2010 China-Japan Symposium on Global Clinical Trials and Ethnic Factors

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Ethnic Differences in PK and PD of Anti-Rheumatic Drugs

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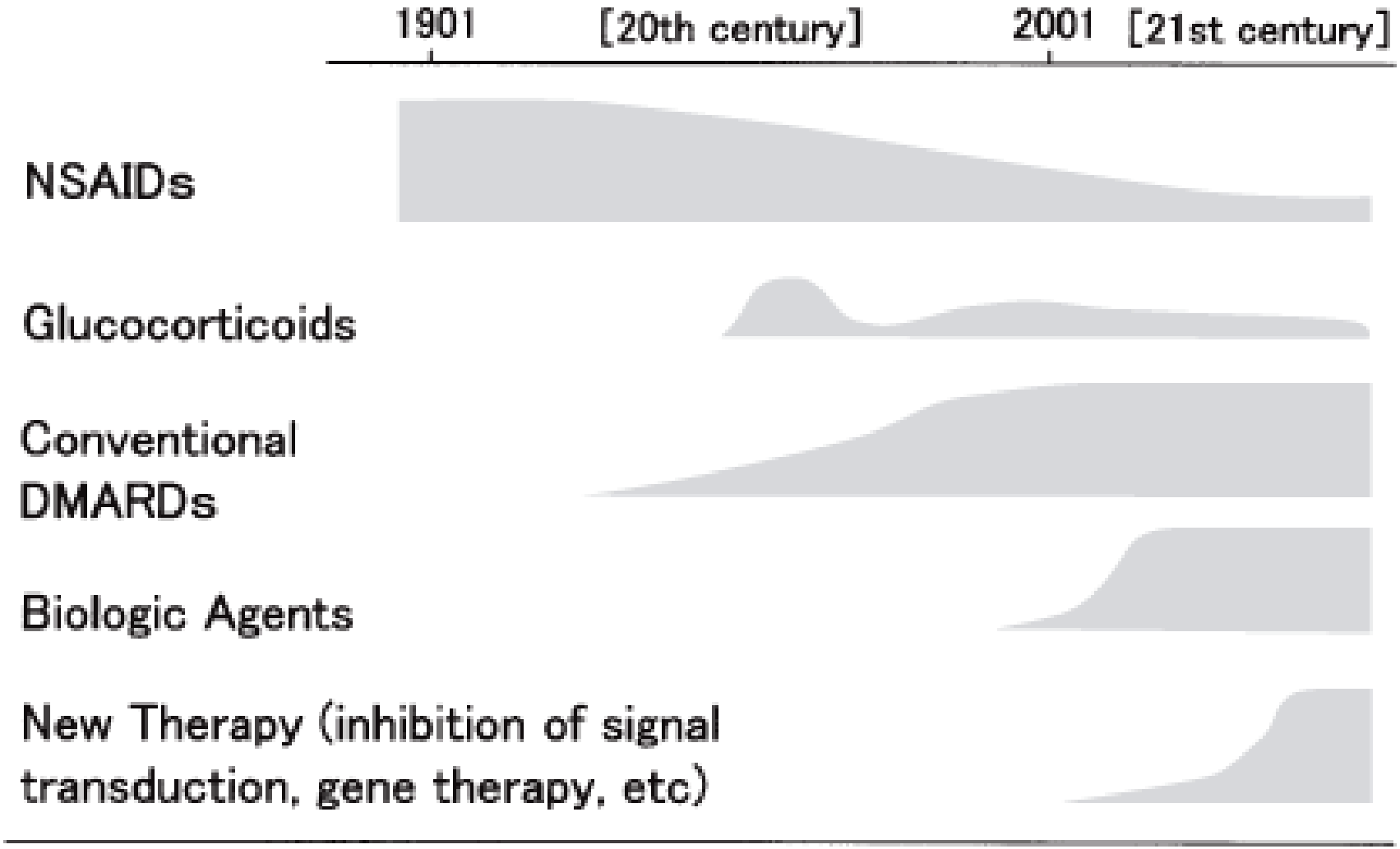
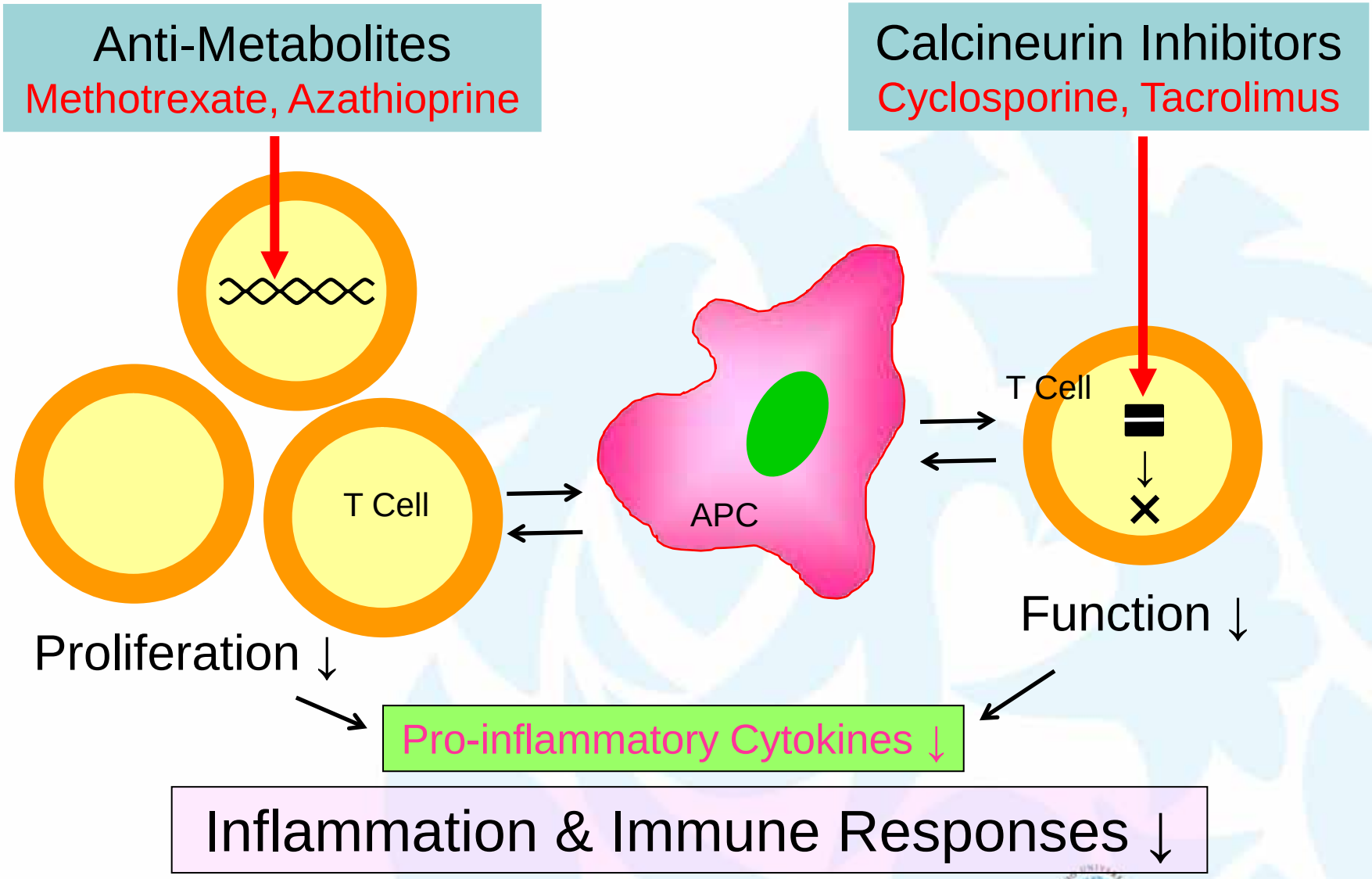
History of Drug Therapy for RA



