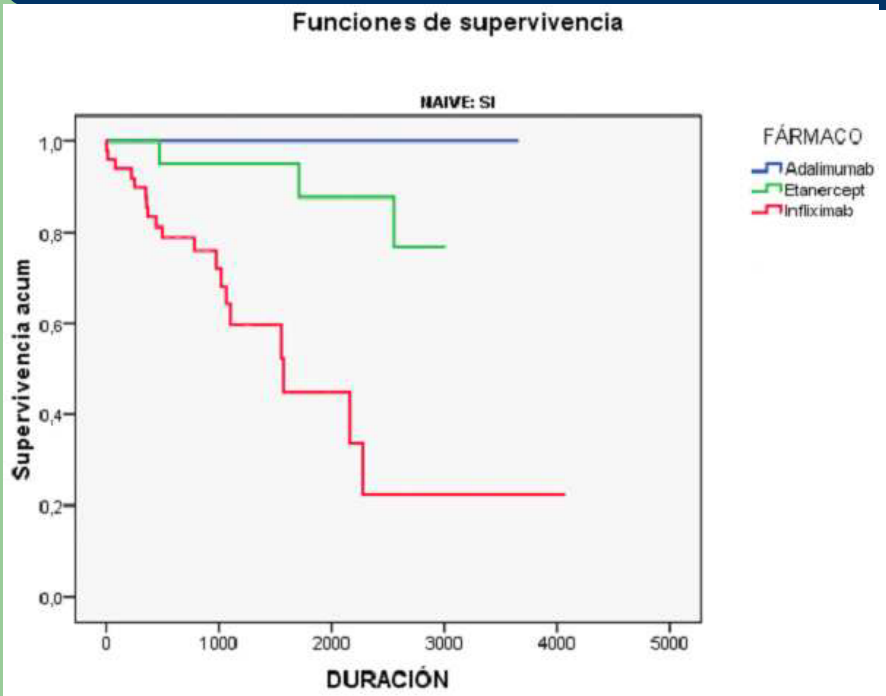
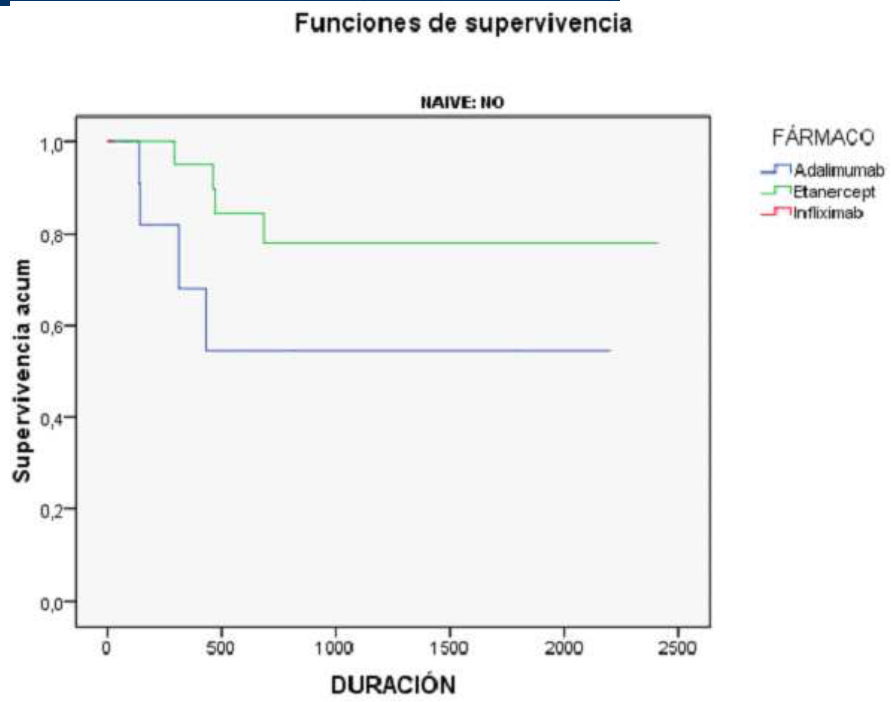
B. Análisis por subgrupos: tratamiento anti-TNF previo

