

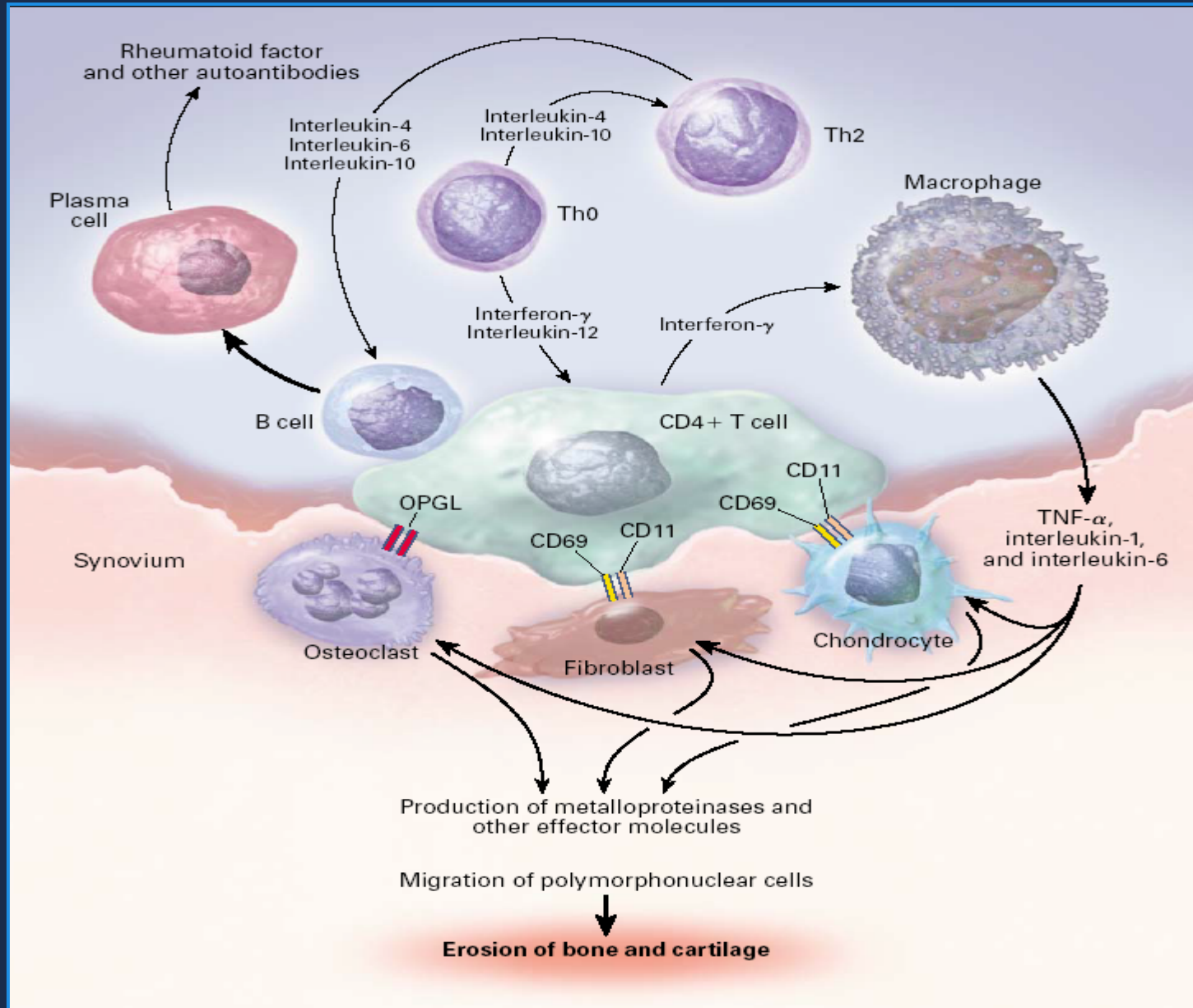
# **Drogas AntiTNF $\alpha$ en Artritis Reumatoide**

Dra. Lilian Soto Sáez

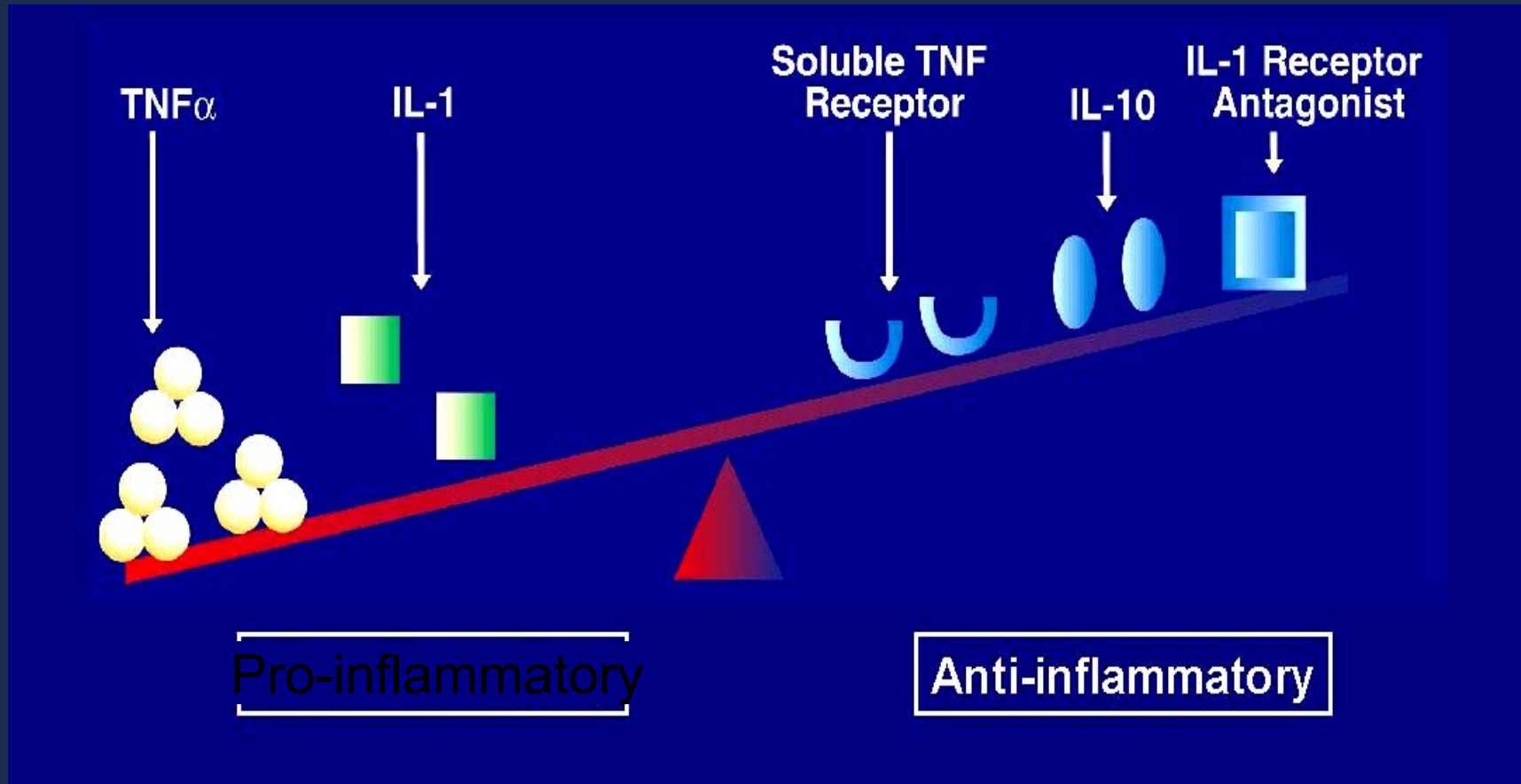
Sección de Reumatología

Departamento de Medicina

Hospital Clínico. Universidad de Chile



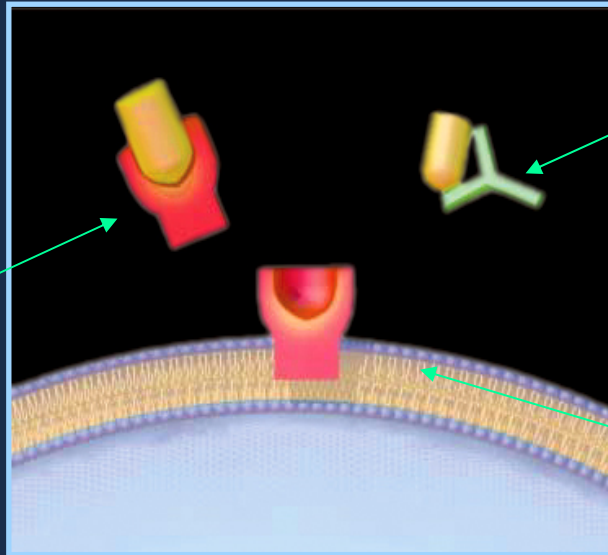
## Desequilibrio de Citoquinas en Articulaciones de Pacientes con Artritis Rheumatoidea