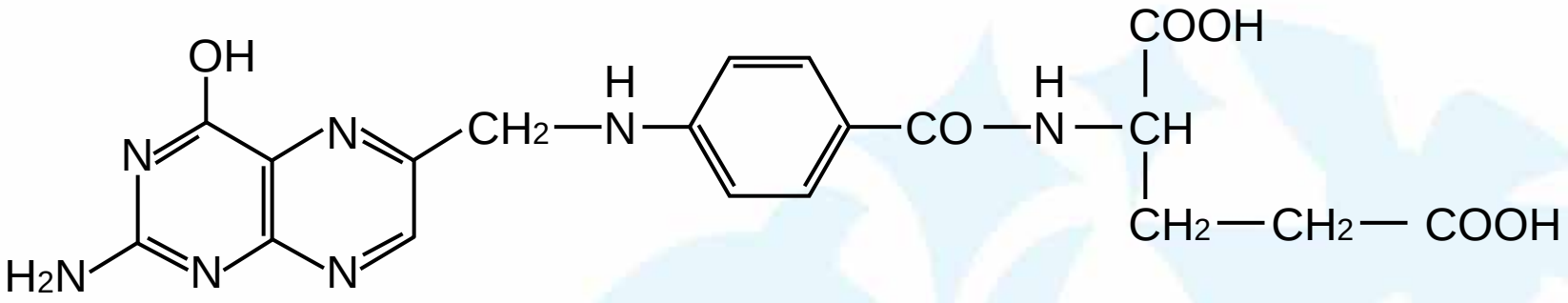
(Kawai S. *J Orthop Sci*. 2003;8:259)

