

Actualización del tratamiento en la AIJ no-sistémica

Consuelo Modesto

10º Congreso SERPE, Granada 2013

2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features

TIMOTHY BEUKELMAN,[1] NIVEDITA M. PATKAR,[1] KENNETH G. SAAG,[1] SUE TOLLESON-RINEHART,[2] RANDY Q. CRON,[1] ESI MORGAN DEWITT,[3] NORMAN T. ILOWITE,[4] YUKIKO KIMURA,[5] RONALD M. LAXER,[6] DANIEL J. LOVELL,[3] ALBERTO MARTINI,[7] C. EGLA RABINOVICH,[8] AND NICOLINO RUPERTO[7]

2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis

Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications

Sarah Ringold,[1] Pamela F. Weiss,[2] Timothy Beukelman,[3] Esi Morgan DeWitt,[4] Norman T. Ilowite,[5] Yukiko Kimura,[6] Ronald M. Laxer,[7] Daniel J. Lovell,[4] Peter A. Nigrovic,[8] Angela Byun Robinson,[9] and Richard K. Vehe[10]

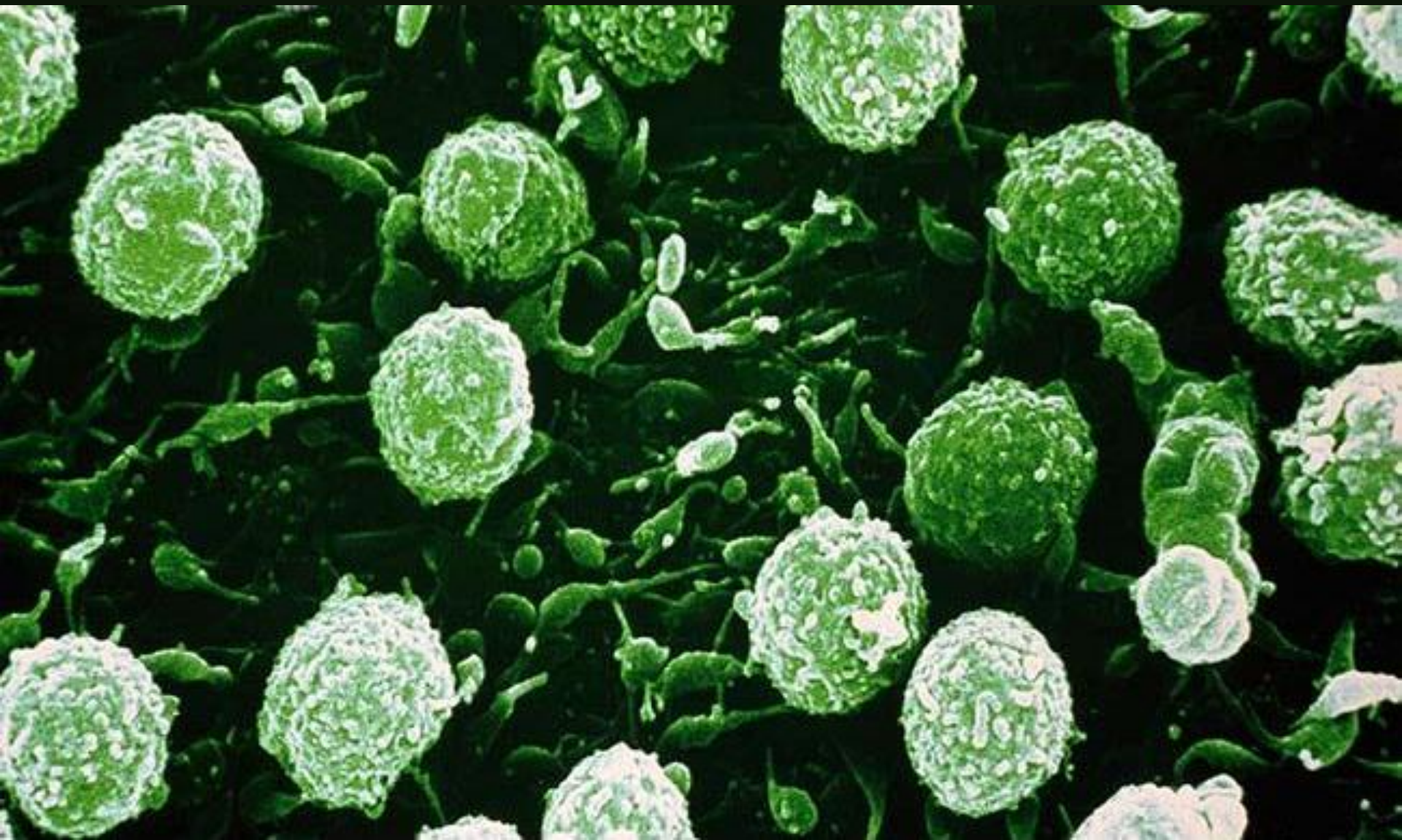
Arthritis Care&Res, 2011 – Arthritis&Rheum 2013



AGENDA

1) Tratamiento farmacológico de la AIJ no-sistémica.
2) ¿Existe una estrategia mejor para el tratamiento de la forma poliarticular?
3) Nuevas aportaciones en la uveítis anterior refractaria asociada a AIJ
4) Posible papel de las pequeñas moléculas en el futuro tratamiento de la AIJ

Tratamiento farmacológico de la AIJ no-sistémica





ARD

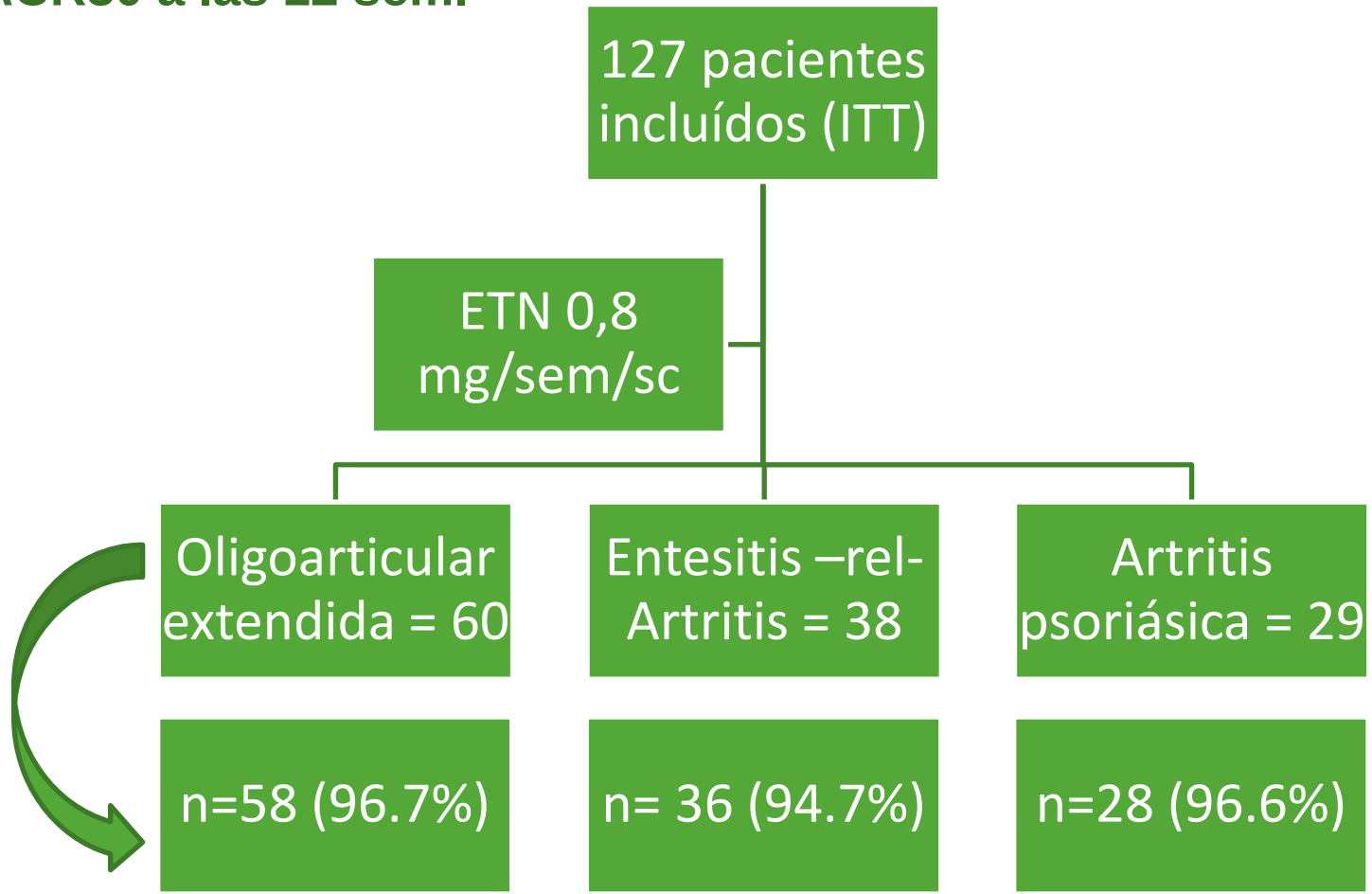
Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study

Gerd Horneff, Ruben Burgos-Vargas, Tamas Constantin, et al.

Ann Rheum Dis May, 2013

The Clipper study

Objetivo primario: porcentaje de pacientes que alcanzan pACR30 a las 12 sem.