## **TNF- $\alpha$ en Artritis Reumatoide**

- Activa a varios tipos celulares involucrados en a patogénesis de la AR.
- En la cima de la cascada de citokinas proinflamatorias
- Principal responsable de las características de la AR
  - Signos y síntomas
  - Destrucción articular
- El bloqueo del TNF- $\alpha$  es altamente efectivo en AR

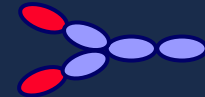
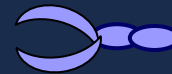
Receptor soluble



Anticuerpo monoclonal

Receptor de citokina

# Características de los Anti -TNF



**Adalimumab<sup>1</sup>**

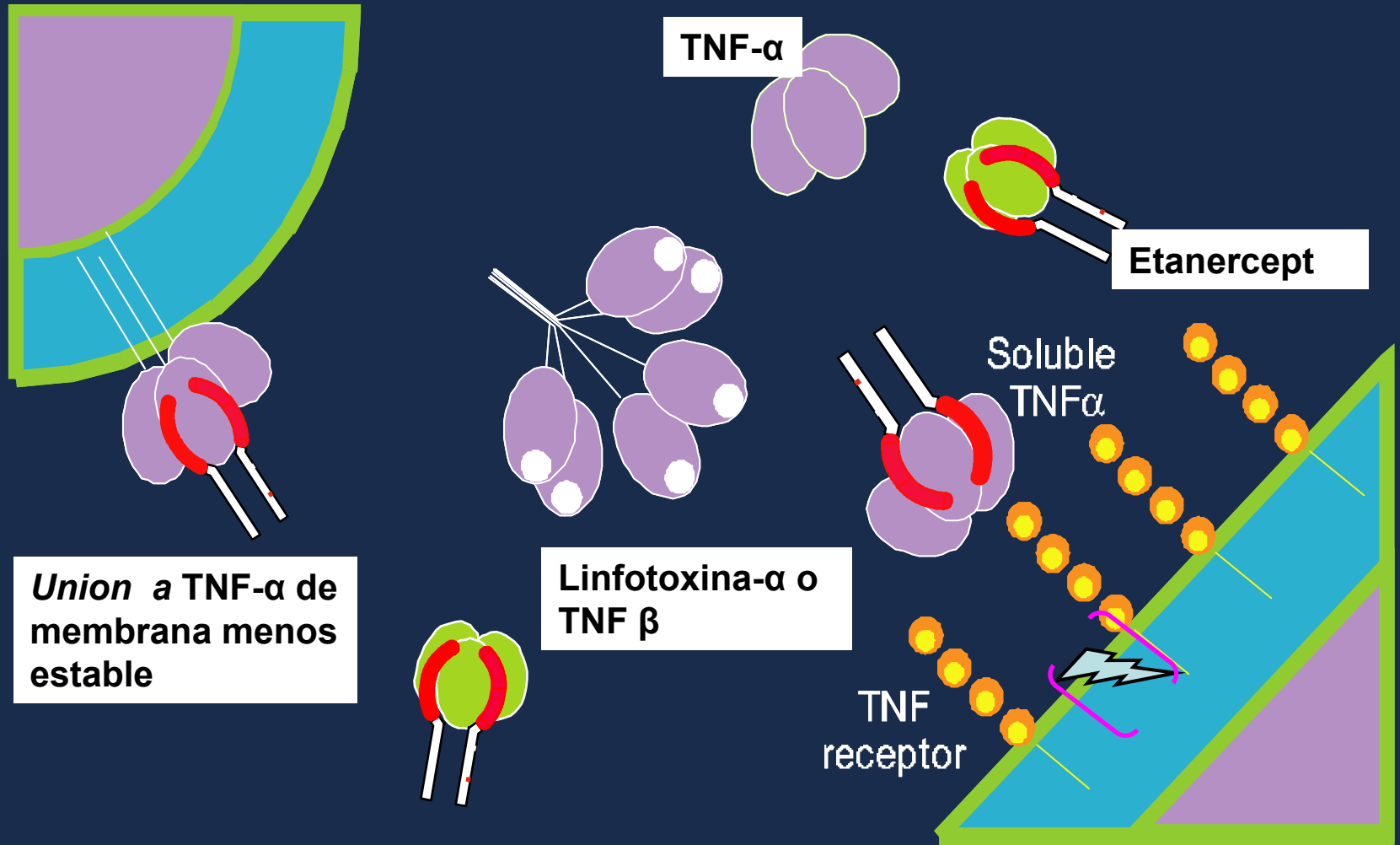
**Etanercept<sup>2</sup>**

**Infliximab<sup>3,4</sup>**

	<i>AcM humano</i>	<i>Proteína de fusión IgG<sub>1</sub> -TNFr</i>	<i>AcM quimérico</i>
<b>Estructura</b>	<i>AcM humano</i>	<i>Proteína de fusión IgG<sub>1</sub> -TNFr</i>	<i>AcM quimérico</i>
<b>Afinidad</b>	<i>TNF<math>\alpha</math></i>	<i>TNF<math>\alpha</math> y <math>\beta</math></i>	<i>TNF<math>\alpha</math></i>
<b>Vida media (días)</b>	<b>12 - 14</b>	<b>4 - 5</b>	<b>8 - 9,5</b>
<b>Administración</b>	<b>sc</b>	<b>sc</b>	<b>iv</b>
<b>Dosis</b>	<b>40 mg sem. alt.</b>	<b>25 mg 2 x sem.</b>	<b>3-5 mg/kg cada 4-8 Semana MTX.</b>
<b>Combinación</b>	<b>mono, MTX.</b>	<b>mono, MTX.</b>	<b>MTX.</b>

1. HUMIRA™ [US package insert]. 2003. 2. Enbrel® [European/US package insert]. 2000/2002.3. Remicade® [US package insert]. 2002. 4. Feldmann M et al. *Annu Rev Immunol.* 1996;14:397-440.