Naïve p=0,001



No Naïve p=0,000



V. Resultados

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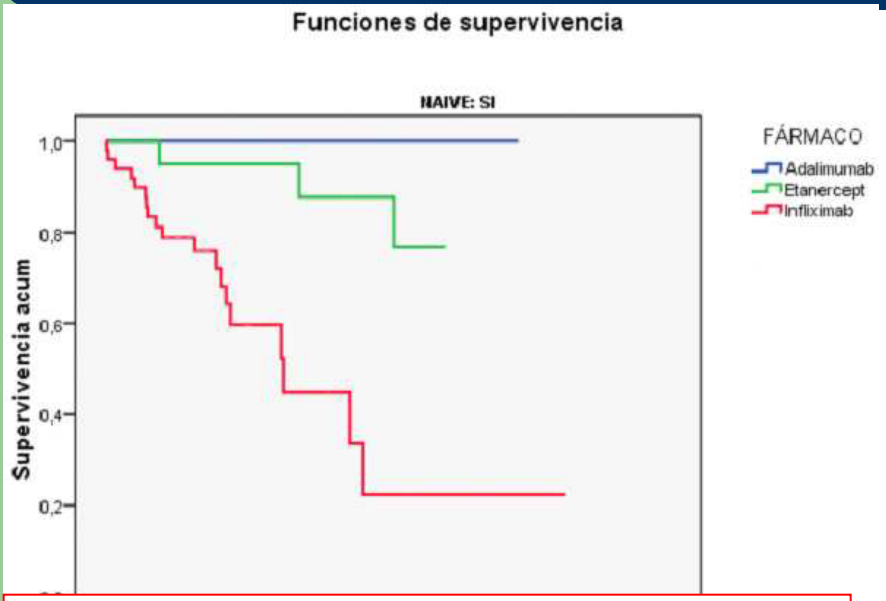
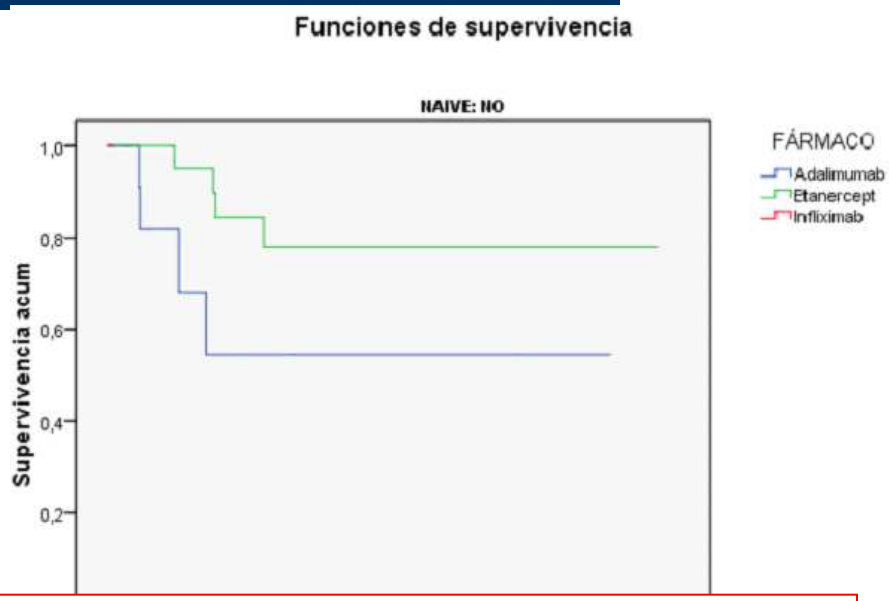
B. Análisis por subgrupos: tratamiento anti-TNF previo

Naïve p=0,001



Tiempo medio hasta el cambio:
Etanercept: 2.735,677 ± 152,534 días
Infliximab: 1.890,816 ± 310,873 días

No Naïve p=0,000



Tiempo medio hasta el cambio:
Etanercept: 1.987,023 ± 188,054 días
Adalimumab: 1.327 ± 333,219 días

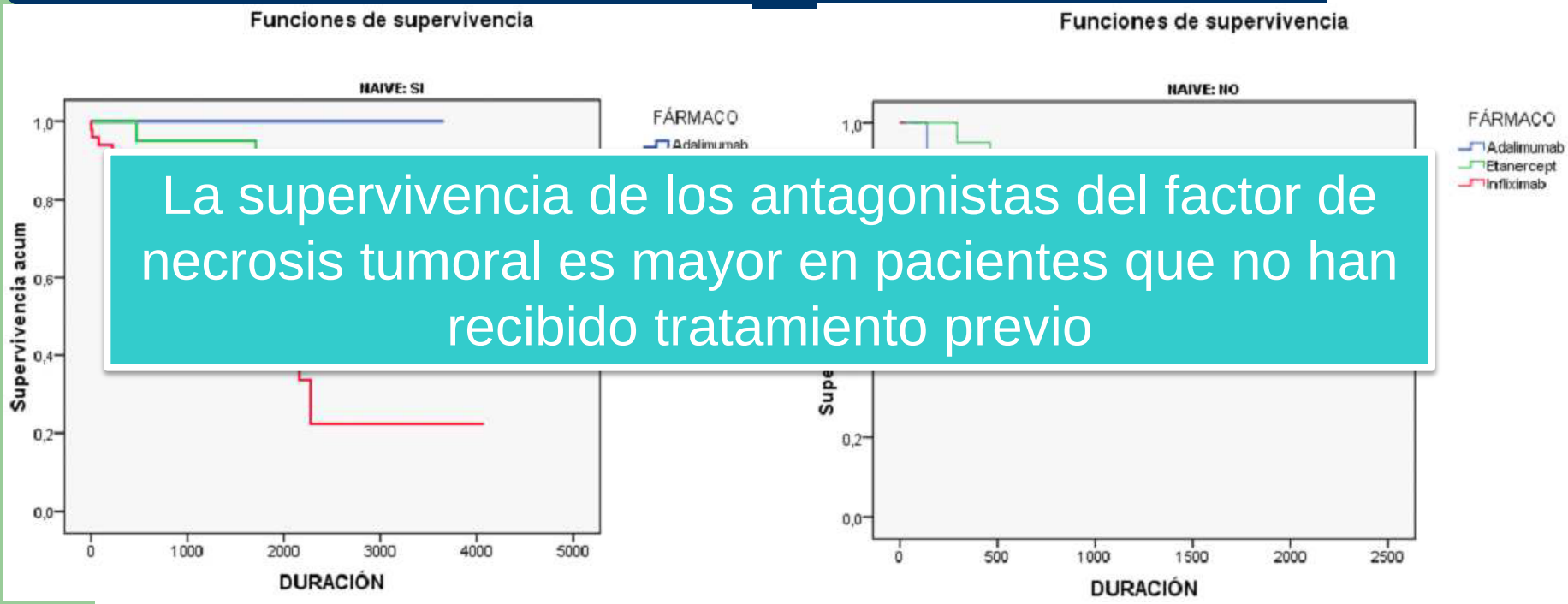
V. Resultados

FUNDACIÓ HOSPITAL DE l'Esperit Sant

B. Análisis por subgrupos: tratamiento anti-TNF previo

Naïve p=0,001

No Naïve p=0,000



La supervivencia de los antagonistas del factor de necrosis tumoral es mayor en pacientes que no han recibido tratamiento previo