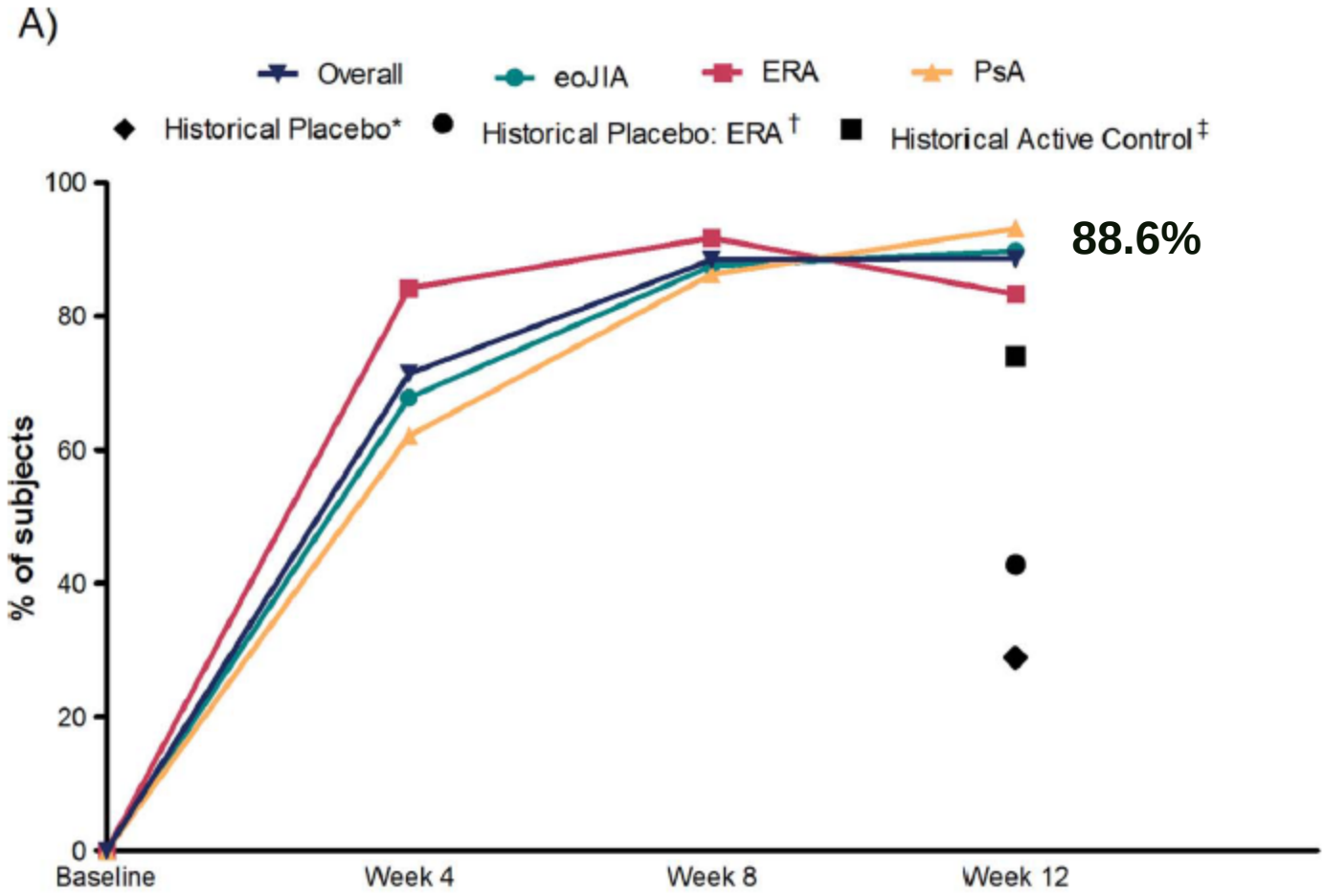
Ann Rheum Dis May, 2013

The Clipper study

Características de la enfermedad	OligoA n= 60	ERA n=38	A.Psoriásica n= 29	Todos n=127
VAS actividad enfermedad	5.0 (1.8)	5.4 (1.9)	4.7 (1.4)	5.0 (1.8)
VAS padres: estado general	4.8 (2.4)	5.4 (2.3)	4.6 (2.2)	5.0 (2.3)
Nº articulaciones activas	7.6 (5.1)	5.2 (3.6)	7.0 (4.3)	6.7 (4.6)
Nº articulaciones limitadas	6.3 (4.4)	4.8 (4.0)	5.6 (4.1)	5.7 (4.2)
Nº articulaciones dolorosas	5.5 (4.1)	6.7 (4.9)	7.8 (7.0)	6.4 (5.2)
Nº articulaciones inflamadas	6.5 (4.8)	3.8 (2.8)	5.6 (3.7)	5.5 (4.2)
PCR, mg/L	**6.3 (10.6)**	**15.3 (21.5)**	**3.2 (4.7)**	8.2 (14.7)
CHAQ	0.9 (0.7)	0.7 (0.5)	0.7 (0.6)	0.8 (0.6)
VAS padres: dolor	4.8 (2.6)	5.8 (2.5)	4.6 (2.3)	5.1 (2.5)
Rigidez matutina, minutos	**72.8 (97.2)**	**89.3 (128.9)**	**54.3 (54.2)**	73.5 (100.6)

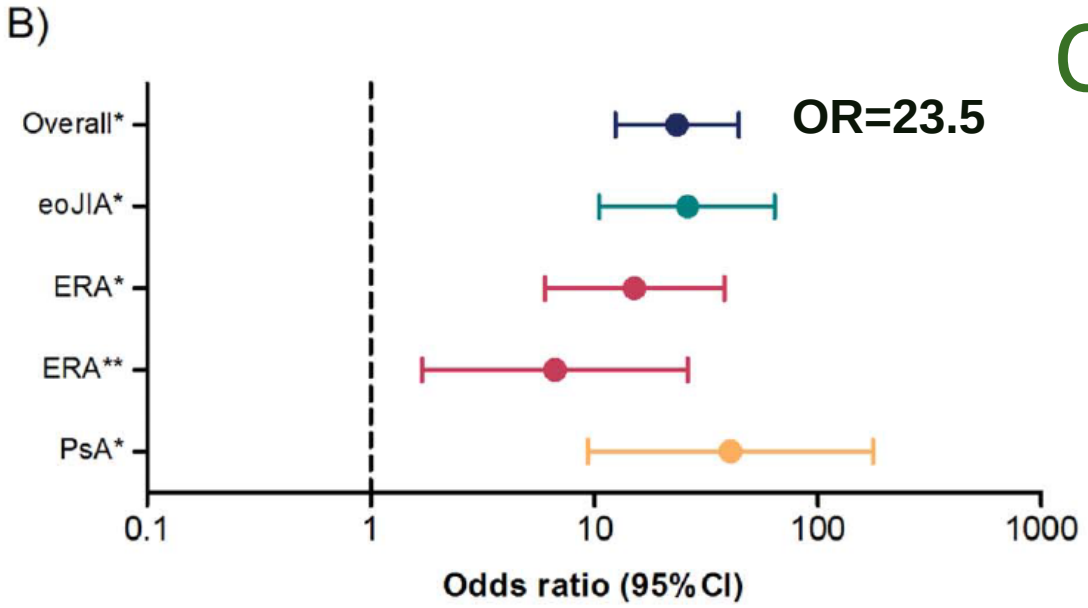
Ann Rheum Dis May, 2013

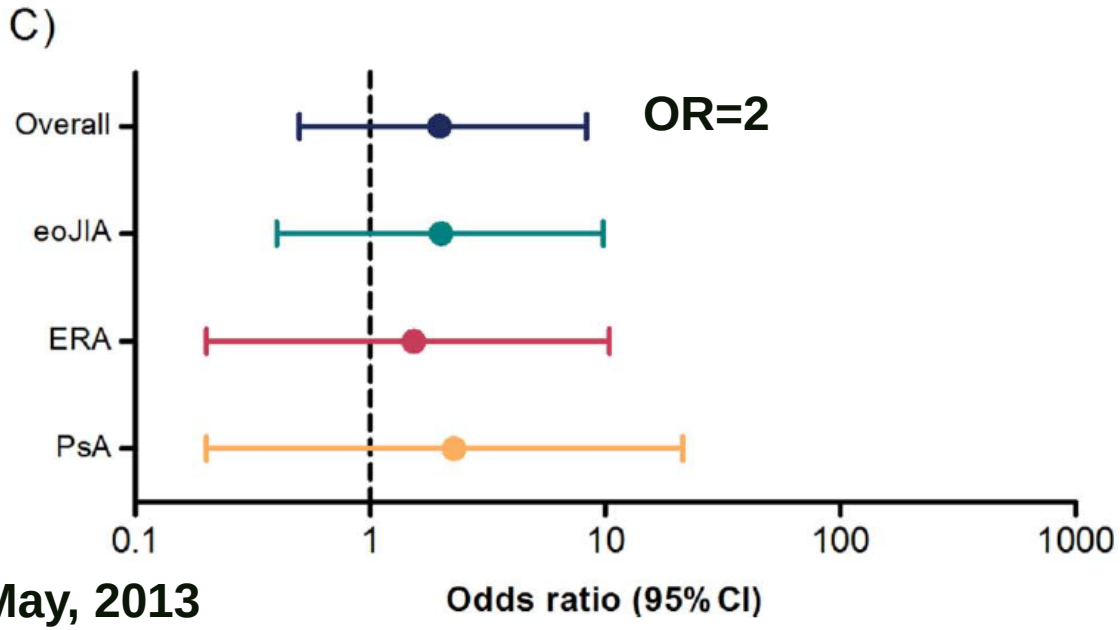
The Clipper study



Ann Rheum Dis May, 2013

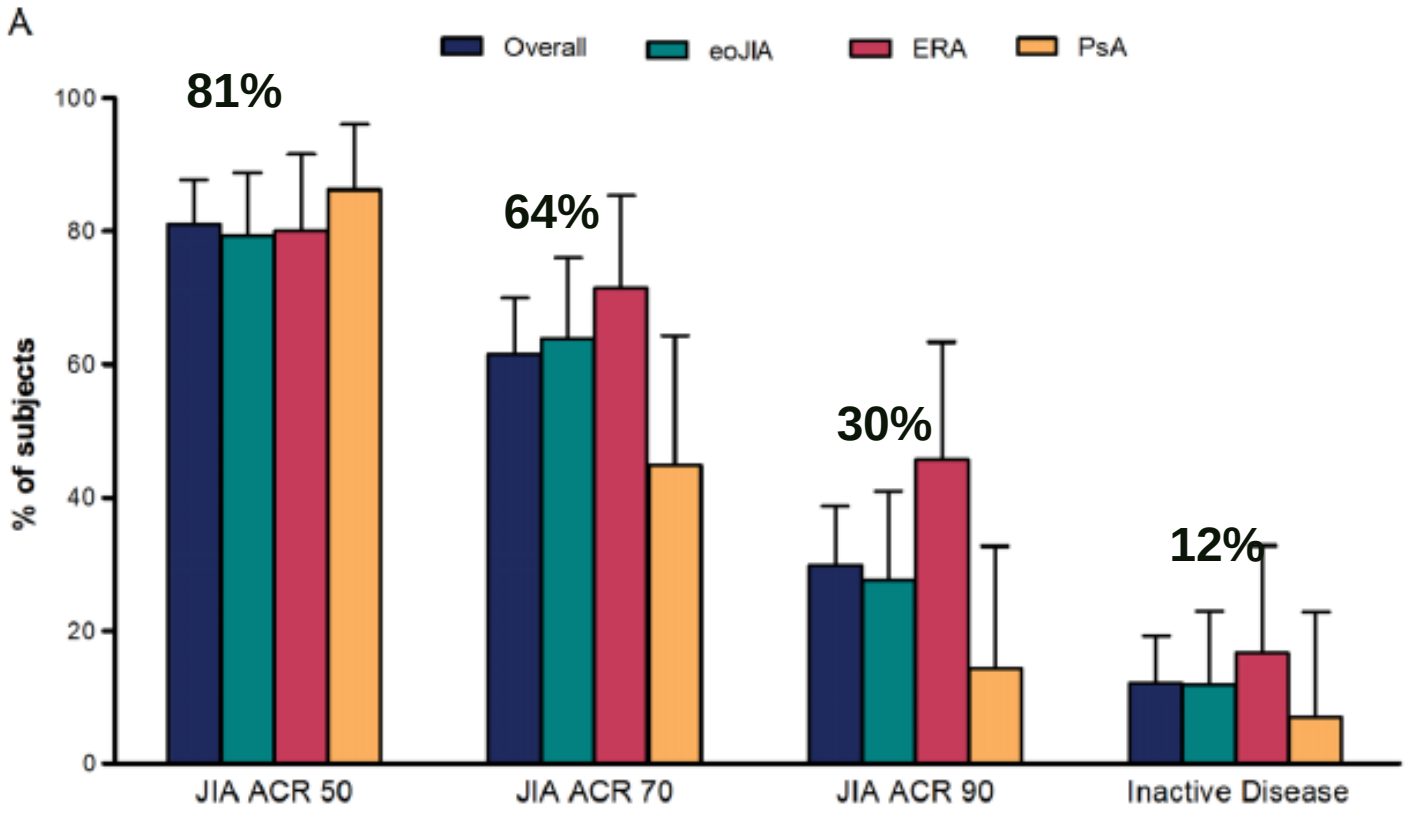
Clipper





Ann Rheum Dis May, 2013

The Clipper study



Ann Rheum Dis May, 2013

ORIGINAL ARTICLE

Safety and efficacy of tocilizumab, an anti-IL-6-receptor monoclonal antibody, in patients with polyarticular-course juvenile idiopathic arthritis

Tomoyuki Imagawa · Shumpei Yokota · Masaaki Mori · Takako Miyamae · Syuji Takei · Hiroyuki Imanaka · Yasuhito Nerome · Naomi Iwata · Takuji Murata · Mari Miyoshi · Norihiro Nishimoto · Tadamitsu Kishimoto

Mod Rheumatol, 2012

Objetivo primario: porcentaje de pacientes que alcanzan pACR30 a las 12 y 48 sem.