Immunosuppressive Drugs

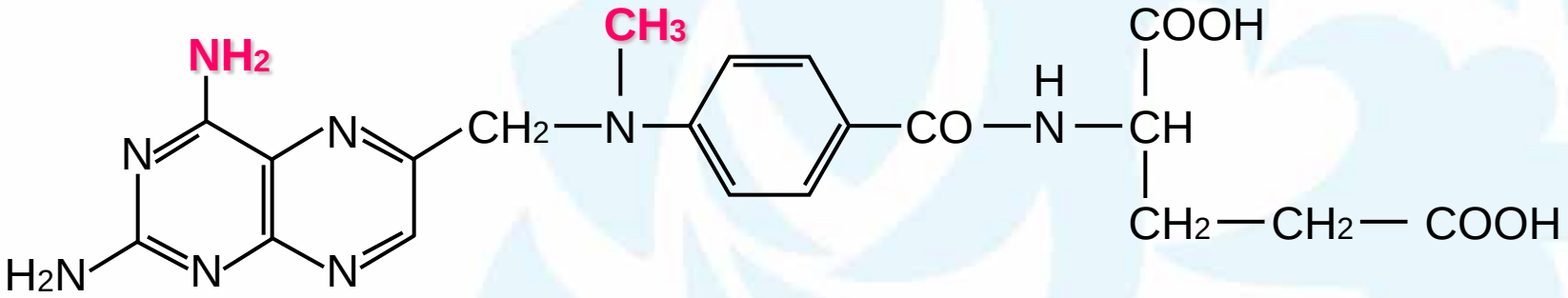
Immunosuppressive Drugs for RA



Folic acid & Methotrexate



Folic acid



Methotrexate

A Chinese Patient (M, 35y.o.) with RA under MTX Therapy of 12.5 mg/w

1st Visit

1 Year After

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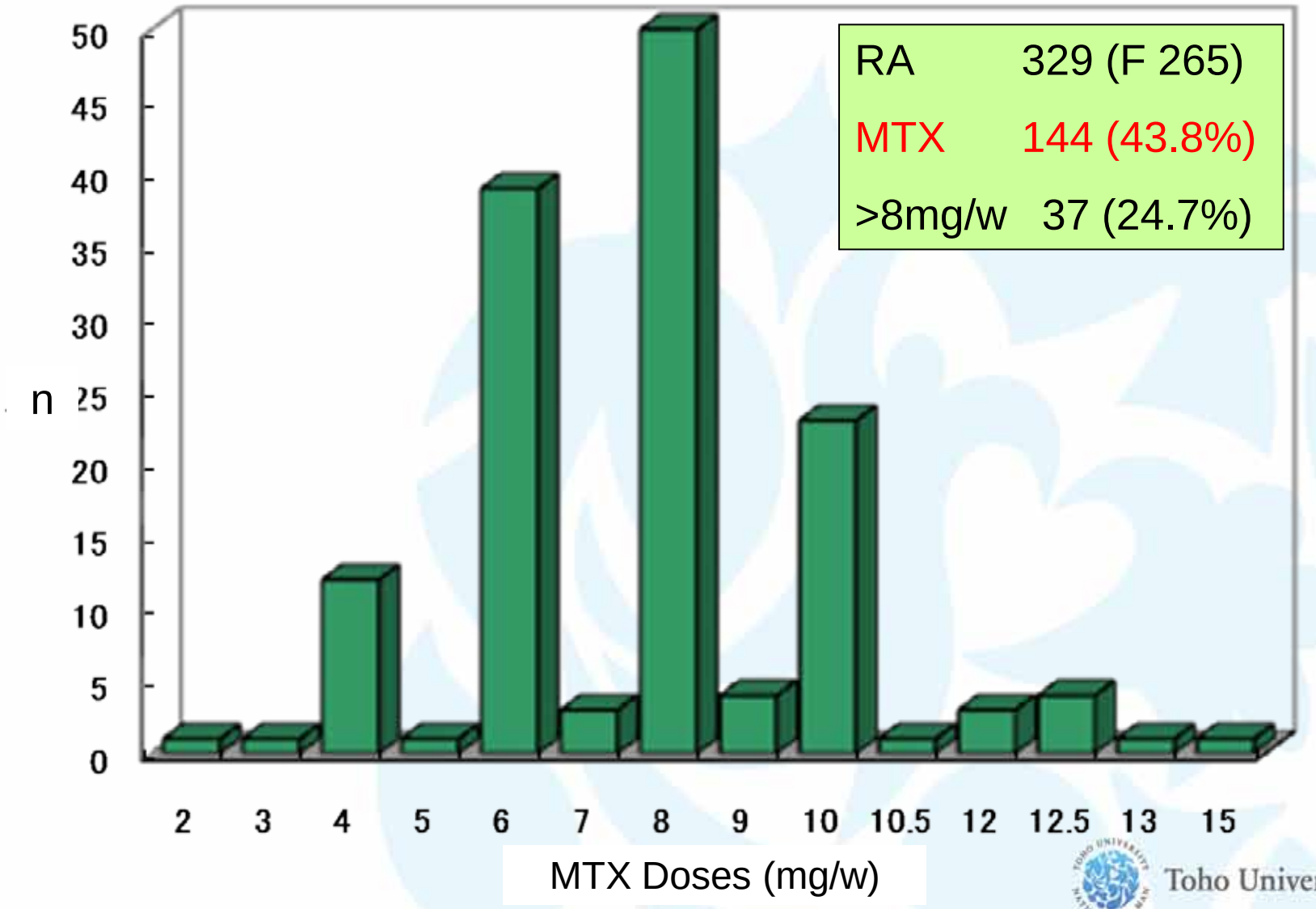
Interstitial Pneumonitis Complicated with MTX Therapy in RA Patient