## Mecanismo de Accion de Etanercept

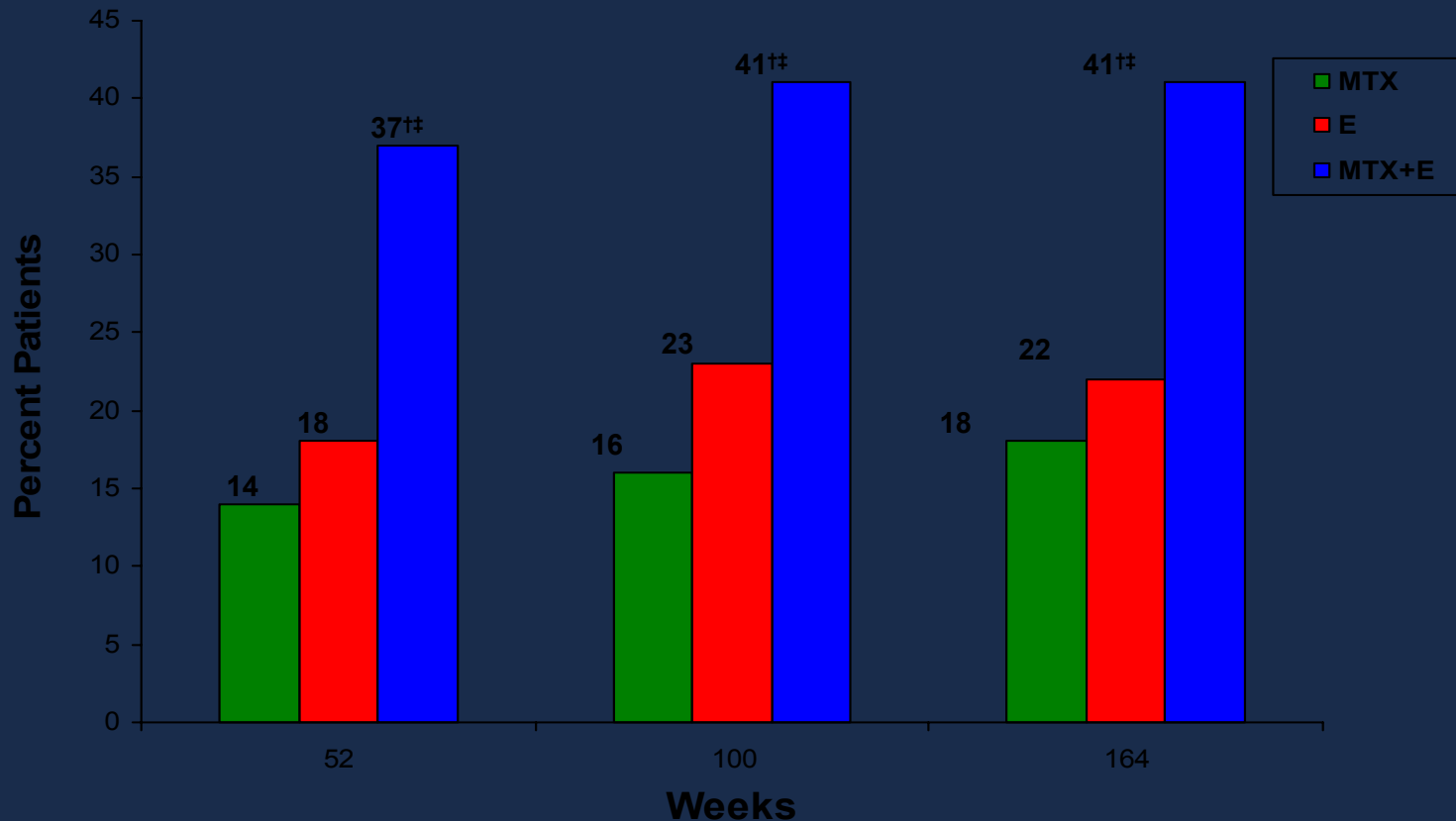


# **TEMPO (Therapeutic effect of the combination of Etanercept and Methotrexate compared with each treatment alone in RA patients)**

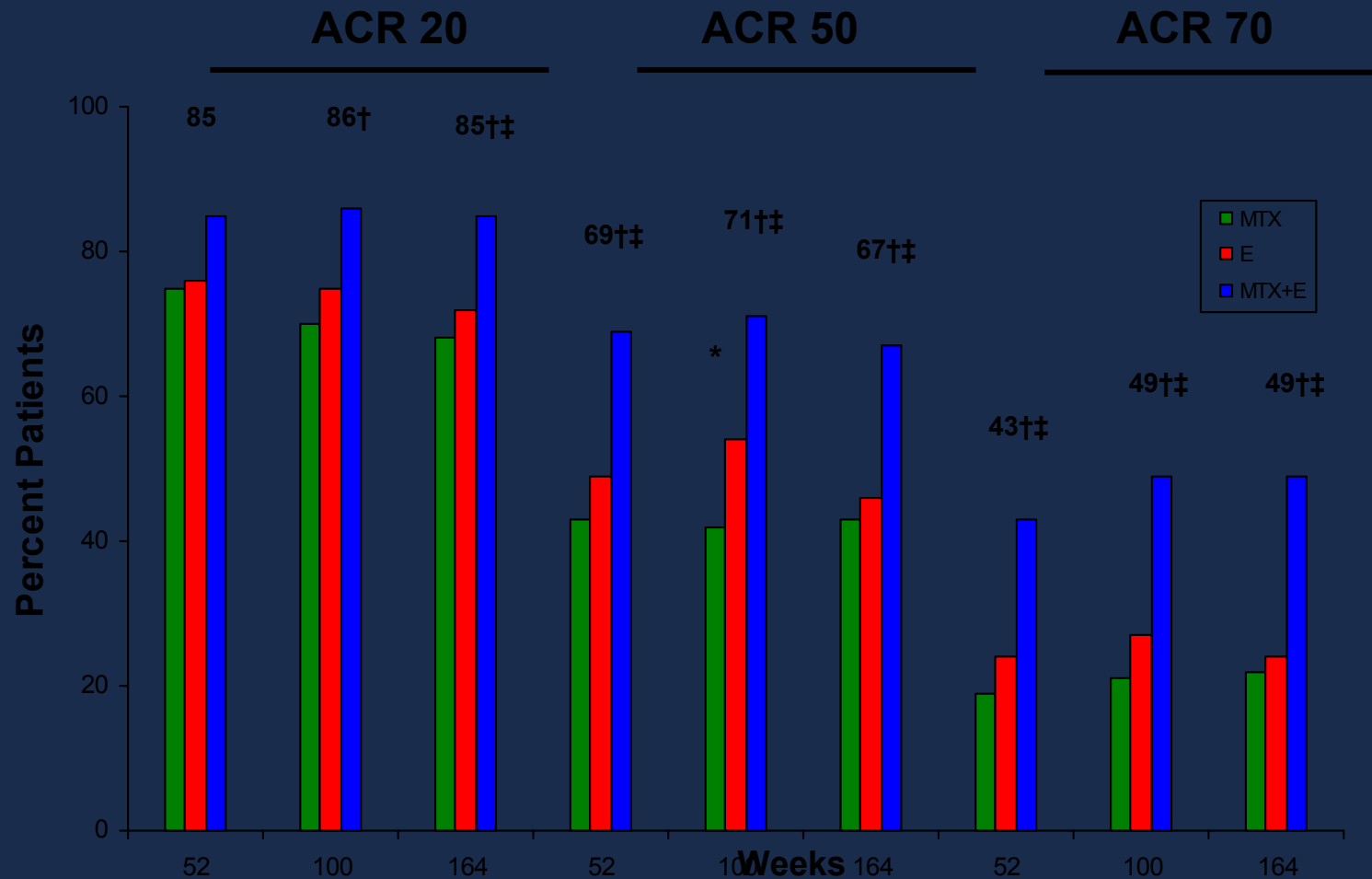
	<b>MTX</b>	<b>E</b>	<b>MTX+ E</b>
<b>Enrolled</b>	<b>228</b>	<b>223</b>	<b>231</b>
<b>Mean Age</b>	<b>53</b>	<b>53.2</b>	<b>52.5</b>
<b>Sex (F/M, %)</b>	<b>79/21</b>	<b>77/23</b>	<b>74/26</b>
<b>Disease Duration (yrs)</b>	<b>6.8</b>	<b>6.3</b>	<b>6.8</b>
<b>RF Positive (%)</b>	<b>72</b>	<b>75</b>	<b>77</b>
<b>No. Prior DMARDs</b>	<b>2.3</b>	<b>2.3</b>	<b>2.3</b>
<b>Prior MTX Use (%)</b>	<b>42</b>	<b>42</b>	<b>44</b>
<b>Corticosteroid Use (%)</b>	<b>64</b>	<b>57</b>	<b>62</b>
<b>NSAID Use (%)</b>	<b>87</b>	<b>88</b>	<b>88</b>