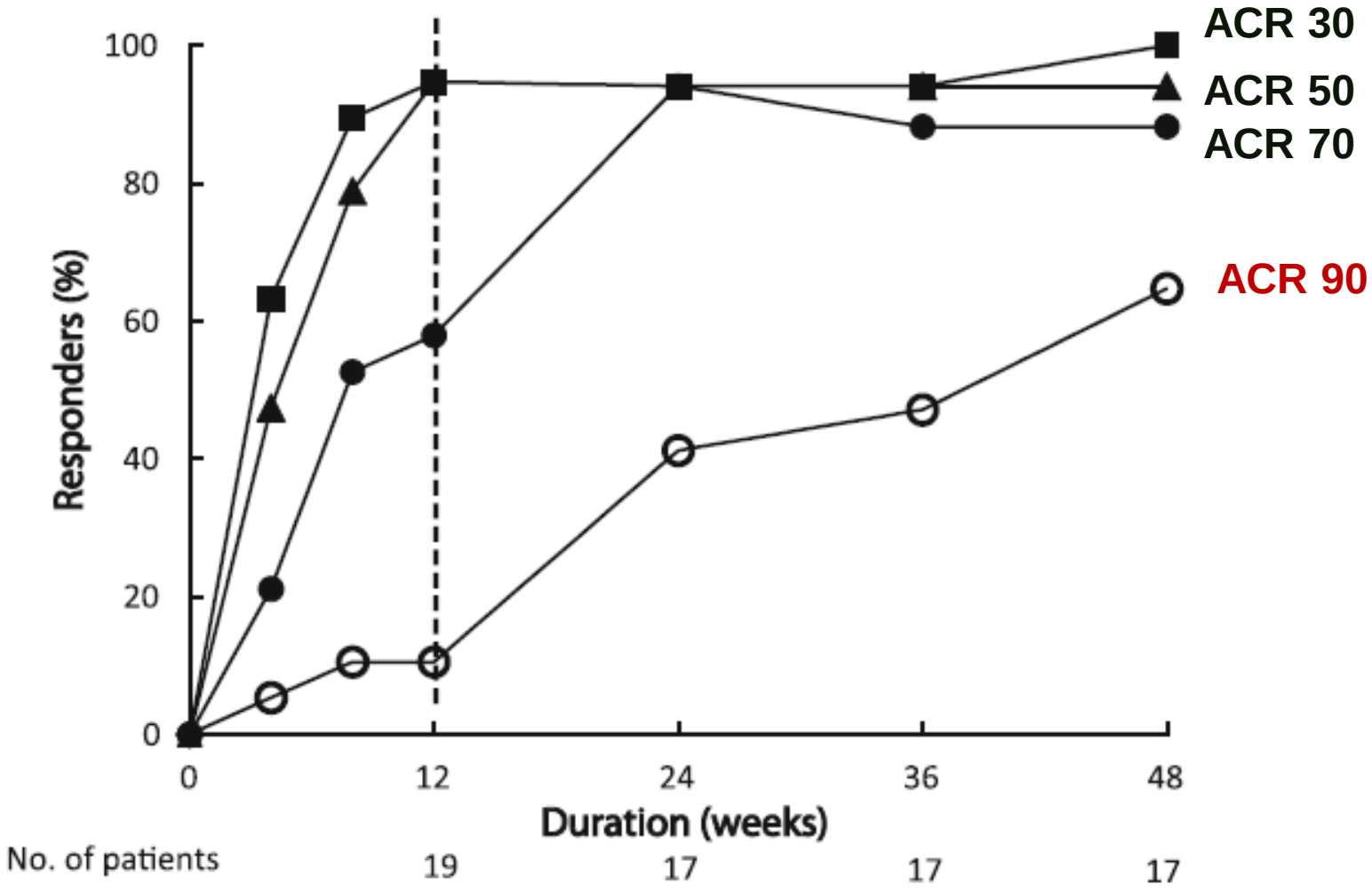
Pacientes incluídos =19

Pacientes fase inicial =19

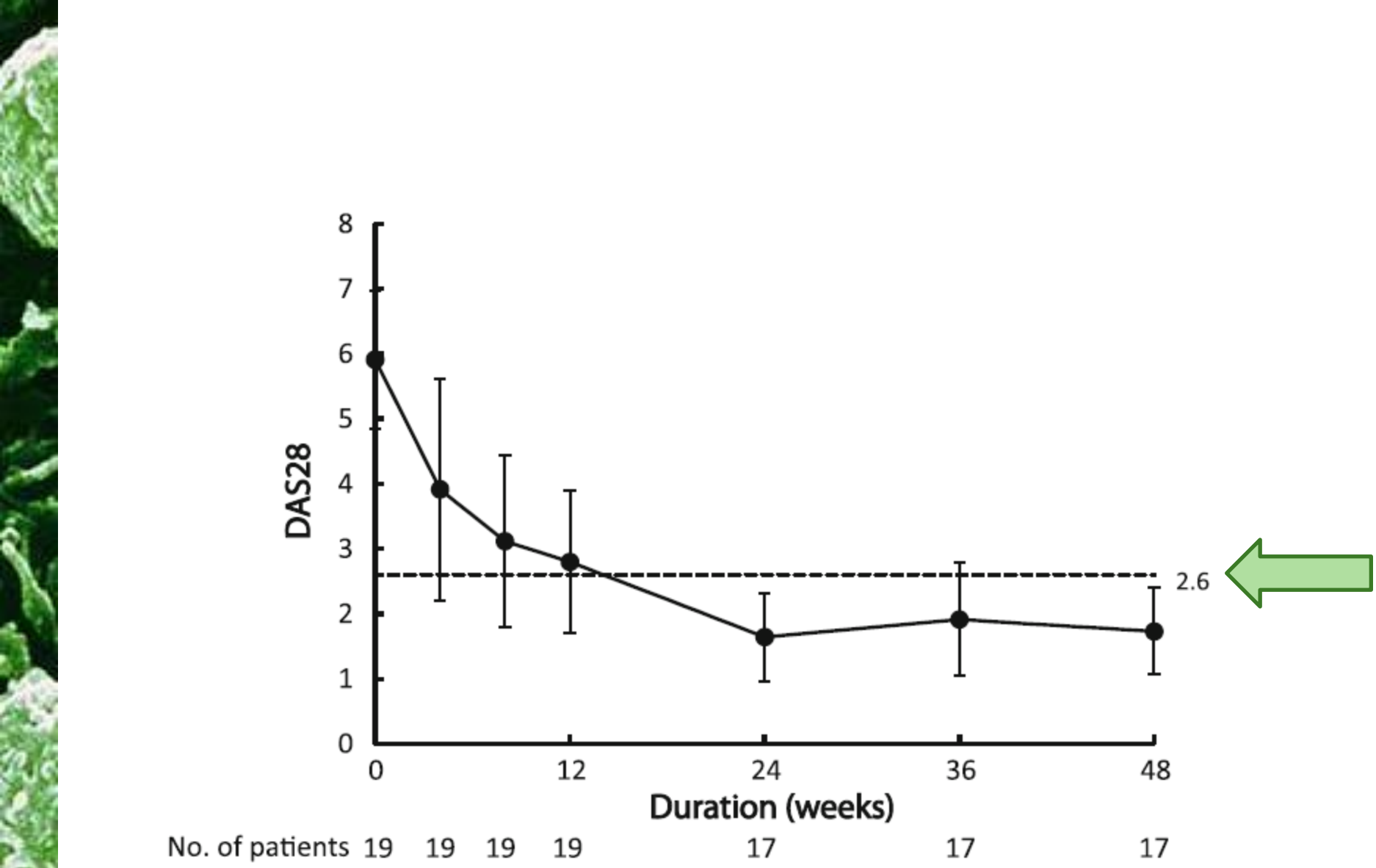
Continuación estudio = 17

un paciente sólo respuesta parcial; un paciente HACA

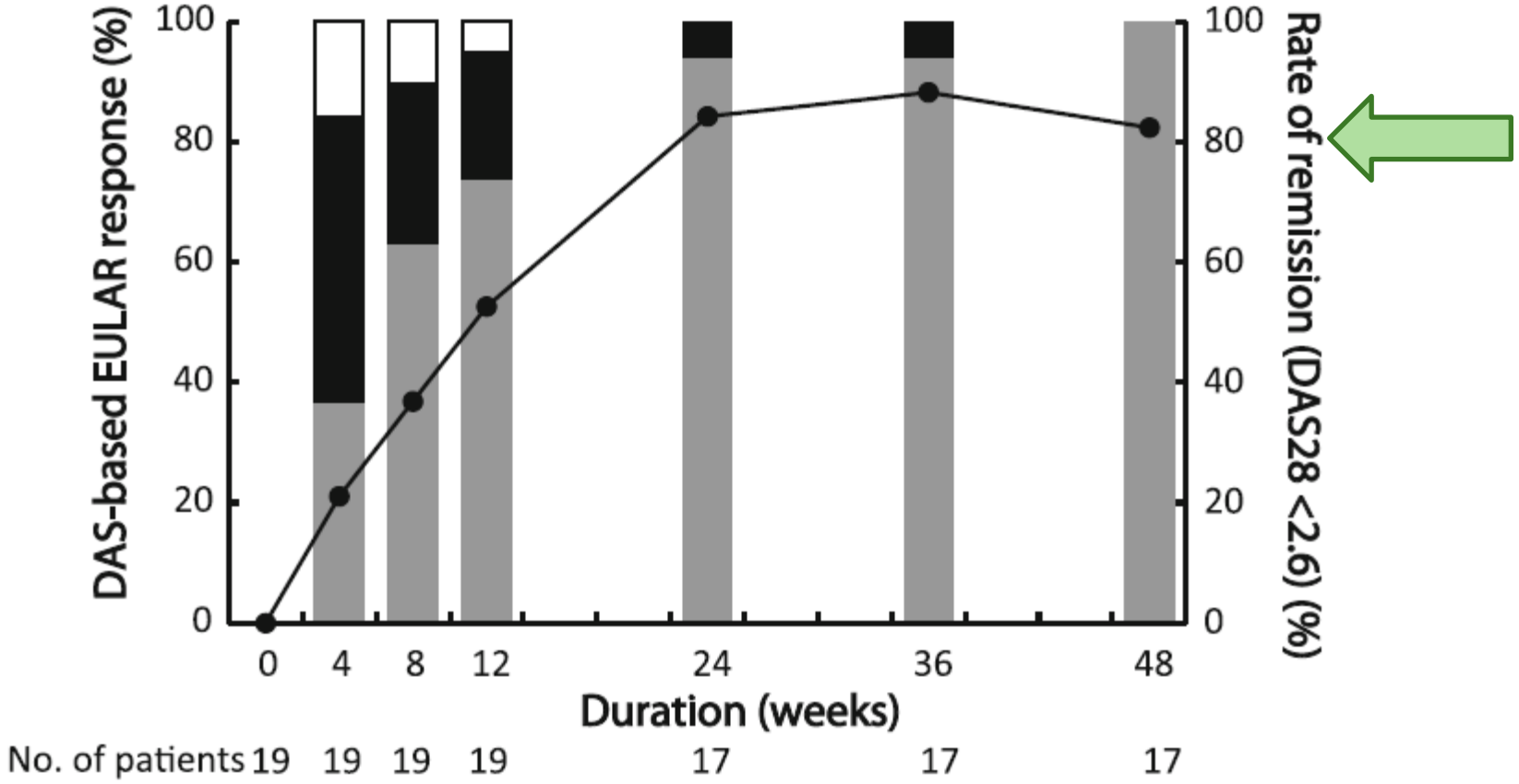
Mod Rheumatol, 2012



Mod Rheumatol, 2012



Mod Rheumatol, 2012



Mod Rheumatol, 2012

Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons

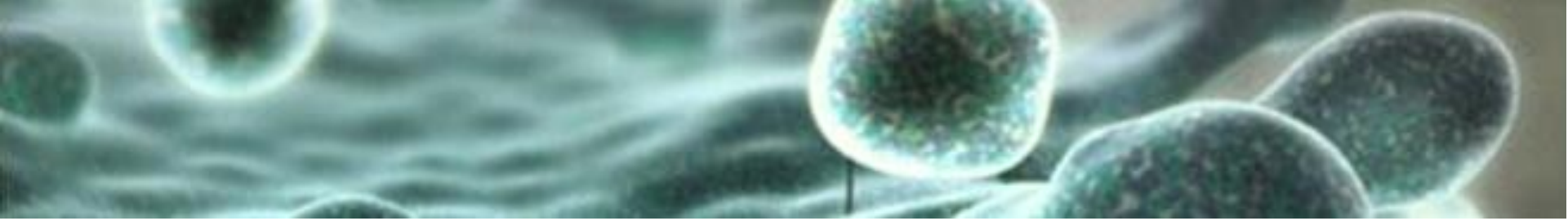
Marieke H Otten, Janneke Anink, Sandra Spronk, et al.



Ann Rheum Dis, 2013

¿Existe una estrategia mejor para el tratamiento de la forma poliarticular?





- Estudio ACUTE
- Estudio TREAT

Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE–JIA): a multicentre randomised open-label clinical trial

Pirjo Tynjälä, Paula Vähäsalo, Maarit Tarkiainen, et al.

Ann Rheum Dis, May 2011

ACUTE, OBJETIVO PRIMARIO = Alcanzar ACR pedi 75



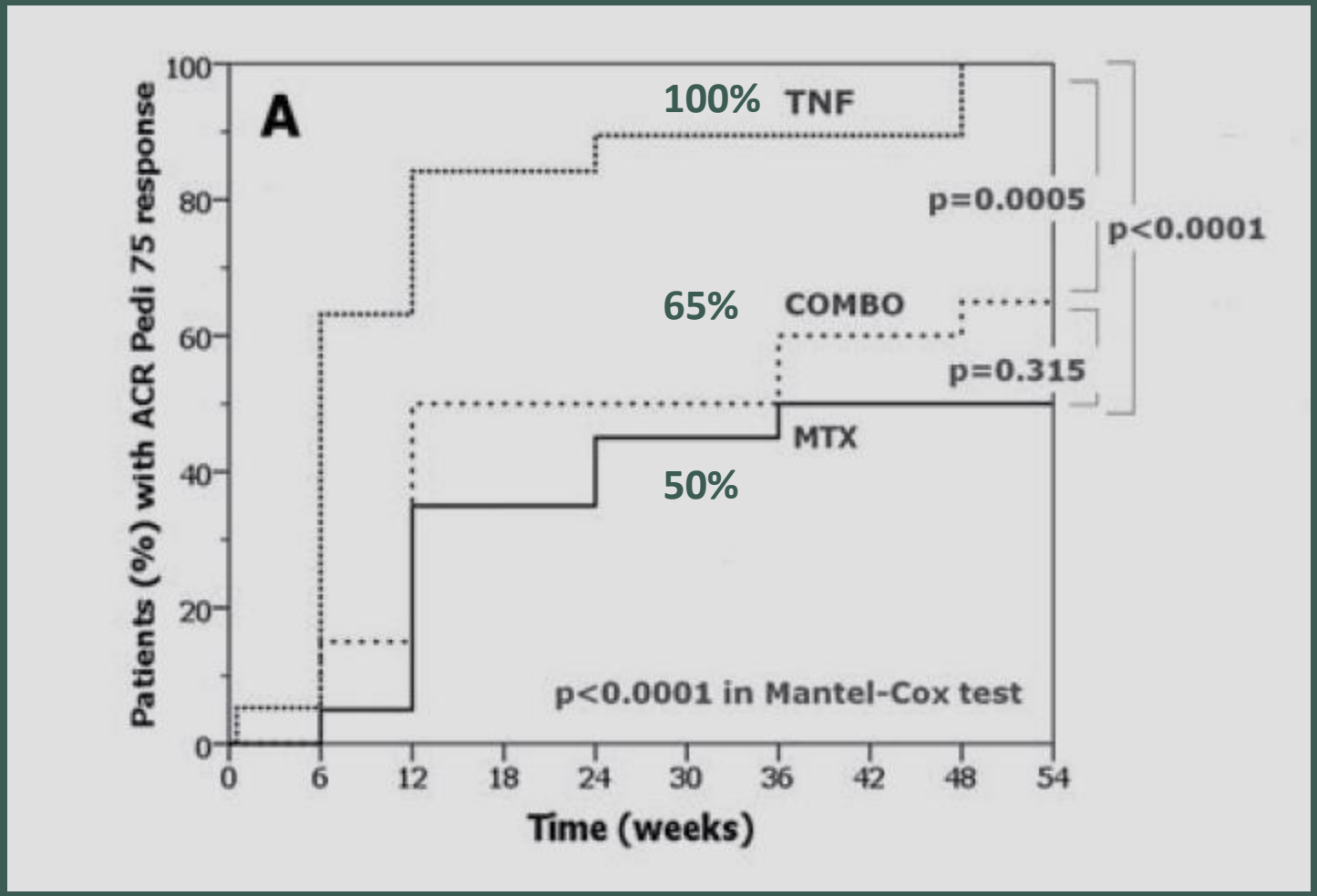
Ann Rheum Dis, May 2011

ACUTE

Datos basales de la enfermedad	TNF n= 19	COMBO n=20	MTX n= 20	Valor de p
Edad (X±DS, mediana)	10.5±3.1(11.6)	8.3±2.7 (7.7)	10.1±3.5 (9.6)	0.07
Duración artritis (meses)	**1.5±0.3(1.5)**	**2.3±1.8(1.5)**	**1.8±1.1(1.5)**	0.44
VAS del médico, actividad enfermedad (mm)	49±18	55±19	60±18	0.13
VAS padres/pacientes, estado general (mm)	**18±19**	**31±26**	**41±25***	0.009
Nº articulaciones activas	18±10	17±10	18±12	0.81
Nº articulaciones dolorosas y/o limitadas	11±8	10±8	10±7	0.13
VSG	28±20	41±33	39±30	0.53
CHAQ	**0.51±0.55**	**0.71±0.63**	**1.06±0.6***	0.02