MTX Doses (mg/w) for RA Patients in Various Countries

	Start	Regular Doses	Upper Limit
USA	7.5	Increasing	30
UK	7.5	10-15	20
Canada	7.5	Increasing	20
Germany	7.5	10-15	20
China	7.5	Increasing	20
Korea	7.5	Increasing	20
Japan	6	6	8

(Modified from Kawai S. Nikkei Medical, Oct 2008)

MTX Doses for RA Patients in Our Clinic of Toho University Omori Medical Center



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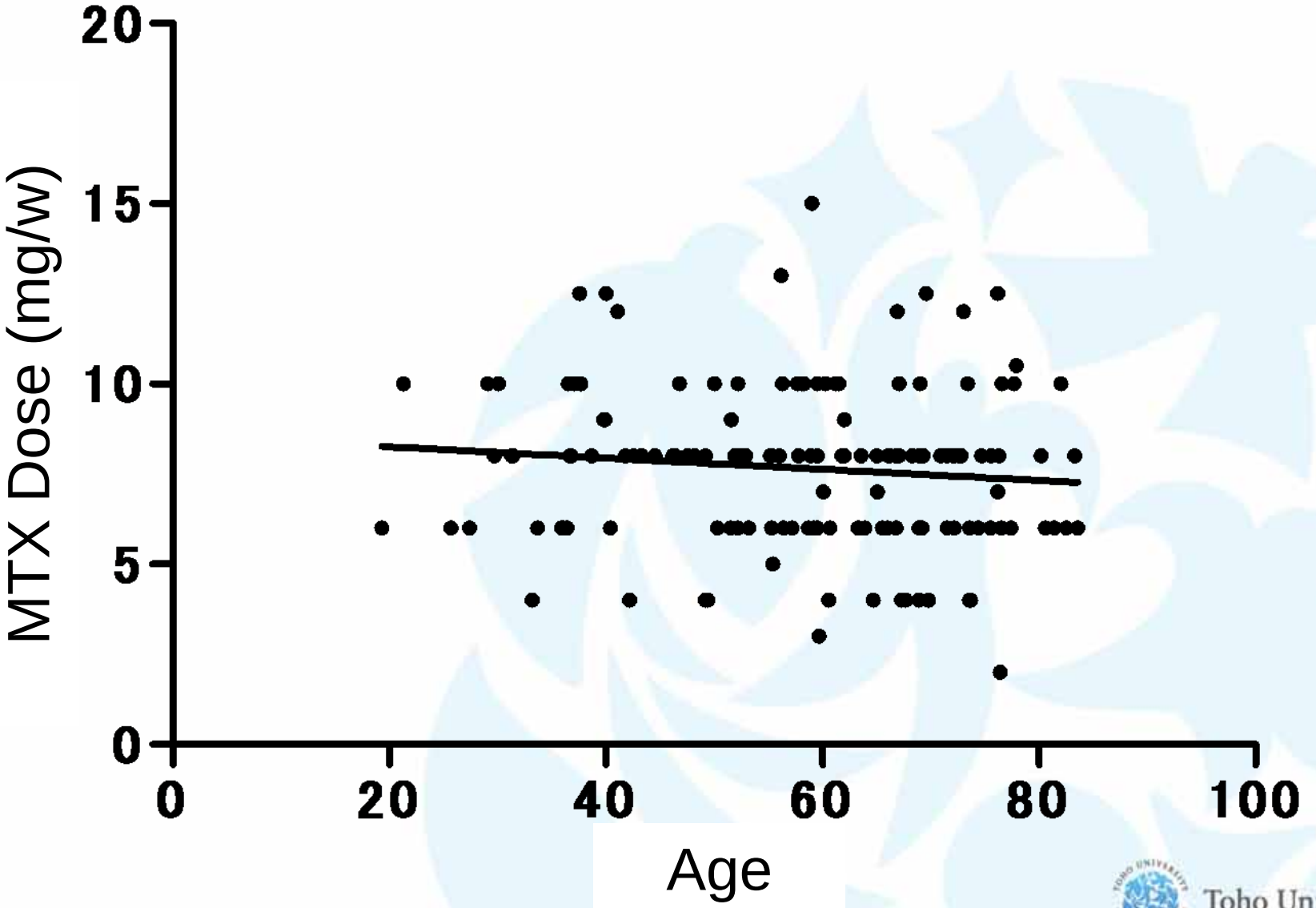
Relationship between Ages and MTX Doses of RA Patients in Our Clinic