V. Resultados

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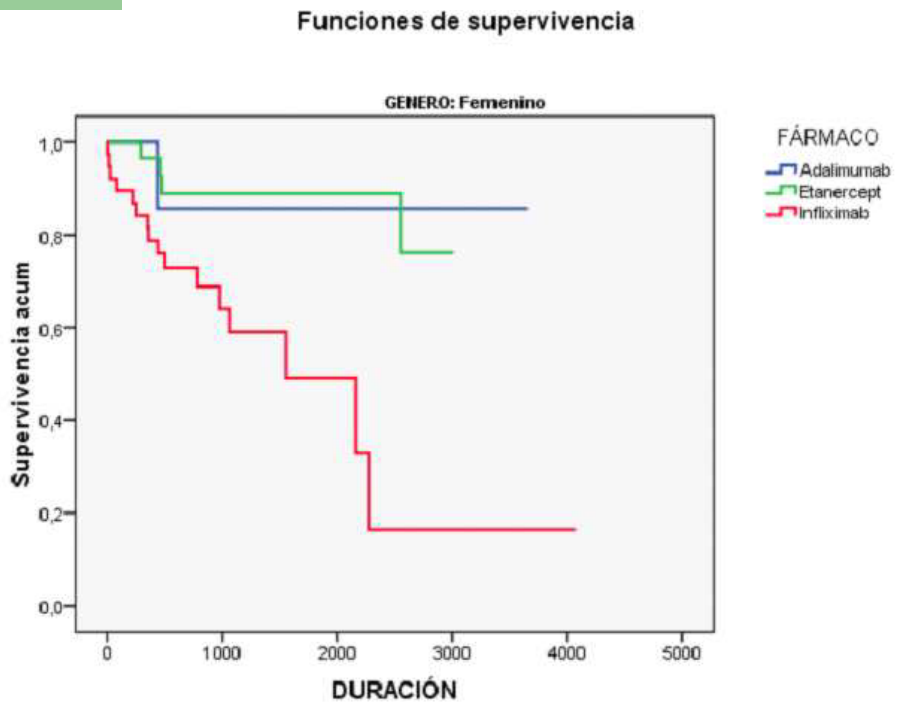
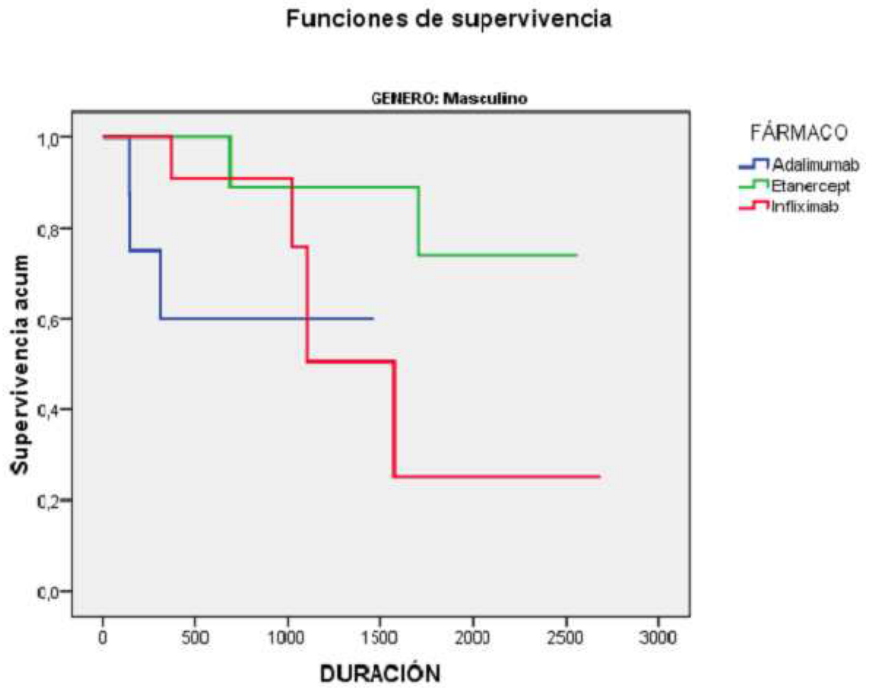
B. Análisis por subgrupos: sexo