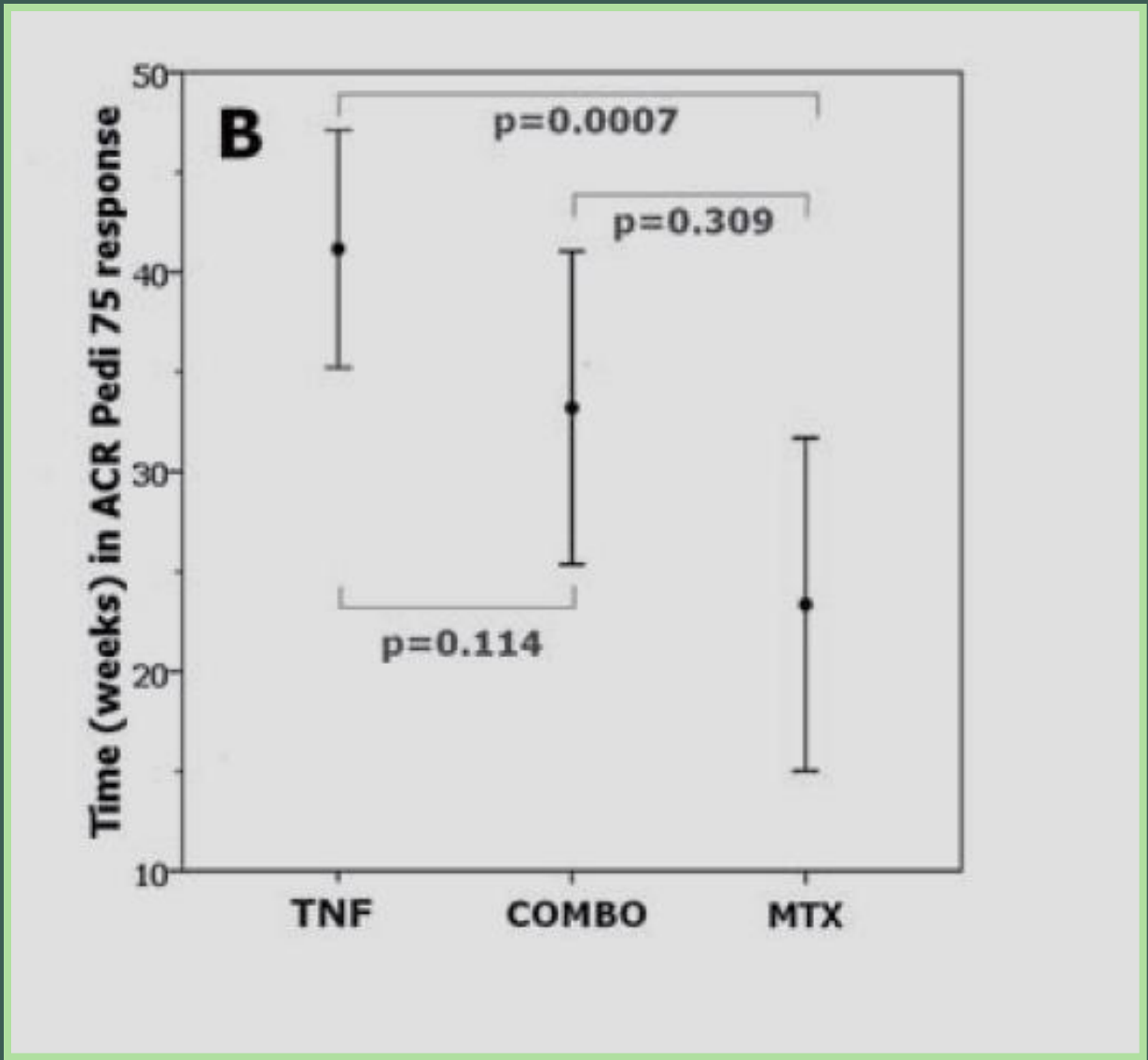
Ann Rheum Dis, May 2011

ACUTE



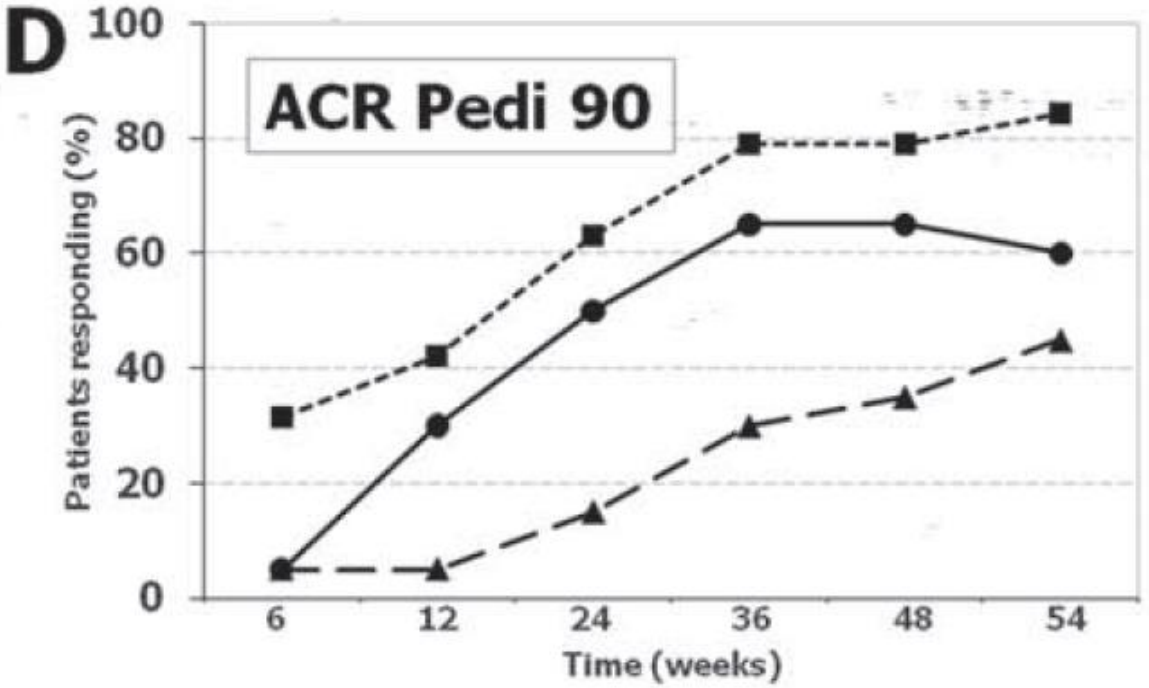
Ann Rheum Dis, May 2011

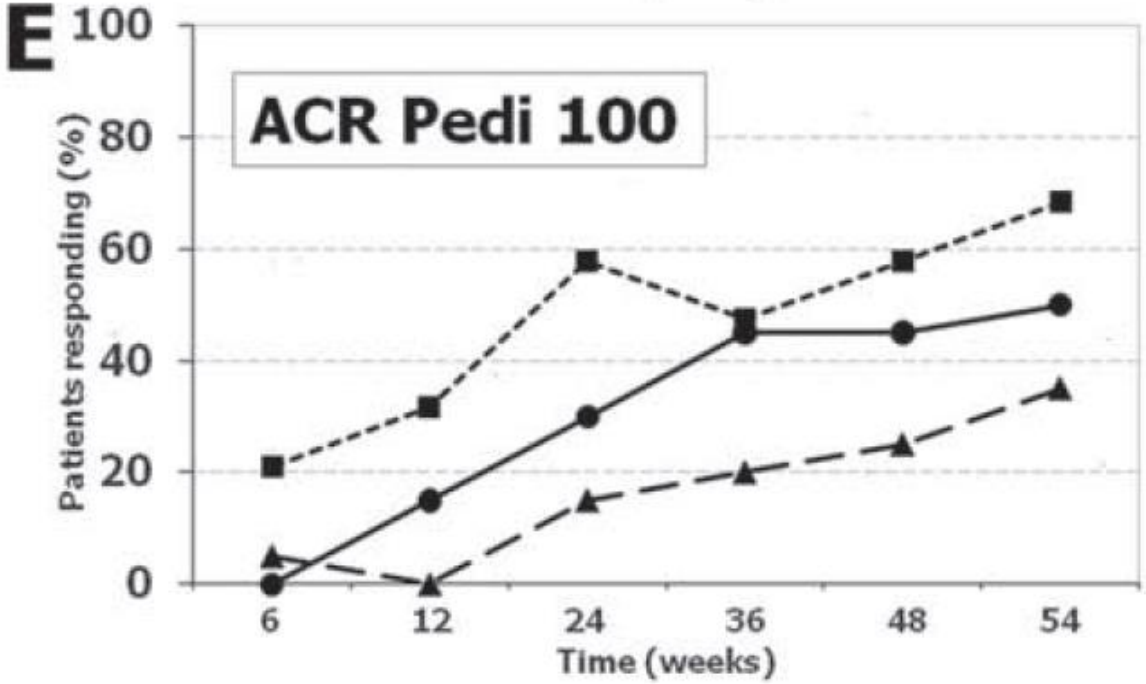
ACUTE



Ann Rheum Dis, May 2011

ACUTE


D
ACR Pedi 90
Patients responding (%)
0
20
40
60
80
100
6
12
24
36
48
54
Time (weeks)

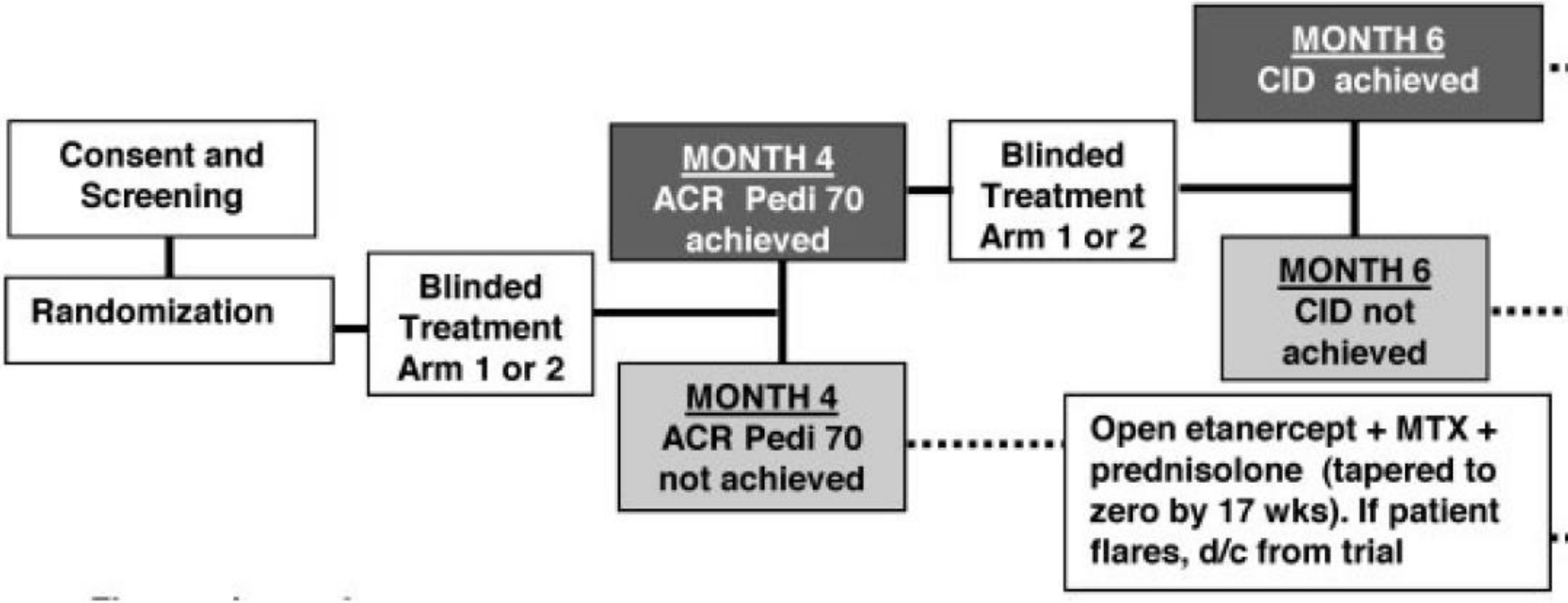

E
ACR Pedi 100
Patients responding (%)
0
20
40
60
80
100
6
12
24
36
48
54
Time (weeks)

Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis

Carol A. Wallace,[1] Edward H. Giannini,[2] Steven J. Spalding,[3] Philip J. Hashkes,[3] Kathleen M. O'Neil,[4] Andrew S. Zeft,[5] Ilona S. Szer,[6] Sarah Ringold,[1] Hermine I. Brunner,[2] Laura E. Schanberg,[7] Robert P. Sundel,[8] Diana Milojevic,[9] Marilynn G. Punaro,[10] Peter Chira,[11] Beth S. Gottlieb,[12] Gloria C. Higgins,[13] Norman T. Ilowite,[14] Yukiko Kimura,[15] Stephanie Hamilton,[1] Anne Johnson,[2] Bin Huang,[2] and Daniel J. Lovell,[2] for the Childhood Arthritis and Rheumatology Research Alliance