# TEMPO % de Pacientes en Remisión

## DAS <2.6



# TEMPO: respuestas ACR

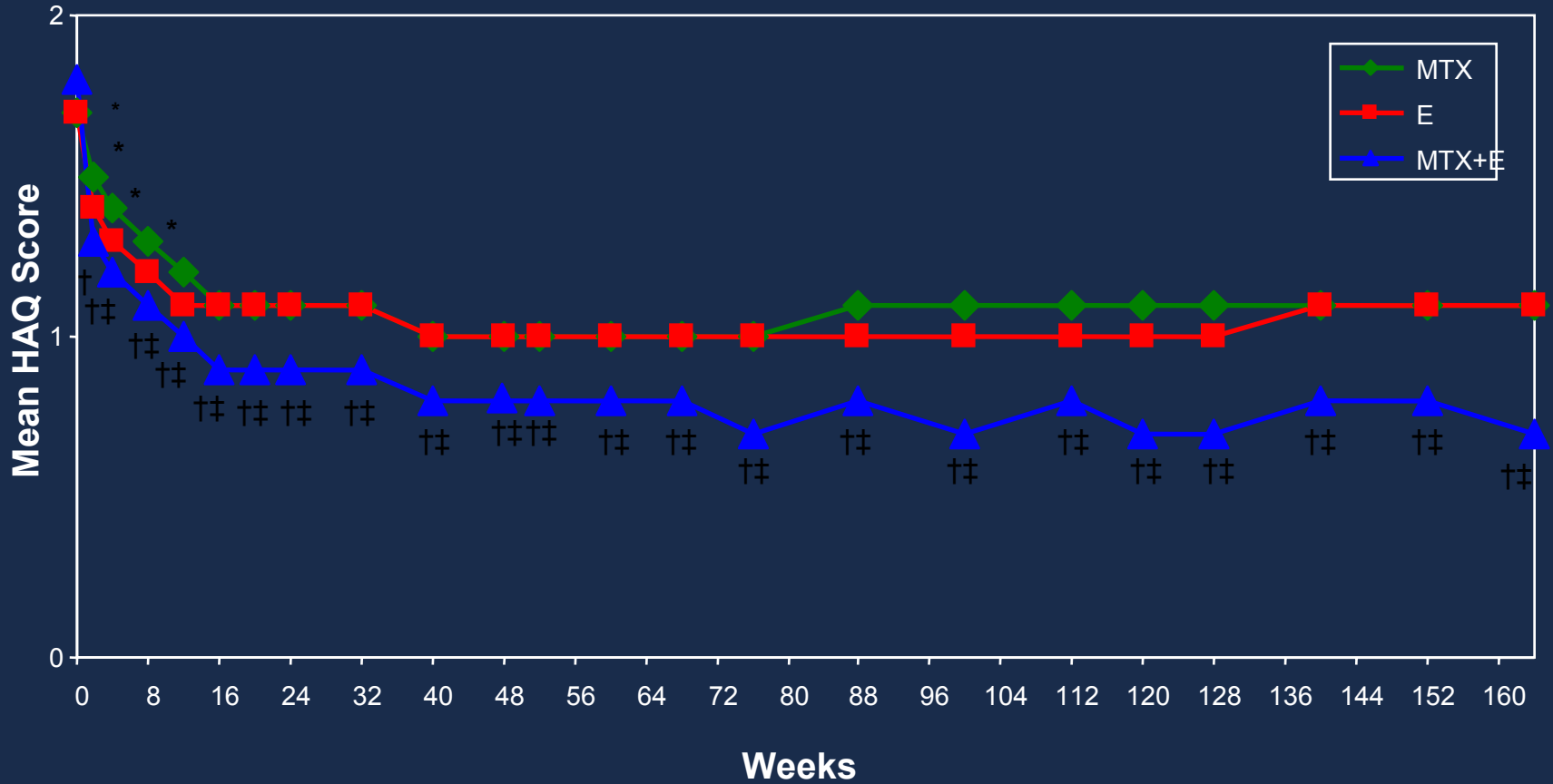


\*p<0.05, E versus MTX

†p<0.05, combination versus MTX

‡p<0.05, combination versus E

# TEMPO: valores HAQ

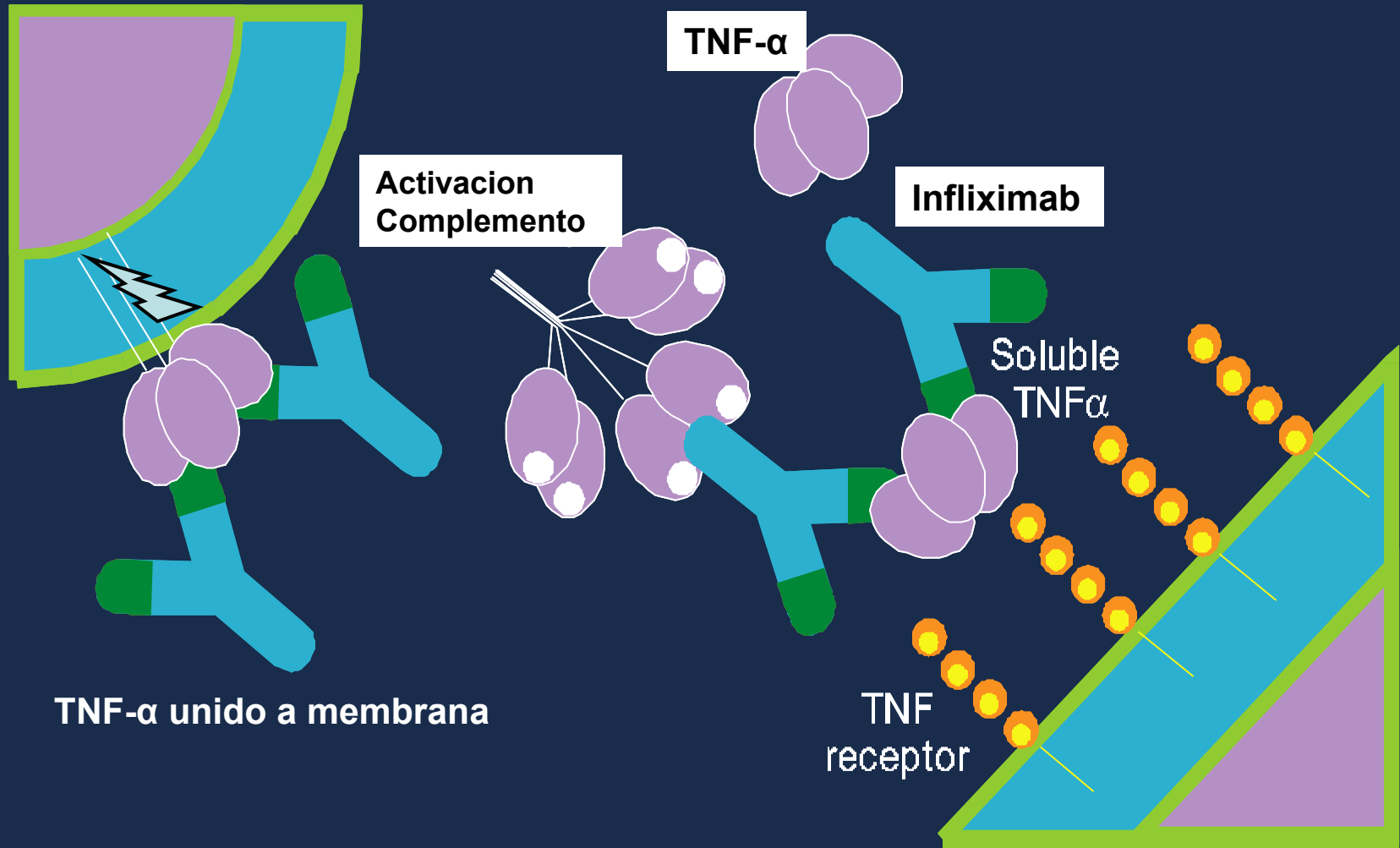


\*p<0.05, E vs MTX

†p<0.05, combination vs MTX

‡p<0.05, combination vs E

## Mecanismo de Accion de Infiximab

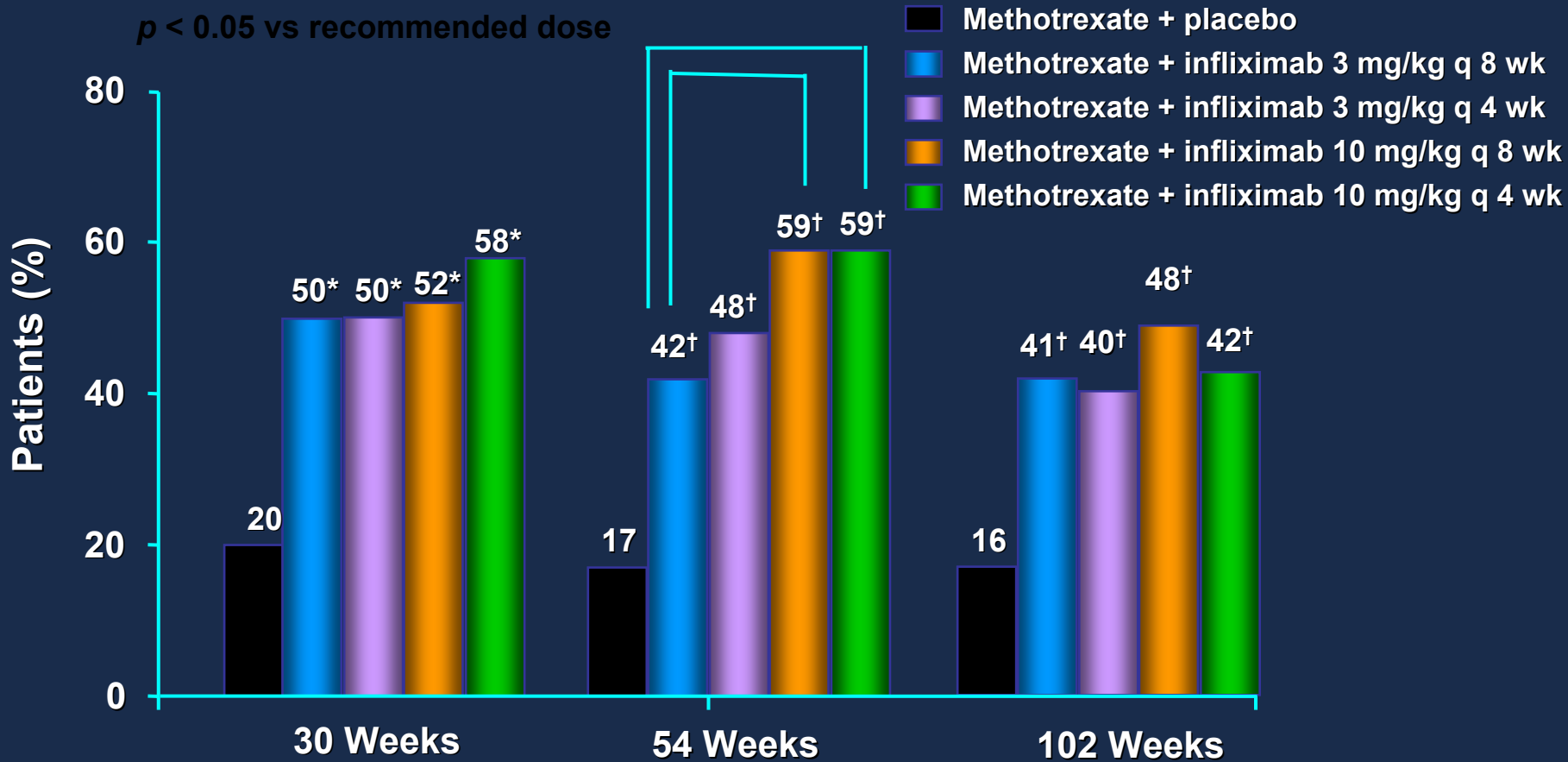


# Inliximab en estudio ATTRACT, Características Basales

Study Name	ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy)
Study population	N = 428 with active RA
Disease duration	9-12 years
MTX duration	< 1-3 years ~50%; > 3 years ~50%
MTX dose	15 mg/week
Drug treatment	NSAIDs 68-79% Corticosteroids 54-65%
Radiographic score	51.3
HAQ	1.8