Mujeres p=0,015



Hombres p=0,036



V. Resultados

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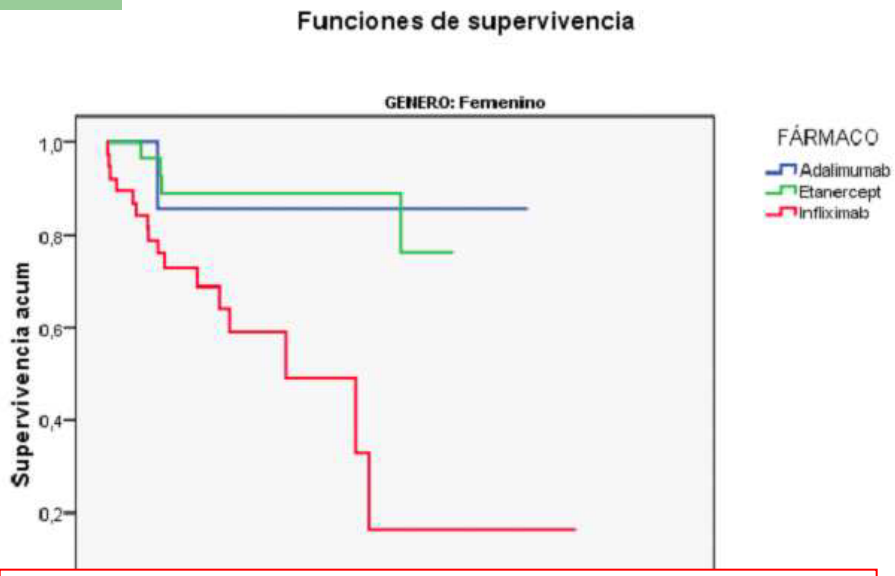
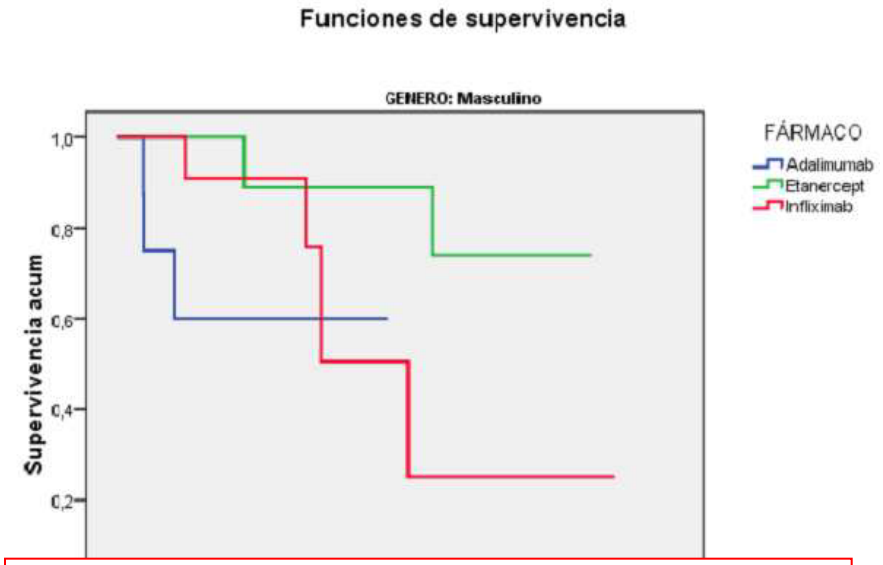
B. Análisis por subgrupos: sexo

Mujeres p=0,015



Tiempo medio hasta el cambio:
Adalimumab: 3.191,571 ± 921,327 días
Etanercept: 2.659,778 ± 470,175 días
Infliximab: 1.743,950 ± 282,907 días

Hombres p=0,036



Tiempo medio hasta el cambio:
Etanercept: 2.224,926 ± 214,699 días
Infliximab: 1.545,687 ± 328,521 días
Adalimumab: 958,625 ± 226,758 días

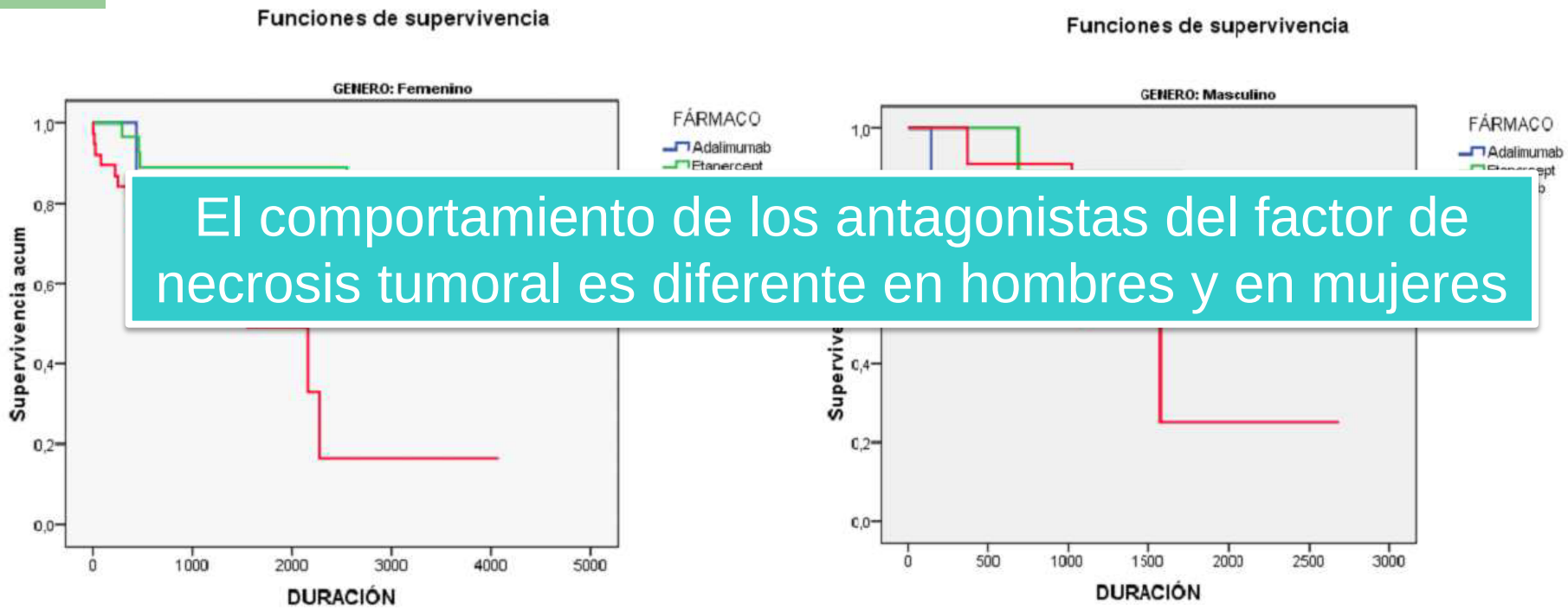
V. Resultados

FUNDACIÓ HOSPITAL DE l'Esperit Sant

B. Análisis por subgrupos: sexo

Mujeres p=0,015

Hombres p=0,036



El comportamiento de los antagonistas del factor de necrosis tumoral es diferente en hombres y en mujeres