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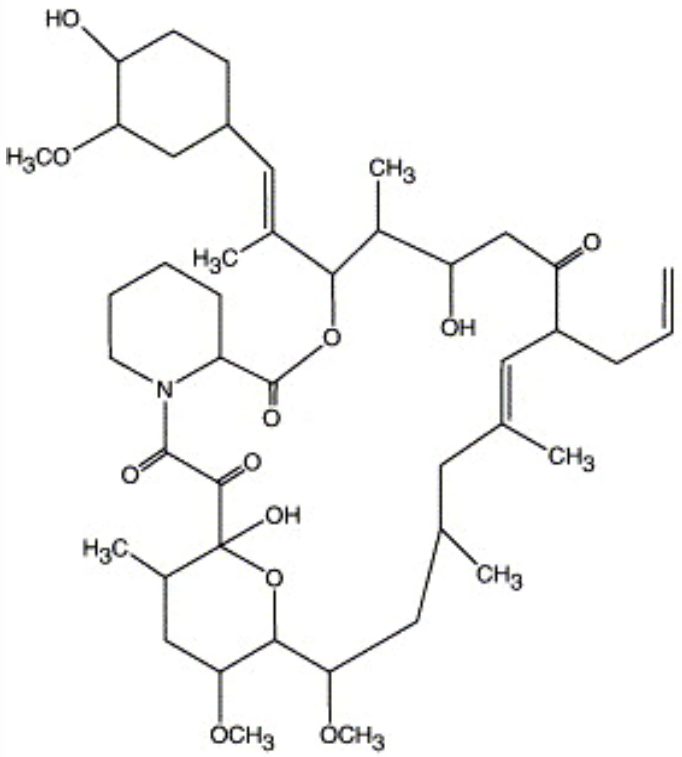
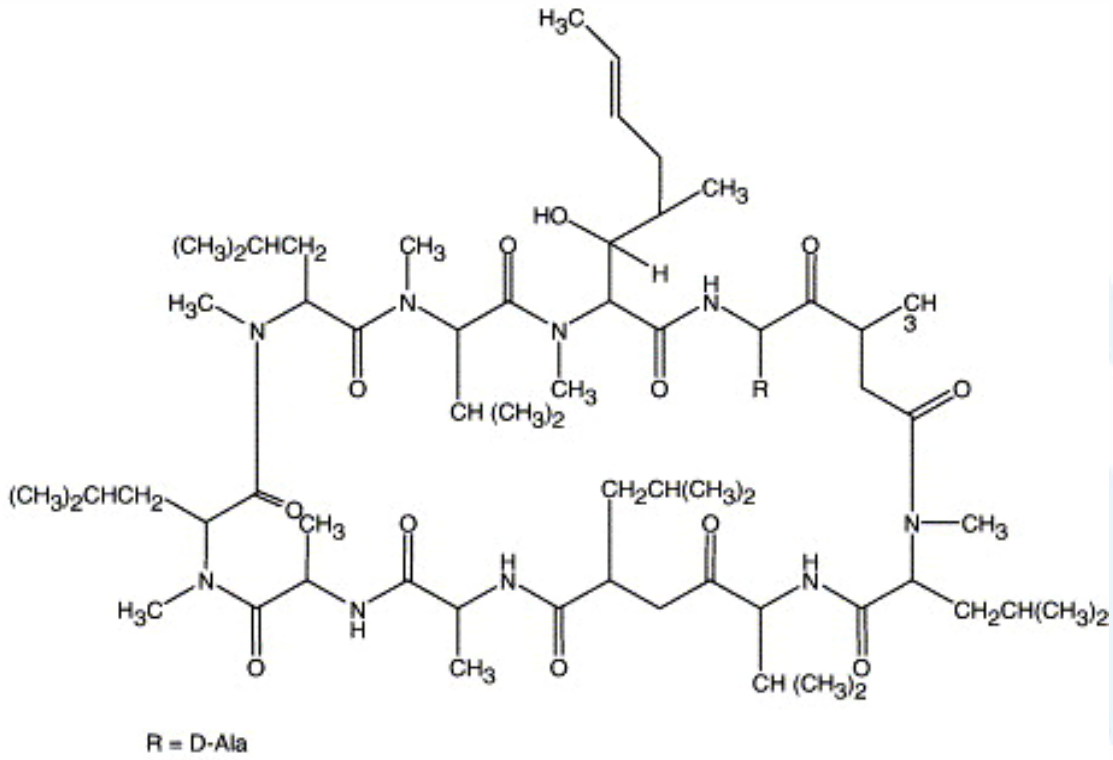
Calcineurin Inhibitors