SF-36	Mental = 46.8-49.9; Physical = 23.9-25.8

# ACR20 Response

## Infliximab / Methotrexate Combination (ATTRACT)



\* $p < 0.001$  vs control

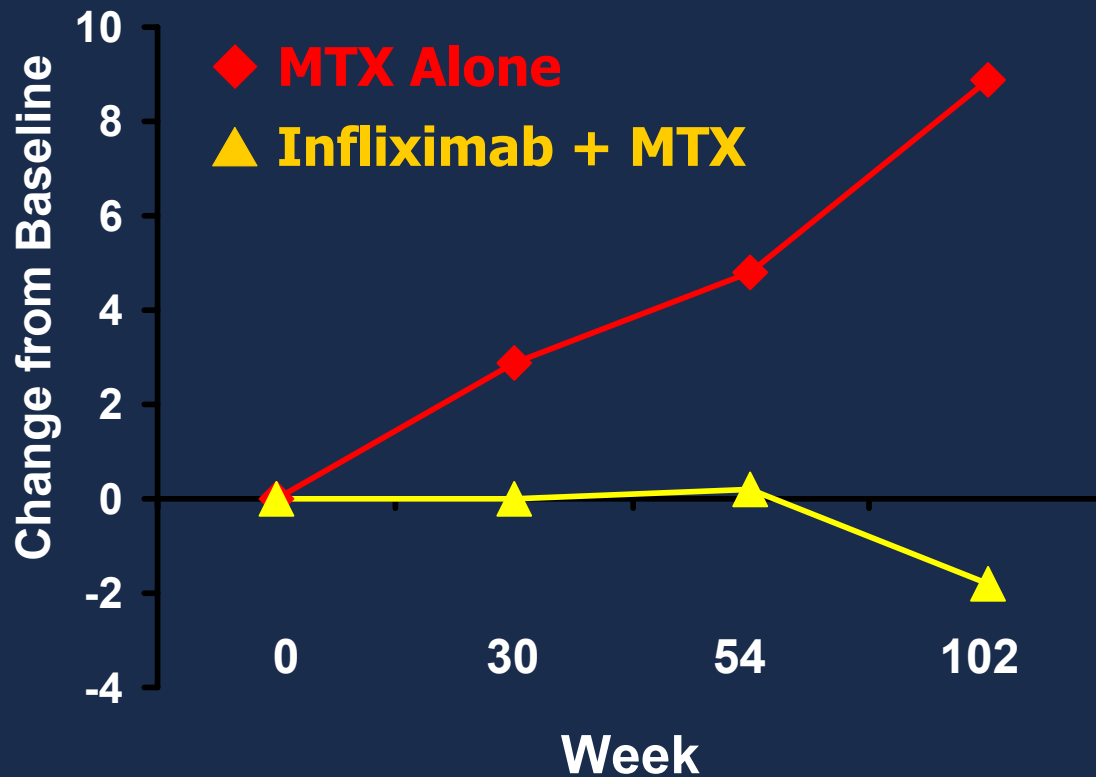
† $p < 0.05$  vs control

Maini. *Lancet*. 1999.

Lipsky. *Arthritis Rheum*. 1999.

Lipsky. *Arthritis Rheum*. 2000.

# Inhibición de Progresión Radiográfica



## ATTRACT Subgroup

- 3 mg/kg Remicade
- n = 82
- 102-week study
- Disease duration  $\leq$  3 yrs
- Age 49-54 yrs
- 75-78% female

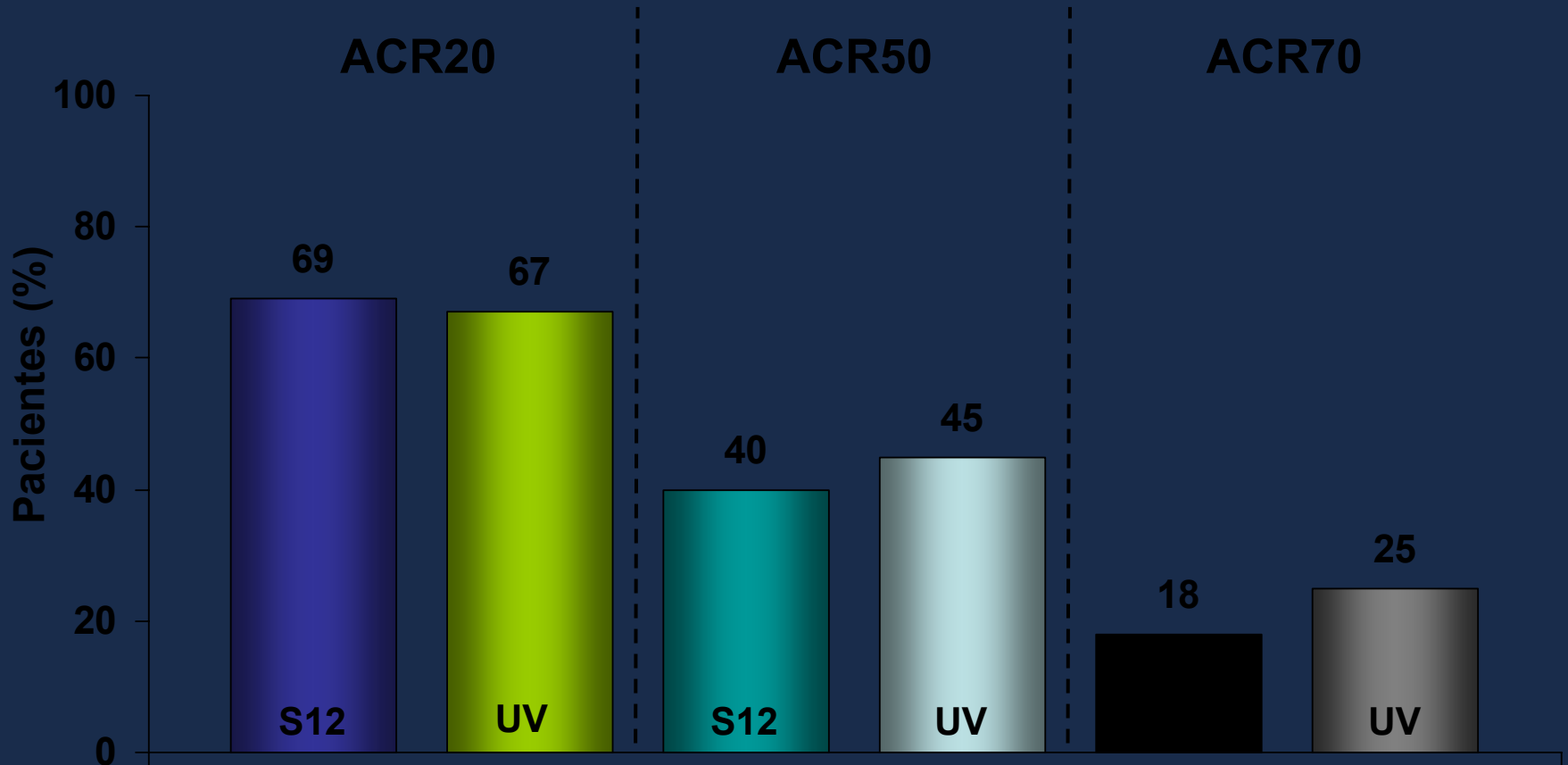
# ReAct

An open-label, multi-center study to **assess the safety and efficacy** of the fully human, anti-TNF monoclonal antibody adalimumab **when added to inadequate standard antirheumatic therapy** in patients with active rheumatoid arthritis