V. Resultados

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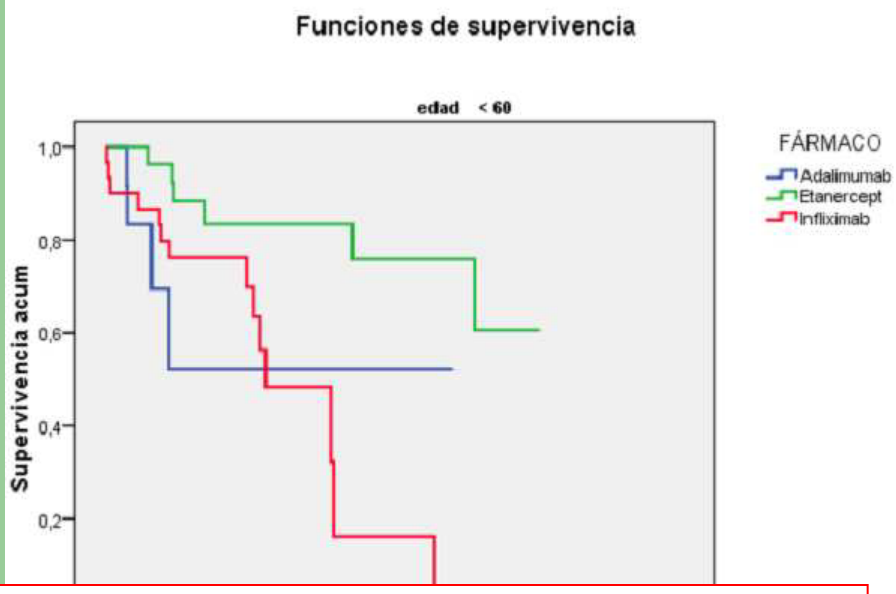
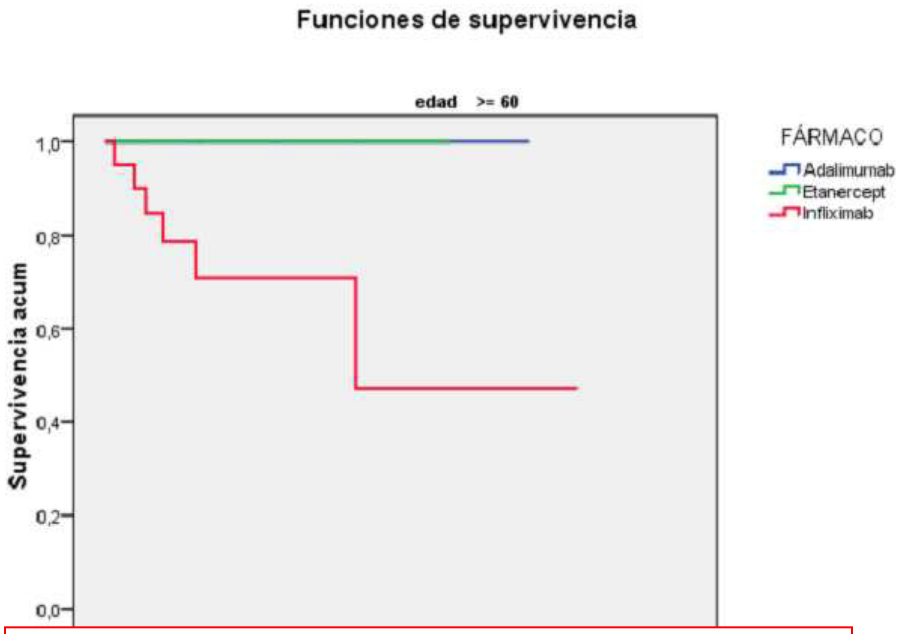
B. Análisis por subgrupos: edad

< 60 años p=0,017

≥ 60 años p=0,031





Tiempo medio hasta el cambio:
Etanercept: 2.421,833 ± 206,470 días
Adalimumab: 1.394,938 ± 393,461 días
Infliximab: 1.213,096 ± 170,453 días