Arthritis&Rheum 2012

TREAT, OBJETIVO PRIMARIO = Alcanzar el estado de enfermedad inactiva



Arthritis&Rheum 2012

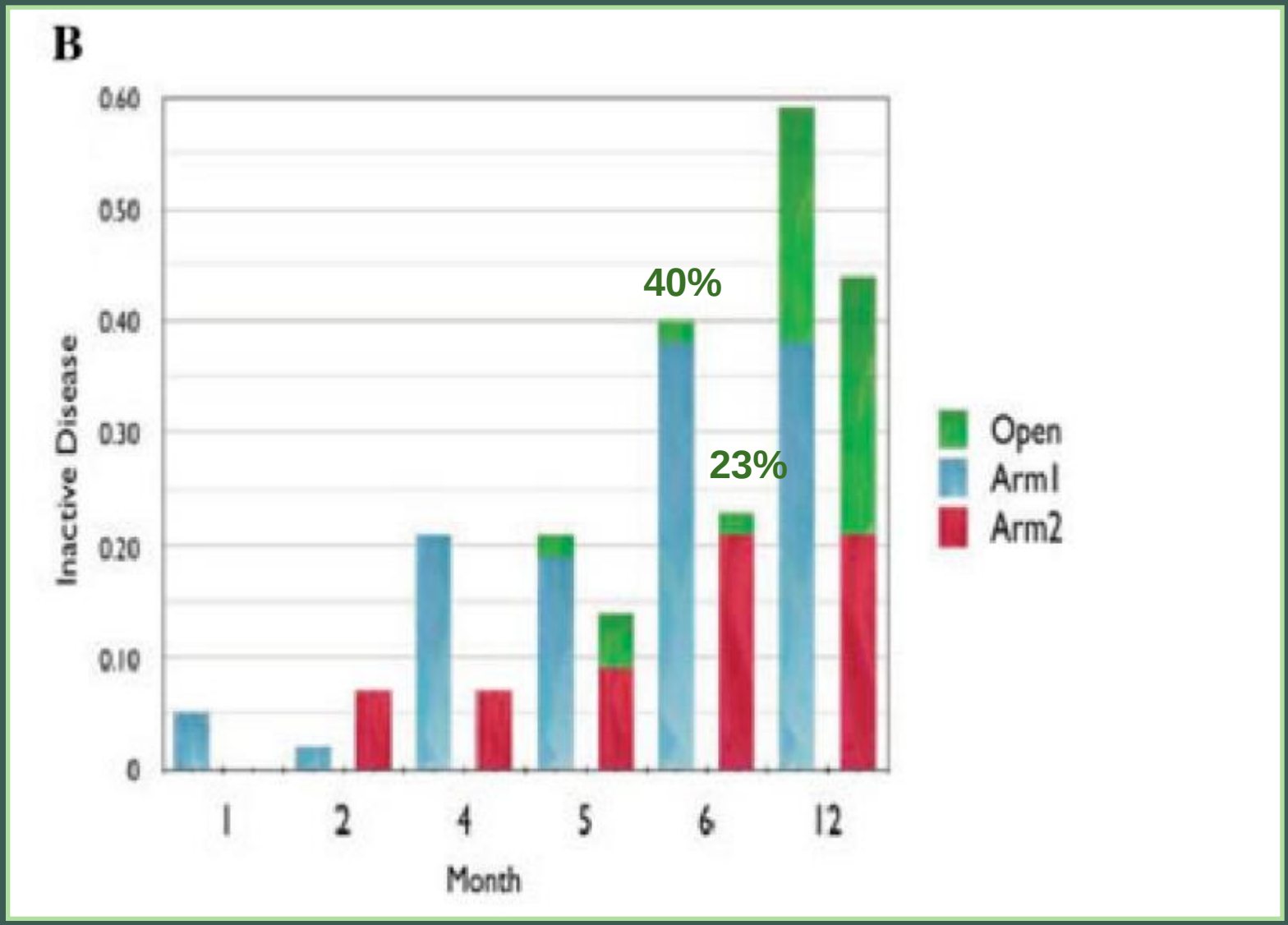
Datos basales y caracterisiticas de la enfermedad	Grupo 1 (MTX+ETN+ Prednisolona)	Grupo 2 (MTX+pETN+ pPrednisolona)
Edad (X±DS)	9.9 ± 4.6	11.1 ± 4.1
Duración artritis (meses)	**4.9 ± 0.5**	**5.2 ± 0.6**
VAS del médico, actividad de la enfermedad	7.0 ± 1.8	7.1 ± 1.9
VAS padres/pacientes, estado general	5.6 ± 2.1	5.2 ± 2.8
Nº articulaciones activas	**18.3 ± 11.0**	**25.5 ± 14.4**
Nº articulaciones dolorosas y/o limitadas	13.6 ± 11.8	16.3 ± 13.2
VSG	29 ± 21	44.6 ± 30
CHAQ	**1.1 ± 0.8**	**1.3 ± 0.7**
FR positivo	14 (33%)	16 (39%)
Anti-CCP positivo	14 (35%)	16 (39%)
ANA positivo	33 (78%)	25 (59.5%