- El estudio más grande con adalimumab
  - 6610 pacientes
  - 11 países de Europa más Australia; 450 sitios
- Estudio abierto con carácter de ‘vida real’
  - Inclusión semejante a guías nacionales/criterio de reembolso
  - Adición de adalimumab al cuidado estándar
  - Amplia población de pacientes, incluyendo aquellos con experiencia previa en biológicos
  - Los datos son de estudio abierto (falta control con placebo)

## ReAct: Respuesta ACR a la semana 12 (S12) y en la última visita (UV)

Todos los pacientes (N=6110)



## Seguridad de los Anti TNF

**Table. *Mycobacterium tuberculosis* in patients with rheumatoid arthritis treated with tumor necrosis factor antagonists**

	Etanercept	Infliximab	Adalimumab*
Patients treated	150,000	200,000	2,500
Patient-years exposure	230,000	230,000	4,900
TB reports	38	172	13
Distribution: Use of agents			
USA	90%	64%	60%
Outside USA	10%	36%	40%
Distribution: TB cases			
USA	20 (52%)	55 (32%)	3 (23%)
Outside USA	18 (48%)	117 (68%)	10 (67%)
Time to onset of TB	1–22 mo (median, 11.2)	75% by 6 wk; 97% by 7 mo	3–8 mo
Extrapulmonary/miliary involvement	50%	45%	40%

Data through 4<sup>th</sup> quarter 2002.

\*All data for adalimumab are from clinical trials.

From Conrath A, Cush JJ, *HOTLINE* 20032(<http://www.rheumatology.org/research/hotline/0803chf.asp>).<sup>88</sup>

# British Society for Rheumatology Biologics Register

Table 4. Rates of all serious infections, by drug\*

	DMARD (n = 1,354)	Etanercept (n = 3,596)	Infliximab (n = 2,878)	Adalimumab (n = 1,190)
Person-years	1,352	4,075	4,618	1,175
No. of infections	56	209	255	61
Rate of infections/1,000 person-years (95% CI)	41.4 (31.4–53.5)	51.3 (44.7–58.5)	55.2 (48.8–62.2)	51.9 (39.9–66.2)
Adjusted IRR†	Referent	0.97 (0.63–1.50)	1.04 (0.68–1.61)	1.07 (0.67–1.72)

\* DMARD = disease-modifying antirheumatic drug; 95% CI = 95% confidence interval; IRR = incidence rate ratio.

† Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking.

# British Society for Rheumatology Biologics Register

Table 5. Rates of site-specific infections\*

	DMARD		Anti-TNF		Adjusted IRR (95% CI)†
	No.	Incidence rate/ 1,000 person-years	No.	Incidence rate/ 1,000 person-years	
Lower respiratory tract	36	26.6 (18.7–36.7)	203	20.6 (17.9–23.6)	0.77 (0.46–1.31)
Skin and soft tissue	4	3.0 (0.8–7.6)	118	12.0 (9.9–14.3)	4.28 (1.06–17.17)
Bone and joint	4	3.0 (0.8–7.6)	68	6.9 (5.4–8.7)	1.12 (0.32–3.88)
Urinary tract	3	2.2 (0.5–6.5)	45	4.6 (3.3–6.1)	1.70 (0.32–9.03)

\* Anti-TNF = anti-tumor necrosis factor (see Table 4 for other definitions).

† Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking.

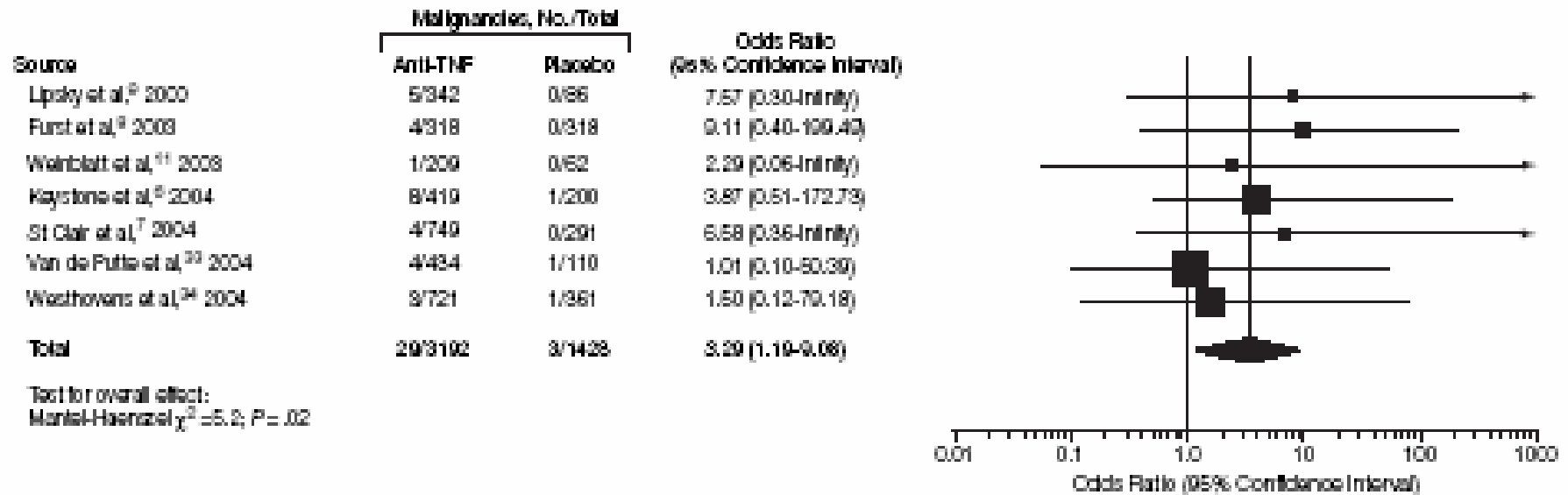
# British Society for Rheumatology Biologics Register

**Table 6.** Details of bacterial intracellular infections

Patient age/sex	Ethnicity	Organism	Site of infection	Treatment	Months from treatment start date
59/F	Caucasian	<i>Mycobacterium tuberculosis</i> (probable)	Cervical lymph node	Infliximab	7
74/F	Caucasian	<i>Mycobacterium tuberculosis</i>	Colon	Infliximab	3
47/M	Caucasian	<i>Mycobacterium tuberculosis</i>	Omentum	Infliximab	2
47/M	Caucasian	<i>Mycobacterium tuberculosis</i> (presumed)	Pleura	Infliximab	3
66/F	Caucasian	<i>Mycobacterium tuberculosis</i>	Lower respiratory tract	Infliximab	16
77/F	Caucasian	<i>Mycobacterium tuberculosis</i>	Posterior pharyngeal wall	Adalimumab	11
50/F	Pakistani	<i>Mycobacterium tuberculosis</i>	Cervical lymph node	Infliximab	4
71/M	Caucasian	<i>Mycobacterium tuberculosis</i> (presumed)	Meninges	Etanercept	2
66/F	African Caribbean	<i>Mycobacterium tuberculosis</i>	Lower respiratory tract	Etanercept	9
63/F	Not known	<i>Mycobacterium tuberculosis</i> (probable)	Meninges	Infliximab	3
59/M	Caucasian	<i>Legionella pneumophila</i>	Lower respiratory tract	Infliximab	32
49/M	Caucasian	<i>Legionella pneumophila</i>	Lower respiratory tract	Infliximab	4
47/M	Caucasian	<i>Listeria monocytogenes</i>	Meninges	Infliximab	2
67/M	Caucasian	<i>Listeria monocytogenes</i>	Joint	Etanercept	0
60/F	Caucasian	<i>Listeria monocytogenes</i>	Joint	Adalimumab	14
63/F	Caucasian	<i>Mycobacterium fortuitum</i>	Lower respiratory tract	Etanercept	4
80/F	Caucasian	<i>Salmonella</i> sp.	Bowel and joint	Etanercept	9
57/F	Caucasian	<i>Salmonella</i> sp.	Joint	Infliximab	27
54/F	Caucasian	<i>Salmonella</i> sp.	Bowel	Etanercept	2