Tiempo medio hasta el cambio:
Infliximab: 2.559,096 ± 572,3983 días

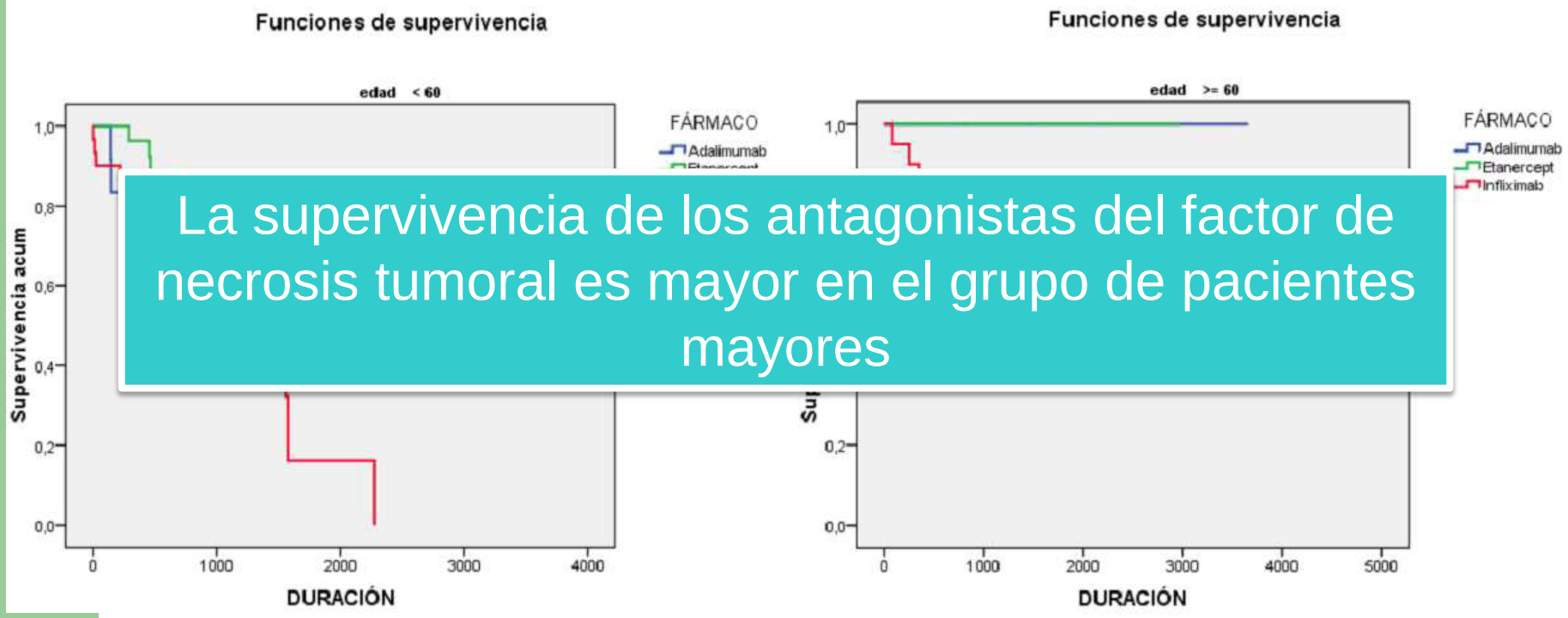
V. Resultados

FUNDACIÓ HOSPITAL DE l'Esperit Sant

B. Análisis por subgrupos: edad

< 60 años p=0,017

≥ 60 años p=0,031



La supervivencia de los antagonistas del factor de necrosis tumoral es mayor en el grupo de pacientes mayores

V. Resultados

FUNDACIÓ HOSPITAL DE l'Esperit Sant

C. Factores predictores de supervivencia

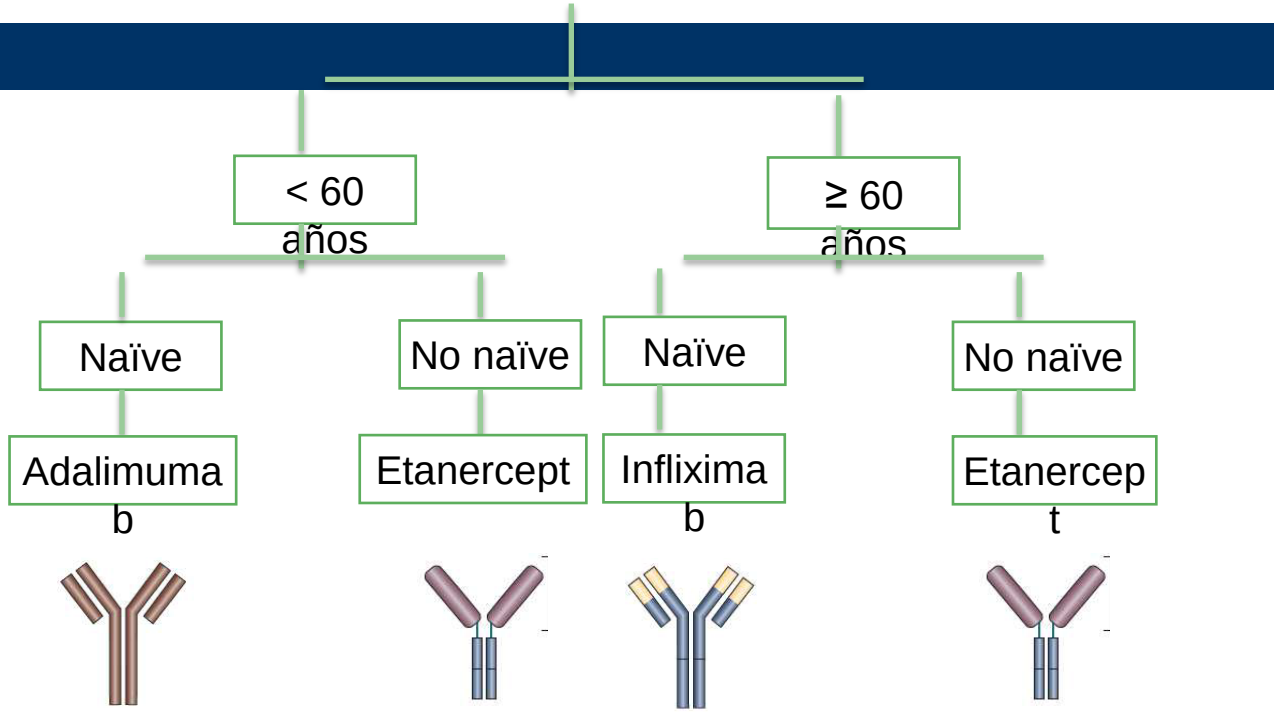
Tabla 6. Modelo de regresión multivariante, Hazard Ratio