TREAT

	Arm 1 (n = 42)	Arm 2 (n = 43)	χ^2	*P*
Month 4				
Met ACR Pedi 70	30 (71)	19 (44)	6.46	0.011
Did not meet ACR Pedi 70	12 (28)	24 (55)		
Month 6				
Clinical inactive disease achieved	17 (40)	10 (23)	2.91	0.088
Clinical inactive disease not achieved	25 (60)	33 (77)		
Month 12/end of study				
Clinical remission on medication achieved	9 (21)	3 (7)	–	0.053†
Clinical remission on medication not achieved	33 (79)	40 (93)		

Arthritis&Rheum 2012

TREAT



Arthritis&Rheum 2012

CASE REPORT Open Access

Onset of polyarticular juvenile idiopathic arthritis with both anti-cyclic citrullinated peptide antibodies and rheumatoid factor in a 3-year-old girl

Kozo Yasui*†, Sonoko Sakata†, Hideaki Ochi, Shinji Itamura, Kenta Hirai, Mieko Takenaka, Osamu Mitani, Kazunori Ogawa and Kuniaki Iyoda

Pediatric Rheumatol 2012

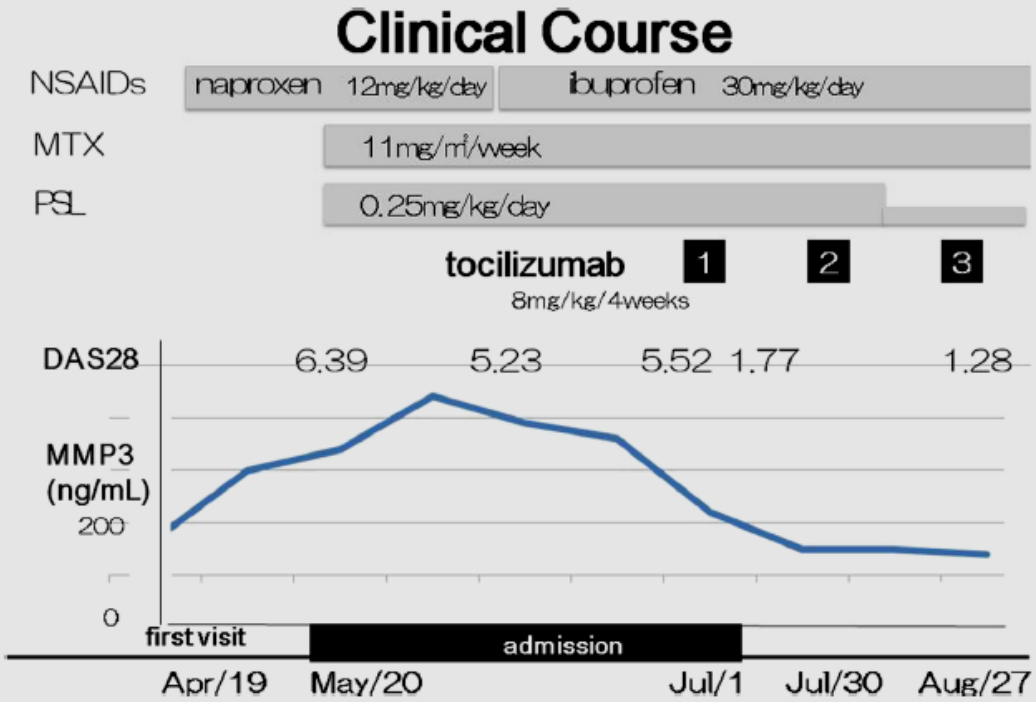
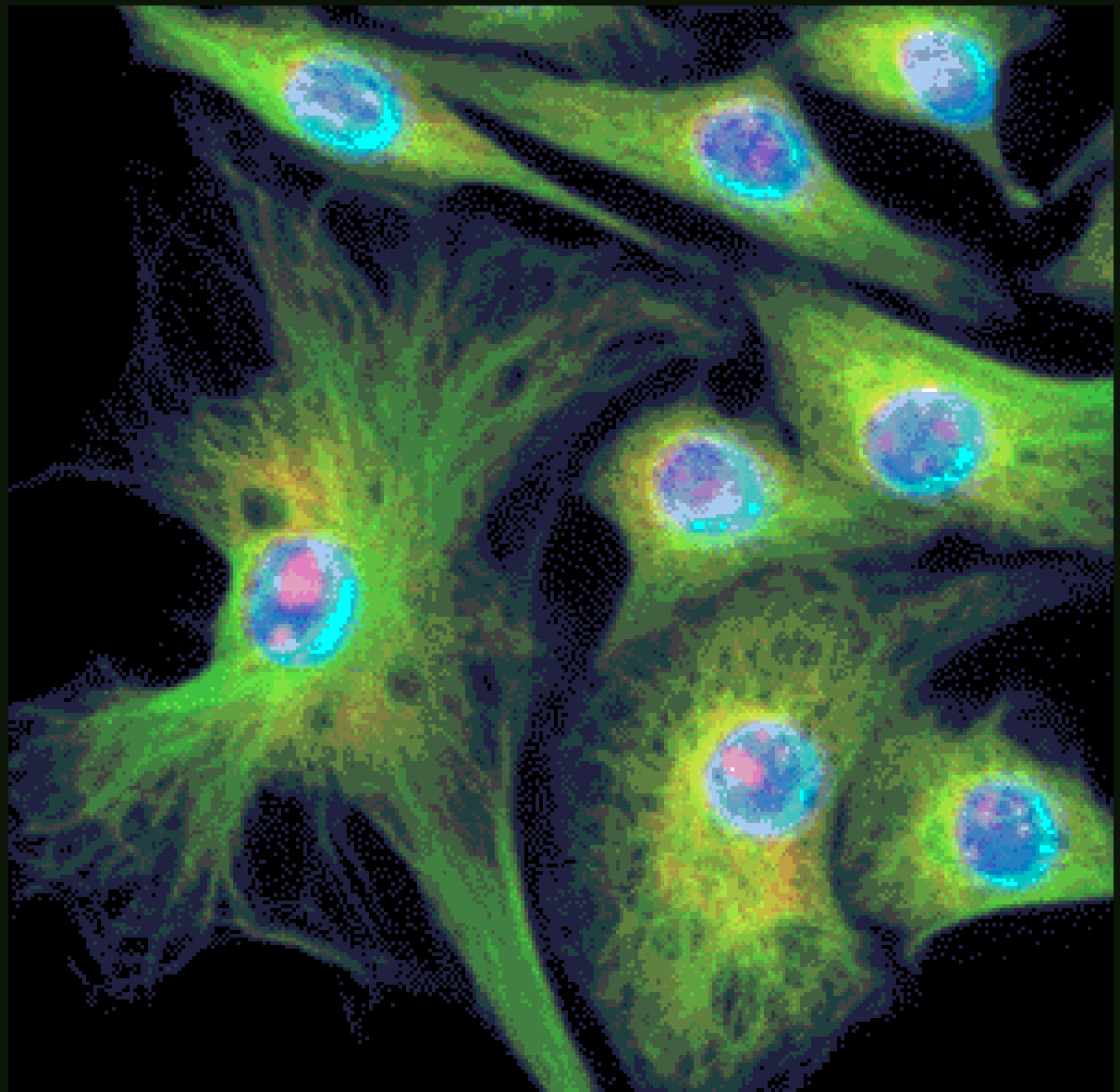


Figure 2 Clinical course of the patient with anti-CCP antibodies and RF. Tocilizumab was administered once every 4 weeks at a dose of 8 mg/kg. Disease activity score (DAS) 28 is defined as $0.56 \times \sqrt{T28} + 0.28 \times \sqrt{S28} + 0.70 \times \ln(ESR) + 0.014$ x general health (GH; patient assessment of disease activity using a 100-mm visual analogue scale with 0=best, 100=worst).

Pediatric Rheumatol 2012

Nuevas aportaciones en la uveítis anterior refractaria asociada a AIJ



THE JOURNAL OF PEDIATRICS • www.jpeds.com

Methotrexate Therapy May Prevent the Onset of Uveitis in Juvenile Idiopathic Arthritis

Charalampia Papadopoulou, MD[1], Mikhail Kostik, MD[1], Marek Böhm, MD[1,2], Juan Carlos Nieto-Gonzalez, MD[1], Maria Isabel Gonzalez-Fernandez, MD[1], Angela Pistorio, MD, PhD[1], Alberto Martini, MD[1,3], and Angelo Ravelli, MD[1,3]

J Pediatr 2013

Table I. Demographic, clinical, and therapeutic characteristics of study patients, considered as a whole and by occurrence of uveitis in the first 2 years of follow-up

Characteristic	All patients (n = 254)	Patients without uveitis (n = 211)	Patients with uveitis (n = 43)	P‡
Demographic data				
Female	209 (82.3)	170 (80.6)	39 (90.7)	.11
Age at disease onset, median (IQR), y	2.4 (1.8-4.8)	2.7 (1.8-5.9)	2.0 (1.5-2.6)	.001
Disease duration at first visit, median (IQR), y	0.3 (0.1-0.5)	0.3 (0.2-0.5)	0.2 (0.1-0.5)	.18
ILAR category				.69
Persistent oligoarthritis	157 (61.8)	127 (60.1)	30 (69.7)	
Extended oligoarthritis	57 (22.4)	50 (23.7)	7 (16.3)	
RF-negative polyarthritis	36 (14.2)	30 (14.2)	6 (14.0)	
Psoriatic arthritis	2 (0.8)	2 (1.0)	0 (0.0)	
Undifferentiated arthritis	2 (0.8)	2 (1.0)	0 (0.0)	
Articular course				.34
Oligoarticular	161 (63.4)	131 (62.1)	30 (69.8)	
Polyarticular	93 (36.6)	80 (37.9)	13 (30.2)	
Patients with positive ANA (n = 251)	230 (91.6)	188 (90.0)	42 (100.0)	.03
Use of medications during follow-up				.31
NSAIDs (n = 253)	158 (62.4)	131 (62.4)	27 (62.8)	.96
IACIs	222 (87.4)	183 (86.7)	39 (90.7)	.47
MTX	86 (33.9)	77 (36.5)	9 (20.9)	.049