Tacrolimus and Cyclosporine



Tacrolimus



Cyclosporine

	Tacrolimus		Cyclosporine
Molecular formula	$C_{44}H_{69}NO_{12}\times H_2O$	Macrolide	$C_{62}H_{111}N_{11}O_{12}$
Molecular weight	**822.03**		**1202.61**

Cyclic Polypeptide

(Kitahara K & Kawai S. *Curr Opin Rheumatol*. 2007;19:238)

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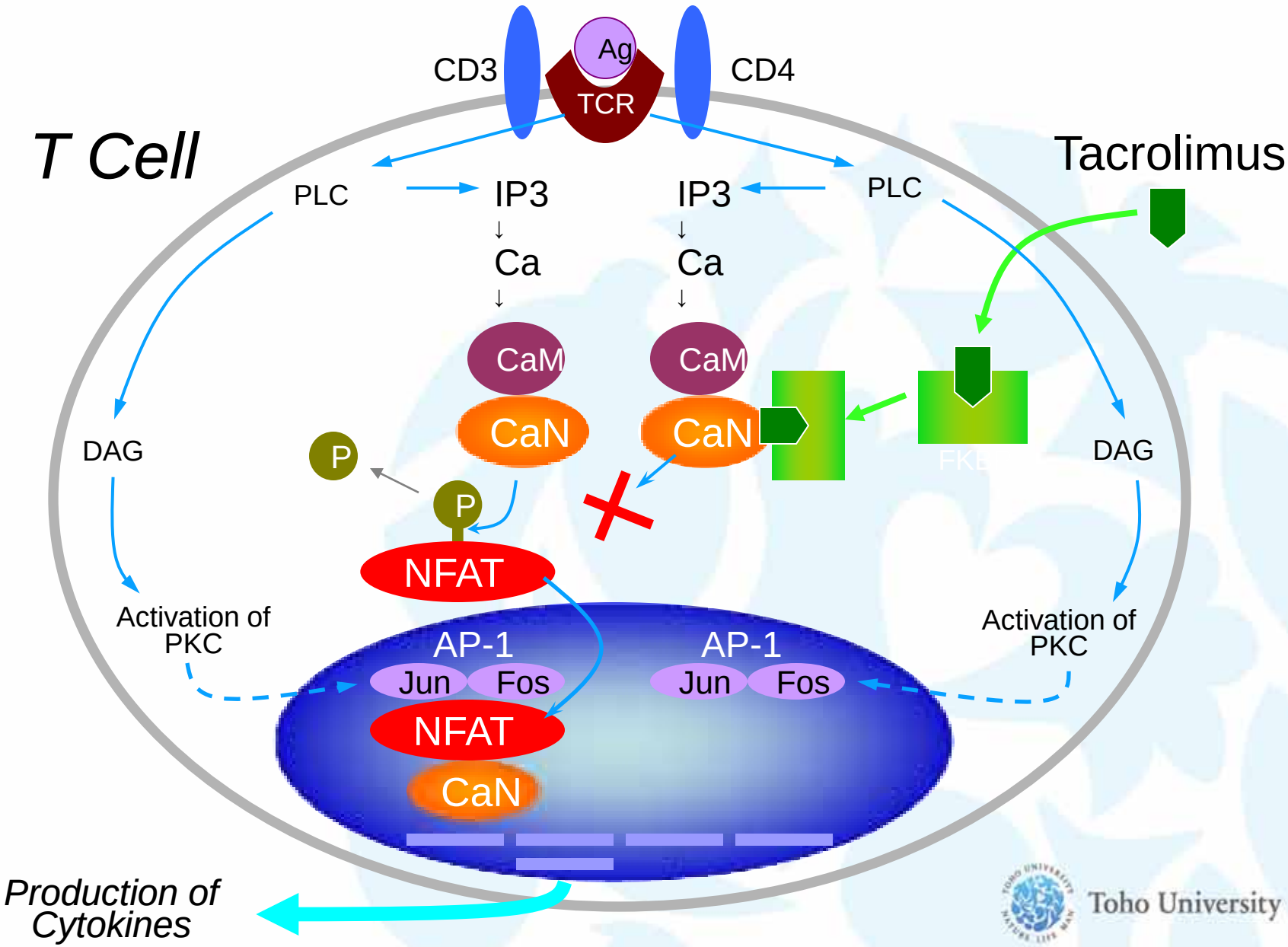
Mechanism of Action of Tacrolimus in T Cell