Variables en la ecuación

	p	HR	95,0% IC para HR	
			Inferior	Superior
Infliximab (Ref.)	,001			
Adalimumab	,116	,270	,053	1,380
Etanercept	,000	,070	,016	,301
FACTOR REUMATOIDE (Positivo vs. Negativo)	,033	5,229	1,143	23,926
Edad (<60 vs. >= 60)	,002	4,864	1,780	13,292
Sexo(Mujeres vs. Hombres)	,663	1,195	,536	2,666
NAIVE (NO vs. SI)	,037	4,664	1,094	19,888

V. Resultados

Paciente
Artritis Reumatoide



VI. Conclusiones

- El antagonista del factor de necrosis tumoral con menor supervivencia en artritis reumatoide es infliximab
- Son factores predictores de supervivencia: FR-, edad ≥ 60 años y naïve

Patient Prefer Adherence. 2013 Jul 29;7:719-27. doi: 10.2147/PPA.S47453. eCollection 2013.

Comparison of drug survival rates for tumor necrosis factor antagonists in rheumatoid arthritis.

Martínez-Santana V[1], González-Sarmiento E, Calleja-Hernández M, Sánchez-Sánchez T.

IF=1,67
Q2

Patient Preference and Adherence

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ORIGINAL RESEARCH

Comparison of drug survival rates for tumor necrosis factor antagonists in rheumatoid arthritis

This article was published in the following Dove Press journal:
Patient Preference and Adherence
16 July 2012
Number of times this article has been viewed

Virginia Martínez-Santana[1]
E González-Sarmiento[2]
MA Calleja-Hernández[2]
T Sánchez-Sánchez[1]

[1]Pharmacy Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [2]Internal Medicine Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [3]Pharmacy Department, Hospital Universitario Virgen de las Nieves de Granada, Granada, Spain

Background: Persistence of anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis (RA) is an overall marker of treatment success.

Objective: To assess the survival of anti-TNF treatment and to define the potential predictors of drug discontinuation in RA, in order to verify the adequacy of current practices.

Design: An observational, descriptive, longitudinal, retrospective study.

Setting: The Hospital Clínico Universitario de Valladolid, Valladolid, Spain.

Patients: RA patients treated with anti-TNF therapy between January 2011 and January 2012.

Measurements: Demographic information and therapy assessments were gathered from medical and pharmaceutical records. Data is expressed as means (standard deviations) for quantitative variables and frequency distribution for qualitative variables. Kaplan–Meier survival analysis was used to assess persistence, and Cox multivariate regression models were used to assess potential predictors of treatment discontinuation.

Results: In total, 126 treatment series with infliximab (n = 53), etanercept (n = 51) or adalimumab (n = 22) were administered to 91 patients. Infliximab has mostly been used as a first-line treatment, but it was the drug with the shortest time until a change of treatment. Significant predictors of drug survival were: age; the anti-TNF agent; and the previous response to an anti-TNF drug.

Limitations: The small sample size.

Conclusion: The overall efficacy of anti-TNF drugs diminishes with time, with infliximab having the shortest time until a change of treatment. The management of biologic therapy in patients with RA should be reconsidered in order to achieve disease control with a reduction in costs.

Keywords: rheumatoid arthritis, biologic agents, tumor necrosis factor, drug administration schedule

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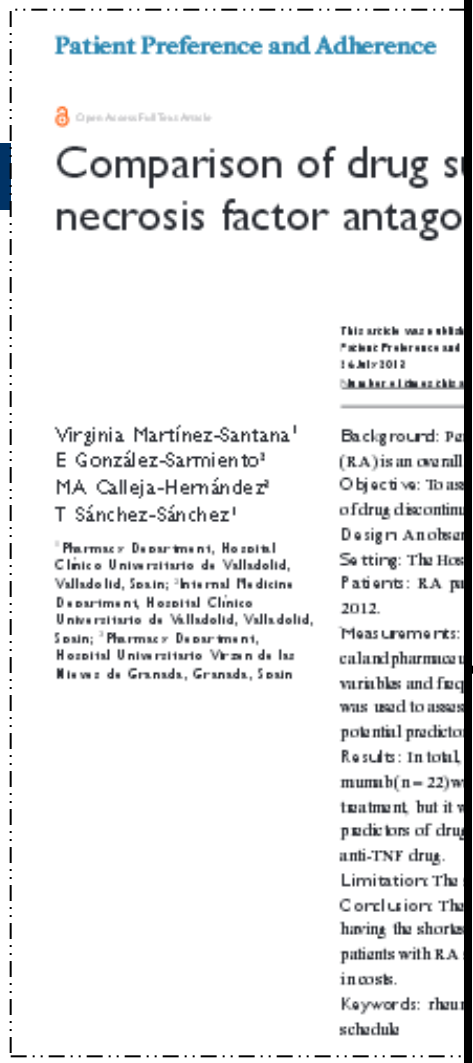
Patient Preference and Adherence

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Comparison of drug s
necrosis factor antago

Virginia Martínez-Santana[1]
E González-Sarmiento[2]
MA Calleja-Hernández[2]
T Sánchez-Sánchez[1]

[1]Pharmacy Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [2]Internal Medicine Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; [3]Pharmacy Department, Hospital Universitario Virgen de las Nieves de Granada, Granada, Spain

Conclusion

In conclusion, choosing infliximab indiscriminately as a firstline anti-TNF therapy is not an appropriate practice, because starting a course of treatment with a drug that will probably become less effective over time will ultimately increase the overall cost of therapy. The long-term management of RA is not only a desirable goal on a medical level; it is also a worthwhile strategy from a pharmacological and economic point of view. Anti-TNF therapies should be chosen on the basis of patient characteristics, in order to ensure that treatment is successful. This study has shown etanercept to be superior to the other anti-TNF agents across most of the subgroups. It would therefore be useful to try to discover the reasons why etanercept is superior among patients suffering from RA, so that treatment can be optimized as a result.