J Pediatr 2013

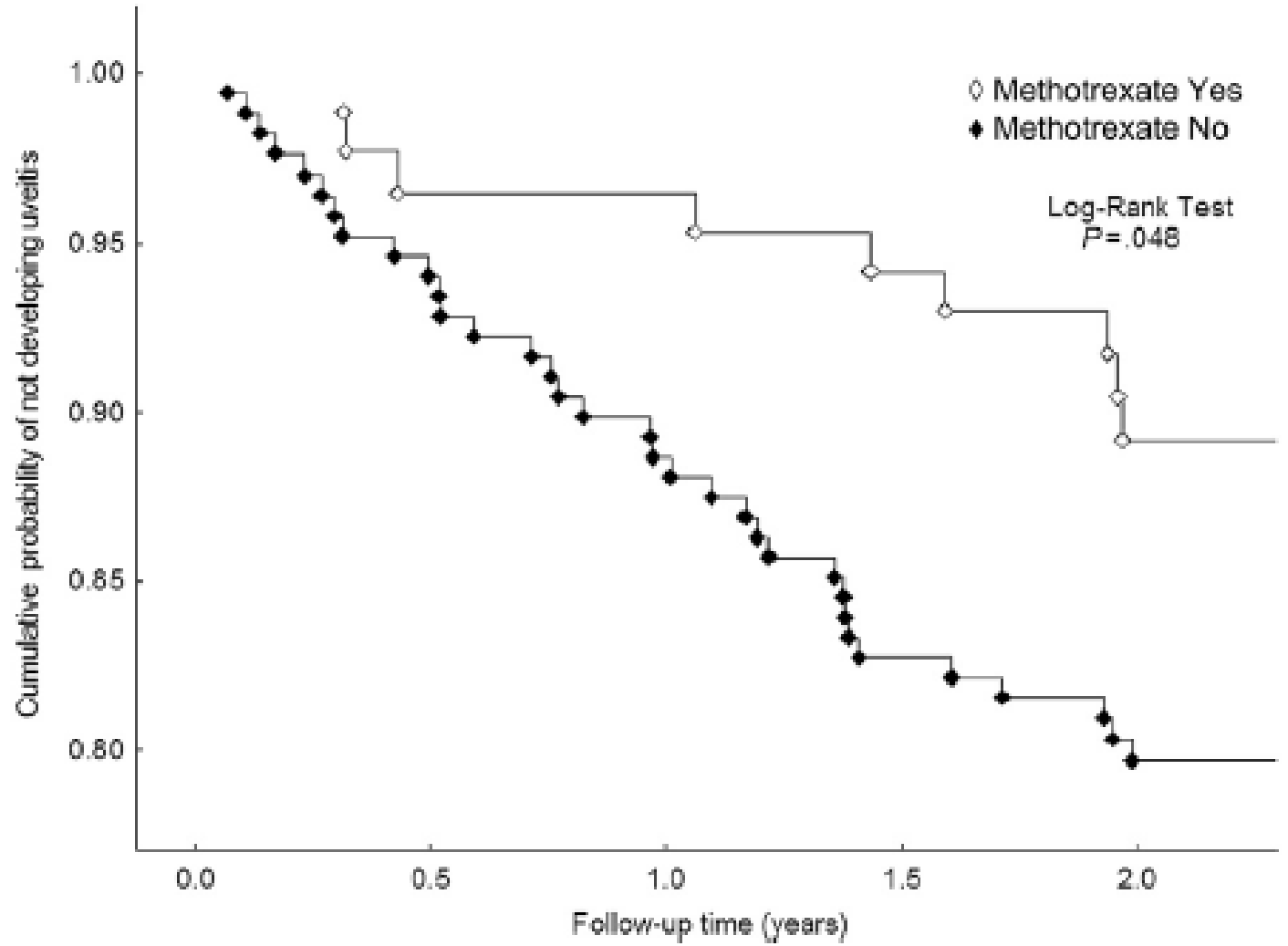


Figure. Cumulative probability of not developing uveitis with MTX therapy; Kaplan-Meier method.

J Pediatr 2013

The Journal of Rheumatology Volume 40, no. 1

Safety and Efficacy of Infliximab and Adalimumab for Refractory Uveitis in Juvenile Idiopathic Arthritis: 1-year Followup Data from the Italian Registry

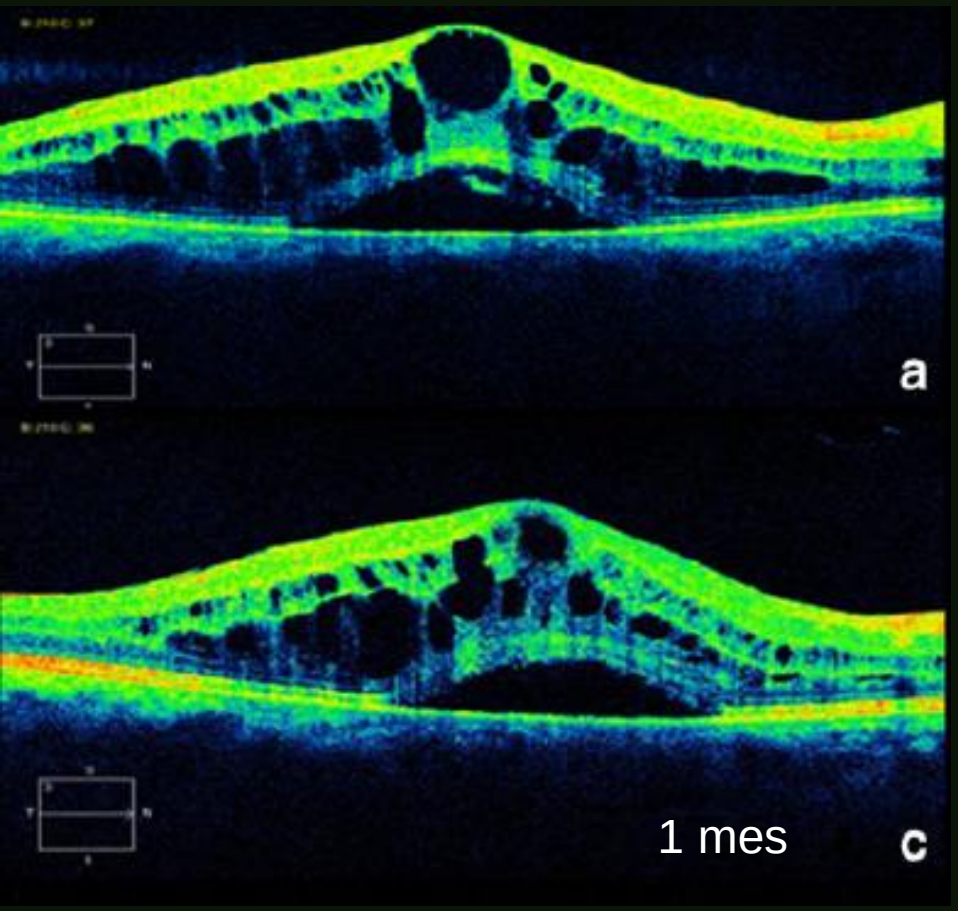
MARIA E. ZANNIN, CAROLINA BIROLO, VALERIA M. GERLONI, ELISABETTA MISEROCCHI, IRENE PONTIKAKI, MARIA P. PAROLI, CLAUDIA BRACAGLIA, ALISON SHARDLOW, FULVIO PARENTIN, ROLANDO CIMAZ, GABRIELE SIMONINI, FERNANDA FALCINI, FABRIZIA CORONA, STEFANIA VIOLA, RICCARDO DE MARCO, LUCIANA BREDA, FRANCESCO LA TORRE, FABIO VITTADELLO, GIORGIA MARTINI and FRANCESCO ZULIAN

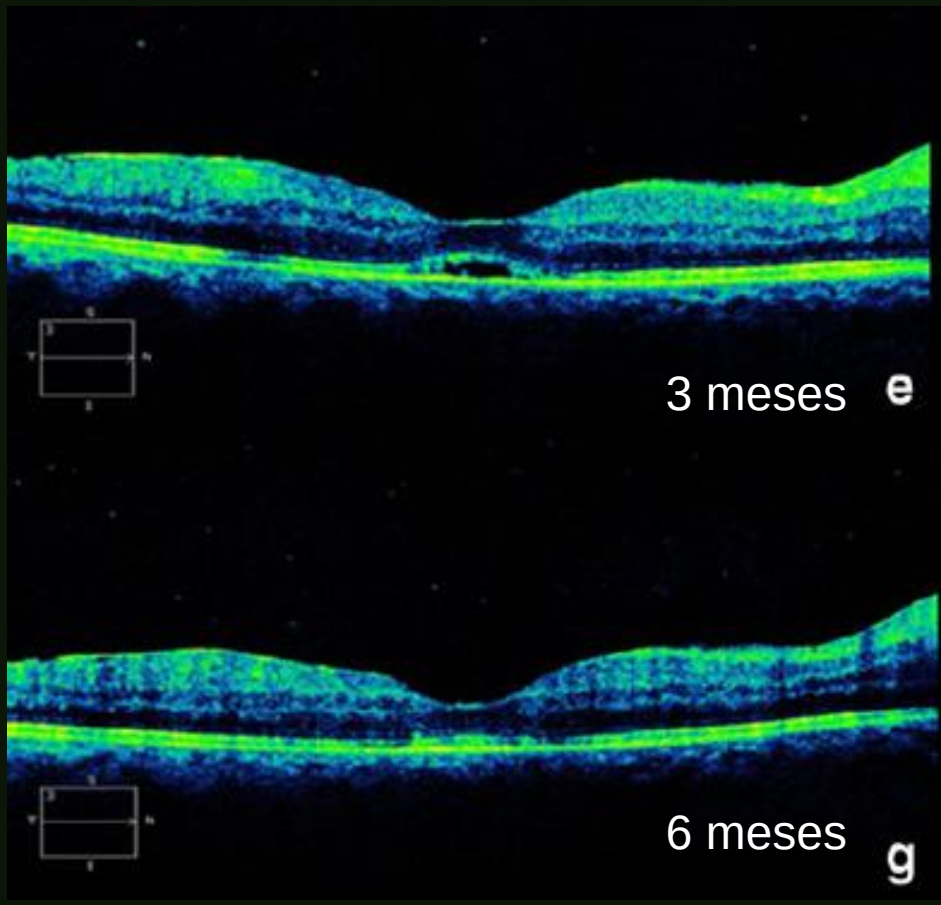
J Pediatr 2013

Tocilizumab treatment for refractory uveitis-related cystoid macular edema

Alfredo Adán · Marina Mesquida · Victor Llorenç · Gerard Espinosa · Blanca Molins · Maria V. Hernández · Laura Pelegrín