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Human Tacrolimus-Binding Proteins

FKBP[a]	Refseq ID	Locuslink[b]	Class	Chromosome
FKBP12	FKBP1	2280	C	20p13
FKBP12.6	FKBP1B	2281	C	2p23
FKBP25	FKBP3	2287	N	14q21
FKBP135	KIAA0674	23307	N	9q32
FKBP36	FKBP6	8468	TPR	7q11
FKBP37	AIP	9049	TPR	11q13
FKBP38	FKBP8	23770	TPR	19p12
FKBP51	FKBP5	2289	TPR	6p21
FKBP52	FKBP4	2288	TPR	12p13
FKBP13	FKBP2	2286	ER	11q13
FKBP19	FKBP11	51303	ER	12q13
FKBP22	FKBP14	55033	ER	7p15
FKBP23	FKBP7	51661	ER	2q31
FKBP60	FKBP9	11328	ER	7p11
FKBP65	FKBP10	60681	ER	17q21

C = cytoplasmic, N = nuclear, TPR = TPR-containing, ER = secretory pathway.
[a]FKBPs are grouped by subfamily (see Results section).
[b]Locuslink IDs and chromosomal positions as recorded in the NCBI Locuslink database are shown.

(Rulten SL, et al. *Mamm Genome* 2006;17:322)

Major Cyclophilins and Their Cellular Distribution

Cyclophilins	kDa	Distribution
CypA	18	cytoplasm
CypB	22	secretory pathways
CypC	23	secretory pathways
CypD	22	mitochondria
CypE	ND	nuclear
Cyp40	40	cytoplasm
CypNK	ND	cytoplasm

ND; not determined

(Kitahara K & Kawai S. *Curr Opin Rheumatol* 2007;19:238)