Int J Rheum Dis. 2012 Aug;15(4):e78-9. doi: 10.1111/j.1756-185X.2012.01740.x. Epub 2012 May 23.

Severe pancytopenia following etanercept administration in rheumatoid arthritis.

Martínez Santana V, Izquierdo Navarro M, Calleja Hernández MÁ, Sánchez Sánchez T, Sainz Gil M.

PMID: 22898233 [PubMed - indexed for MEDLINE]

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Q2

International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2012; **15**: e78–e79

LETTER TO THE EDITOR

Severe pancytopenia following etanercept administration in rheumatoid arthritis

Dear Editor,

Severe cytopenia, including neutropenia and anemia, are adverse effects that are rarely reported in patients receiving tumor necrosis factor (TNF)-blockers, including etanercept.[1] The mechanism of etanercept-induced pancytopenia has not yet been established and little is known about it. Furthermore, patients with rheumatoid arthritis usually receive concomitant treatment with methotrexate, which can also induce this blood dyscrasia.

A 78-year-old woman with rheumatoid arthritis had been receiving treatment with etanercept 50 mg once weekly since July 2011. She had also been taking daily prednisone and weekly methotrexate 20 mg for 7 years. Blood tests were performed before treatment with etanercept: platelets 289 × 10^3/μL, erythrocytes 3.54 ×

admission she had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25. The patient developed severe multilobar pneumonia as a complication of the initial immunodeficiency, which in turn led to acute respiratory distress syndrome. The intensive medicine specialists suspected that *Aspergillus* was the causal agent, but this could not be demonstrated. They used linezolid, piperacillin-tazobactam, azitromycin and fluconazol to treat the respiratory infection. She had no disseminated intravascular coagulation and there was no evidence of Felty's syndrome.

The patient finally died due to multi-organ failure secondary to septic shock of respiratory origin, with hemodynamic, respiratory, renal, hematological and metabolic dysfunction, refractory to medical treatment. Specialists could not identify any definite infection

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International Journal of
Rheumatic Diseases
International Journal of Rheumatic Diseases 2012; 15: e78–e79

LETTER TO THE EDITOR

Severe pancytopenia followi
rheumatoid arthritis

Dear Editor,
Severe cytopenia, including neutropenia and anemia, are adverse effects that are rarely reported in patients

Neither the drug label nor the Federal Drug Administration advises performing regular blood tests during etanercept therapy, since studies suggest that there is no increase in adverse hematological events. However, some reports have been published on neutropenia and other hematological dyscrasias associated with the use of etanercept (Szalay *et al.*,[5] Datta *et al.*[6] and Wenham *et al.*[7]). Patients on anti-TNF therapy with previously documented neutropenia, leukopenia or thrombocytopenia would benefit from monitoring regularly with total blood counts.[8]

admission she had an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25. The patient developed severe multilobar pneumonia as a

This article has been cited by:

1 Onur Boyman, Denis Comte, François Spertini, Adverse reactions to biologic agents and their medical management, *Nature Reviews Rheumatology*, 2014, **10**, 10, 612
CrossRef

2 Nancy J. Olsen, Nada Elmagboul, Neutropenia After the Third Cycle of Etanercept, *JCR Journal of Clinical Rheumatology*, 2014, **20**, 4, 237
CrossRef

Int J Rheum Dis. 2012 Aug;15(4):e78-9. doi: 10.1111/j.1756-185X.2012.01740.x. Epub 2012 May 23.

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PMID: 22898233 [PubMed - indexed for MEDLINE]

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IF=1,5
Q2

Pancitopenia y anemia aplásica

Durante el periodo post-comercialización, se han notificado casos de pancitopenia y anemia aplásica, algunos de los cuales tuvieron desenlace de muerte (ver sección 4.4).

LETTER TO THE EDITOR

4.4 Advertencias y precauciones especiales de empleo

Reacciones hematológicas

En pacientes tratados con Enbrel se han notificado raramente casos de pancitopenia y muy raramente casos de anemia aplásica, algunos con resultado mortal. Se debe tener precaución en pacientes tratados con Enbrel los cuales tengan un historial de discrasias sanguíneas. Todos los pacientes y los padres/cuidadores deben ser advertidos de que si el paciente desarrolla signos y síntomas que sugieren la existencia de discrasias sanguíneas o infecciones (como por ejemplo, fiebre persistente, odinofagia, hematomas, sangrado, palidez) mientras están tratándose con Enbrel deben informar inmediatamente a su médico. Estos pacientes deberán ser estudiados urgentemente incluyendo un recuento de células sanguíneas completo. Si se confirma una discrasia sanguínea, se deberá interrumpir el tratamiento con Enbrel.

weekly since July 2011. She had also been taking daily prednisone and weekly methotrexate 20 mg for 7 years. Blood tests were performed before treatment with eta-

secondary to septic shock of respiratory origin, with hemodynamic, respiratory, renal, hematological and metabolic dysfunction, refractory to medical treatment.

I Jornada de Recerca

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