Graefes Arch Clin Exp Ophtalmol 2013



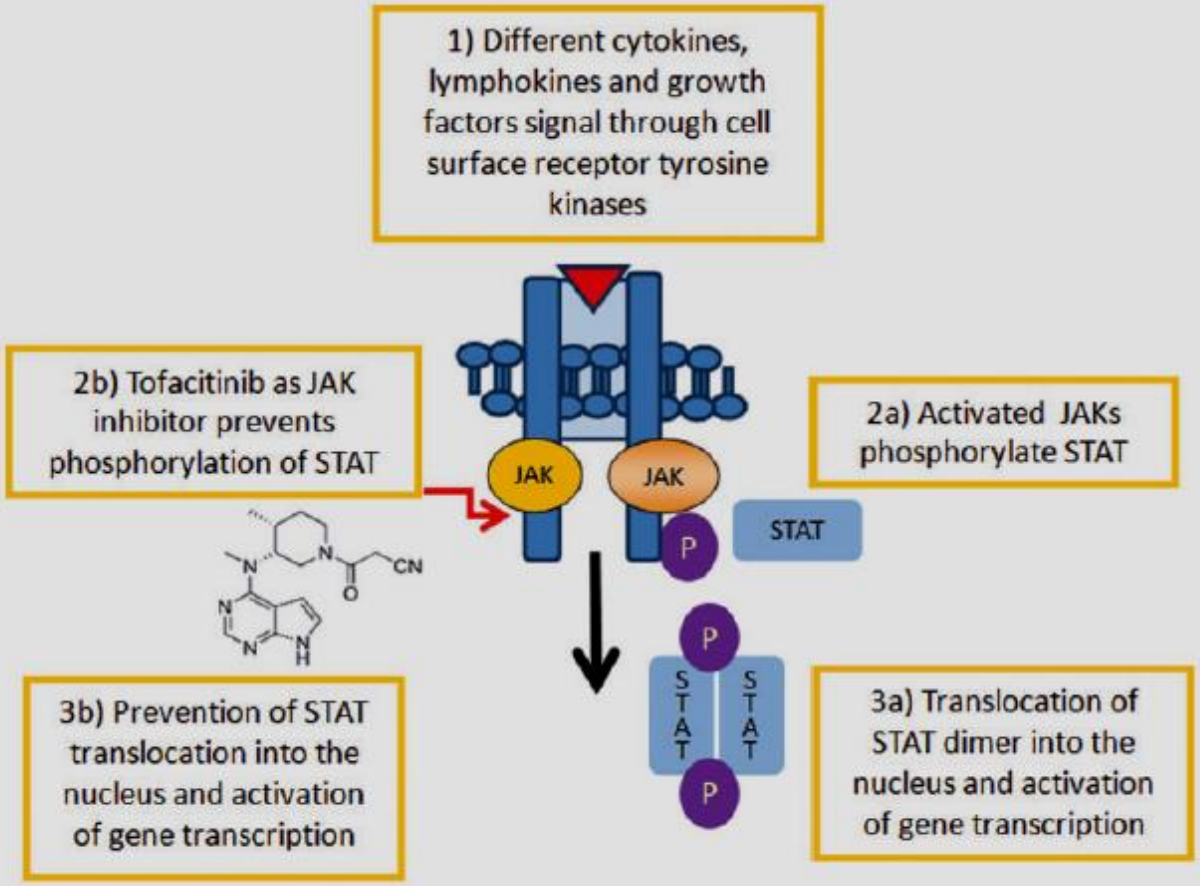


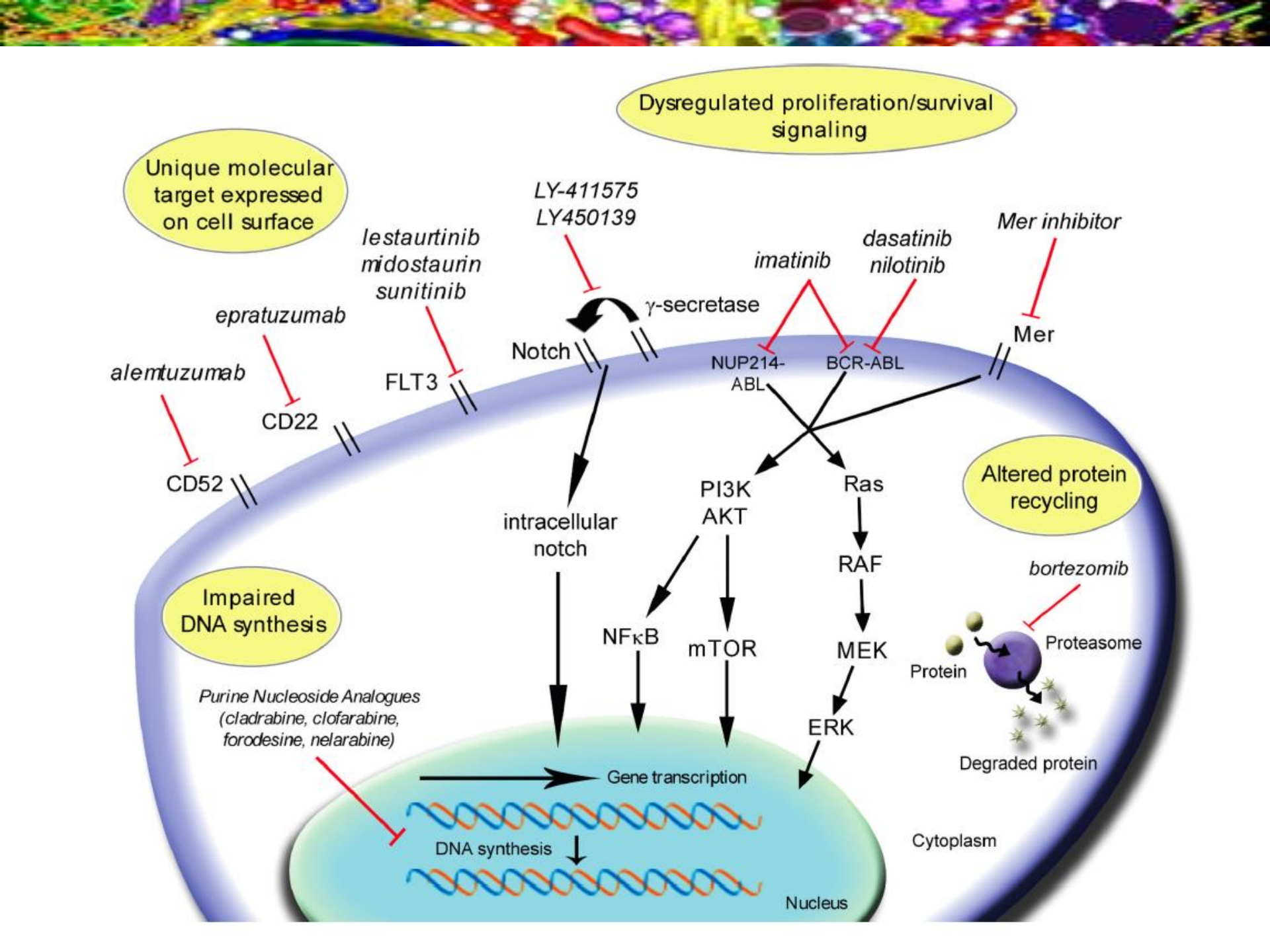
Graefes Arch Clin Exp Ophtalmol 2013

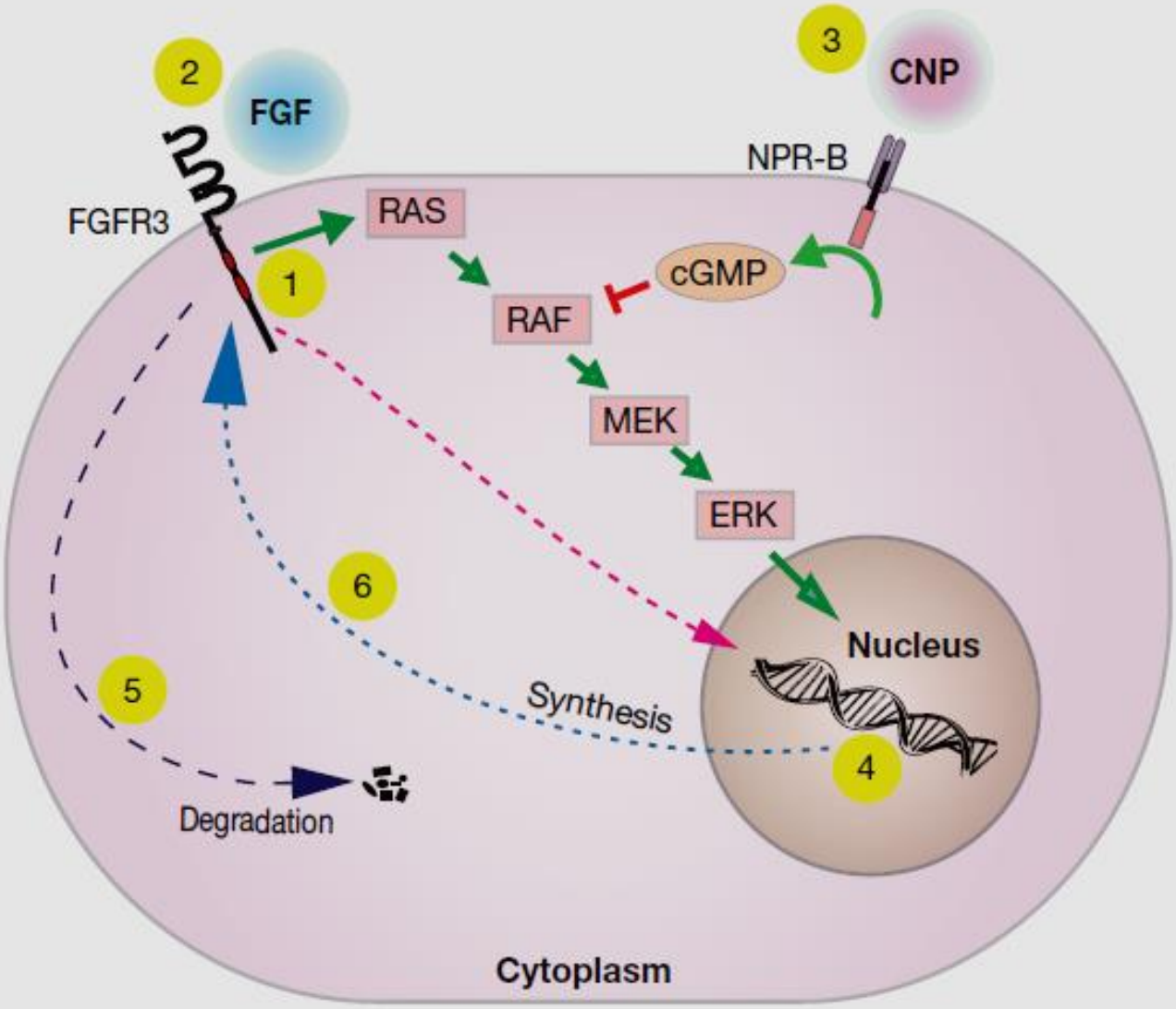


Pequeñas moléculas
“inside the cell”

“inside the cell”




Dysregulated proliferation/survival signaling
Unique molecular target expressed on cell surface
LY-411575
LY450139
lestaurtinib
midostaurin
sunitinib
imatinib
dasatinib
nilotinib
Mer inhibitor
epratuzumab
γ-secretase
Notch
Mer
alemtuzumab
FLT3
NUP214-ABL
BCR-ABL
CD22
CD52
PI3K
AKT
Ras
Altered protein recycling
intracellular notch
RAF
bortezomib
Impaired DNA synthesis
NFκB
mTOR
MEK
Proteasome
Protein
Purine Nucleoside Analogues (cladrabine, clofarabine, forodesine, nelarabine)
ERK
Degraded protein
Gene transcription
DNA synthesis
Cytoplasm
Nucleus



Strategies for therapeutic intervention

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