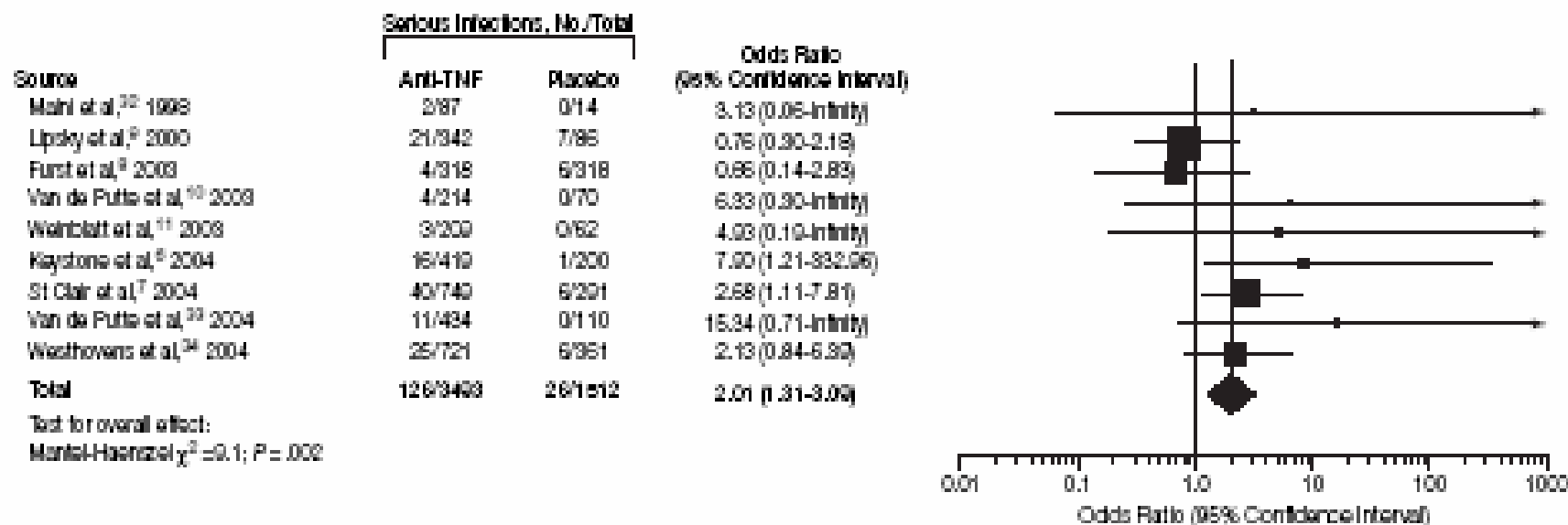
# Metaanálisis : R. de Infección y Malignidad

**Figure 2.** Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

**Figure 3. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Serious Infections in Patients With Rheumatoid Arthritis**



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

**Table 4. Effect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patients With Rheumatoid Arthritis, Stratified by Dose Group**

## Factores de Respuesta

- **PCR en INF** (Buch : Arthritis Rheum. 2005 Jan;52(1):42-8.)
  - Falta de Supresión de PCR a 2 semanas identifica a los no respondedores a futuro (12 semanas)
  - En no respondedores, supresión de PCR a 12 semanas se asocio a una mejoría lenta hacia las 24 semanas
  - Falta de supresión de PCR a las 12 semana se relaciona a una buena respuesta a Switch a ETA

## Factores de Respuesta

- **LUNDEX** Arthritis Rheum. 2006 Feb;54(2):600-6.
  - Índice de eficacia de drogas a 5 años de seguimiento comparativo entre ETA e INF en Suecia
  - Combina la eficacia o respuesta con la proporción de pacientes que se mantiene en tratamiento
  - ETA tiene valores LUNDEX mas altos que INF debido a menores índices de adherencia a este ultimo

## Factores de Respuesta

- **Resistencia a AntiTNF** ( Sidiropoulos and Boumpas: Ann Rheum Dis 2006;65;701-703)
    - Mediada por Proteínas (MRP I)
    - Anticuerpos ¿Pérdida de eficacia o Reacciones Adversas?
      - 21 % a dosis de 3mg/kg y 7% a dosis de 10 mg/kg INF (disminuye con MTX a 7% y 0% respect)
      - 6% ADA monoterapia / 1% con MTX
      - 2% ETA
    - Dosificación /tiempo entre intervalos de tto:
      - INF requiere ajuste de dosis en un 60 a 70 % de los pactes
      - 22-30% tratados con INF :niveles plasmáticos muy bajos antes de siguiente dosis
      - 20% de las discontinuaciones se deberían a pérdida de eficacia
- 2ria van Vollenhoven RF, Ann Rheum Dis 2004;63(suppl)

## Predictores de Respuesta a Terapia AntiTNF: UK

TABLE 3. EULAR response after 6 months of therapy<sup>a</sup>

EULAR response	Overall (3223)	Etanercept (1413)	Infliximab (1810)
Good	584 (18.1)	245 (17.3)	339 (18.7)
Moderate	1602 (49.7)	727 (51.5)	875 (48.3)
None	1037 (32.2)	441 (31.2)	596 (32.9)
Remission	292 (8.6)	120 (8.0)	172 (9.0)

<sup>a</sup>Observed differences between etanercept and infliximab are not statistically significant.

## Predictores de Respuesta a Terapia AntiTNF: UK

### INFLIXIMAB

#### NSAID + SMOKING + HAQ

Where:

NSAID = 1 if patient currently receiving NSAID

SMOKING = 1 if patient a current non-smoker

HAQ = 0 if HAQ score >2  
= 1 if HAQ score between 1.0 and 2.0  
= 2 if HAQ score ≤1.0

### ETANERCEPT

#### NSAID + MTX + HAQ

Where:

NSAID = 1 if patient currently receiving NSAID

MTX = 1 if patient currently receiving MTX

HAQ = 0 if HAQ score >2  
= 1 if HAQ score between 1.0 and 2.0  
= 2 if HAQ score ≤1.0

Alto score > 40% EULAR bueno  
Score 0 < 10% EULAR bueno

FIG. 2. Formulae for predicting response.

**INFLIXIMAB**

**MALE + HAQ + NSAID + DAS28 + PREVDM**

Where:

- MALE = 1 if patient is a male
- NSAID = 1 if patient currently receiving NSAID
- MTX = 1 if patient currently receiving MTX
- HAQ = 0 if HAQ score >2  
= 1 if HAQ score between 1.0 and 2.0  
= 2 if HAQ score ≤1.0
- DAS = 0 if DAS28 score >7.2  
= 1 if DAS28 score between 6.2 and 7.2  
= 2 if DAS28 score ≤6.2
- PREVDM = 0 if >5 previous DMARDs  
=1 if 4 or 5 previous DMARDs  
=2 if 3 or fewer previous DMARDs

Total possible score: 8

**ETANERCEPT**

**MALE + HAQ + MTX + NSAID + DAS28 + PREVDM**

Where:

- MALE = 1 if patient is a male
- NSAID = 1 if patient currently receiving NSAID
- MTX = 1 if patient currently receiving MTX
- HAQ = 0 if HAQ score >2  
= 1 if HAQ score between 1.0 and 2.0  
= 2 if HAQ score ≤1.0
- DAS = 0 if DAS28 score >7.2  
= 1 if DAS28 score between 6.2 and 7.2  
= 2 if DAS28 score ≤6.2
- PREVDM = 0 if >5 previous DMARDs  
=1 if 4 or 5 previous DMARDs  
=2 if 3 or fewer previous DMARDs

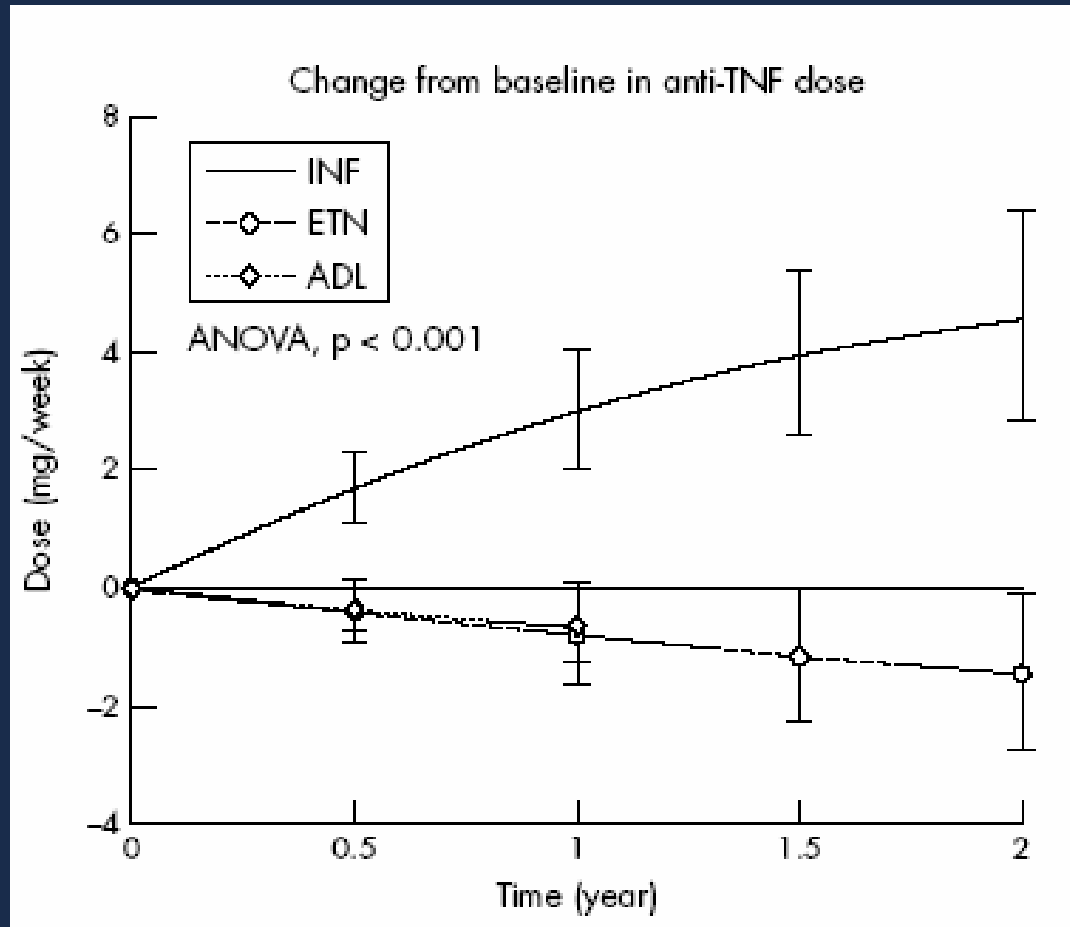
# Predictores de Respuesta a Terapia AntiTNF: UK

TABLE 9. Combined strength of predictors in identifying remission

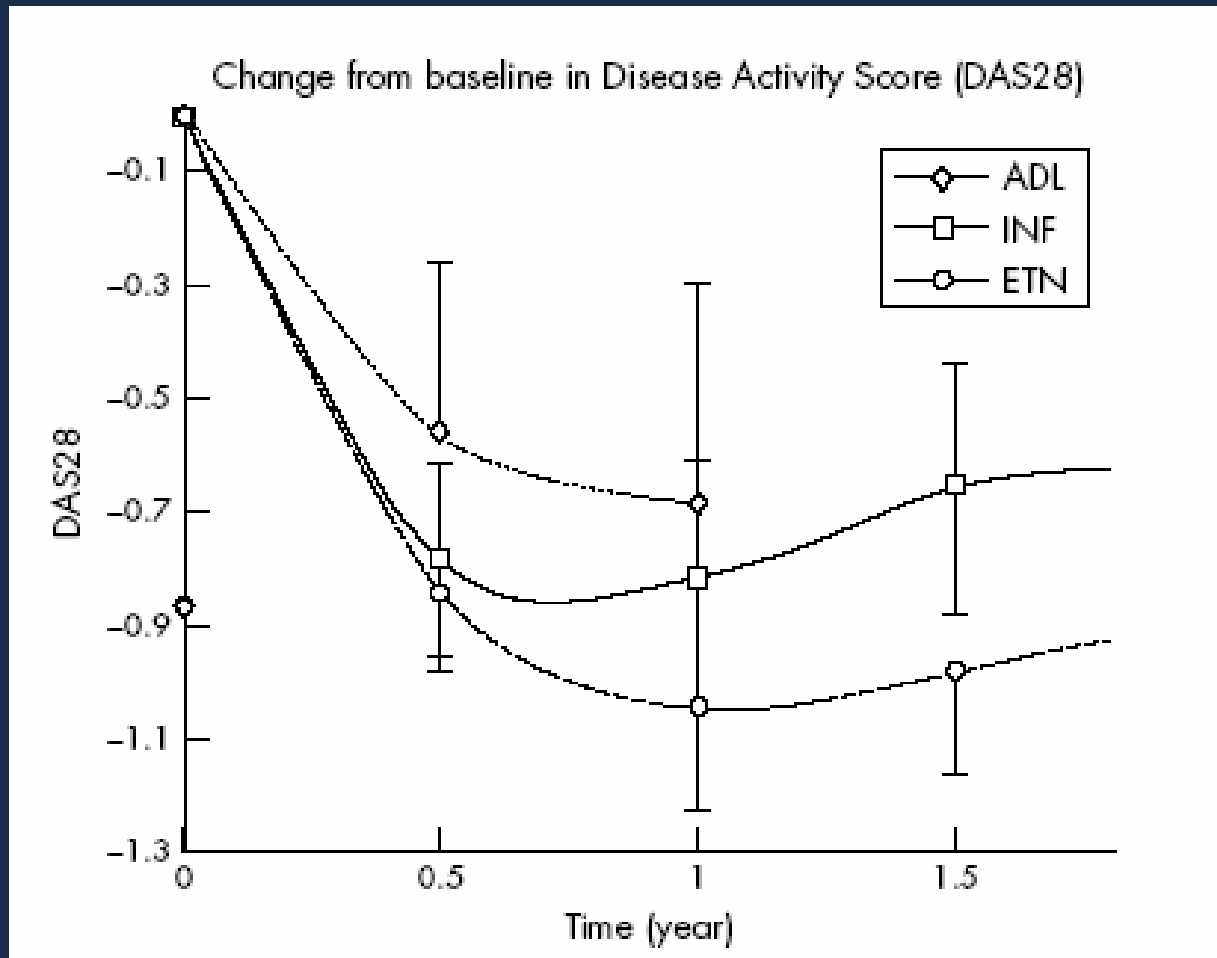
Score	Infliximab		Etanercept	
	<i>n</i>	Remission (%)	<i>n</i>	Remission (%)
0-2	358	3.9	310	2.5
3-4	622	6.7	487	3.3
5-6	378	20.1	294	13.6
>6	48	33.3	67	35.8

FIG. 3. Formulae for predicting remission.

# RESISTENCIA antiTNF SCQM



# RESISTENCIA antiTNF SCQM



## Factores de Respuesta

- Polimorfismo -308 del Promotor del gen TNF $\alpha$ , Metaanálisis  
( Lee YH et al, Rheumatol Int. 2006 Dec;27(2):157-61 )
  - El alelo A estaría relacionado a una menor respuesta a antiTNF
  - La frecuencia de portadores del alelo A fue de 53/240 (22.1%) en respondedores y 32/71 (45.1%) en no-respondedores.
  - Pacientes no respondedores a anti-TNF mostraron una frecuencia aumentada de alelo A.

# Switch entre Anti TNF: BIOBADASER

**Table 1**  
 Rate of discontinuation of three tumor necrosis factor antagonists; reasons for discontinuation and rank of treatment

TNF antagonist	Reason for discontinuation	Rate per 100 patient years exposed	
		First treatment	Second treatment
Infliximab	Adverse events	6.5	32.7
	Lack of efficacy	4.7	38.5
Etanercept	Adverse events	3.8	6.1
	Lack of efficacy	3.6	9.3
Adalimumab	Adverse events	7.2	12.5
	Lack of efficacy	3.2	12.5

TNF, tumor necrosis factor.

# Switch entre Anti TNF: Large UK National Cohort Study

**Table 5. Outcomes of treatment with the second biologic agent\***

Reason for switch	Outcome with second biologic agent		
	Still taking agent at end of April 2005	Stopped for inefficacy	Stopped for adverse event
Inefficacy (n = 503)	375 (74)	78 (16)	50 (10)
Adverse event (n = 353)	249 (71)	33 (9)	71 (20)
Total switches (n = 856)	624 (73)	111 (13)	121 (14)

\* Values are the number (%) of patients.

## **Indicaciones de Agentes Biológicos, anti TNF, en Chile**

- AR seropositiva o erosiva de mas de 6 meses de evolución.
- Signos y síntomas de enfermedad activa y persistente evaluada por reumatólogo.
- Enfermedad activa a pesar del uso de DMARDs solos o en combinación (dosis plena máxima y por tiempo suficiente ) o con toxicidad o intolerancia a DMARDs a esas dosis
- Pacientes que requieran uso de dosis de prednisona mayores a 10 mg/dia

## **Exclusiones de Agentes Biológicos**

- Antecedentes de TBC no tratada con un esquema efectivo
- Artritis séptica durante los últimos 12 meses.
- Infección de prótesis
- Uso de sonda vesical a permanencia
- Enfermedad desmielinizante
- Neoplasias durante los últimos 5 años
- Embarazo y lactancia
- Insuficiencia cardiaca congestiva
- Ulceras cutáneas crónicas

## Aprobación FDA para uso de Drogas Biológicas mayo/2007

Aprobación FDA	Etanercept	Infliximab	Adalimumab		
AR	+	+	+		
ARJ	+				
EAA	+	+	+		
APs	+	+	+		
Placa Ps	+	+			
Crohn		+*	+		
CUI		+			

\* Adultos y niños / fístulas