Cyclosporine

RCT of Cyclosporine and Other Drugs in RA Patients

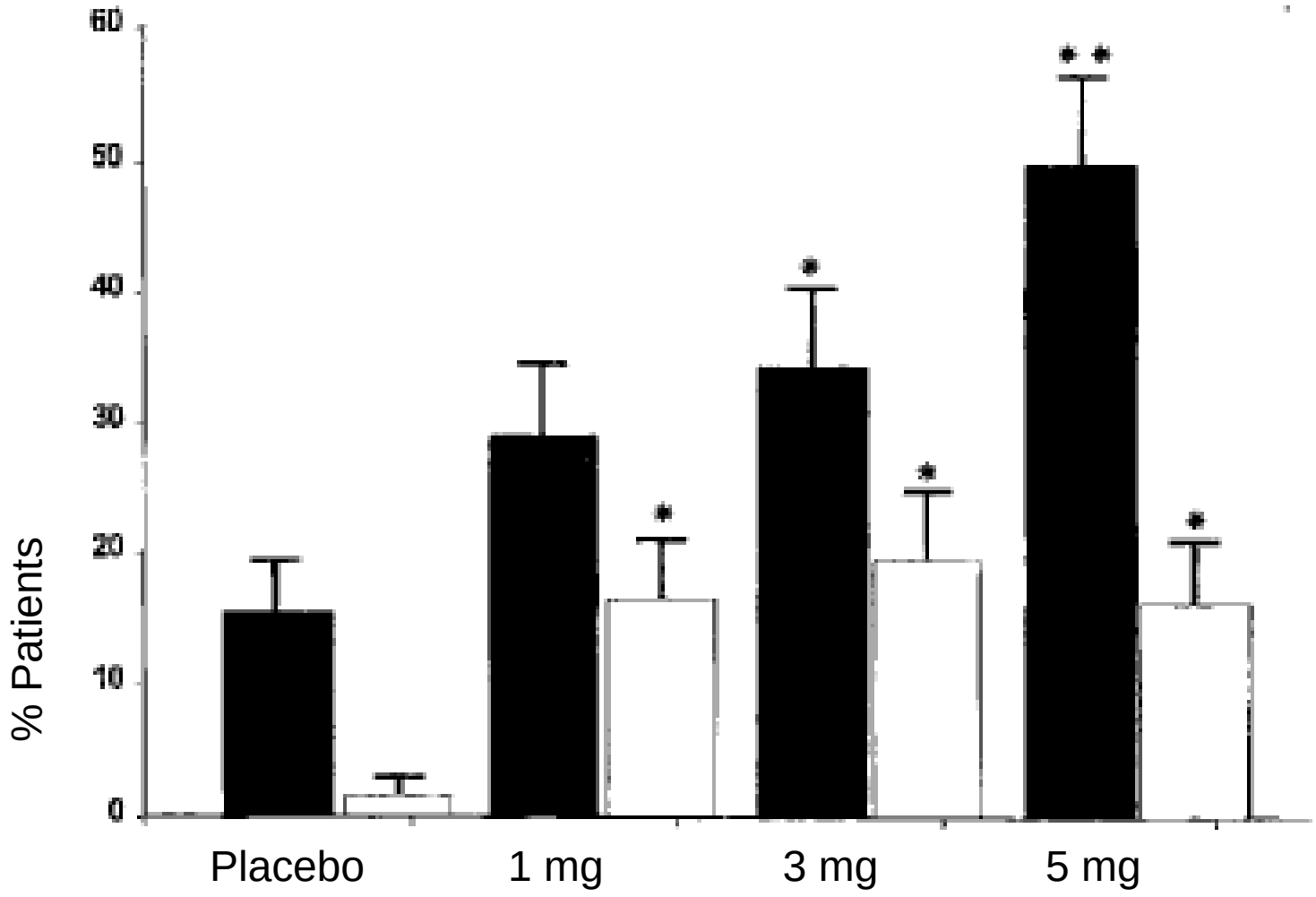
Year	Author	Study design	Period	Dose	No. of patients	Results	Ref.
2006	Hetland et al.	R, DB, PC	52wk	(1) MTX 7.5mg/wk + CyA 2.5mg/kg/day + i.a. Betamethasone (2) MTX 7.5mg/wk + i.a. Betamethasone	160	CyA+MTX > MTX	50
2006	Karanikolas et al.	O, R, P	12mo	(1) CyA 2.5-5mg/kg/day (2) LEF 20mg/day (3) (1) + (2)	106	CyA+LEF > CyA or LEF	49
2005	Sarzi-Puttini et al.	O, R	12mo	(1) CyA 3-5mg/kg/day + MTX 7.5-10mg/wk (2) CyA 3-5mg/kg/day + HCQ 400mg/day (3) CyA 3-5mg/kg/day	105	CyA+MTX > CyA+HCQ	48
2004	Miranda et al.	R, DB, PC	12mo	(1) CyA 2.5-5mg/kg/day + Clq 150mg/day (2) CyA 2.5-5mg/kg/day	149	NS	47
2003	Gerards et al.	R, DB, PC	48wk	(1) CyA 2.5-5mg/kg/day + MTX 7.5-15mg/wk (2) CyA 2.5-5mg/kg/day	120	CyA+MTX > CyA	46
2003	Marchesoni et al.	R, SB	12mo	(1) CyA 3-4mg/kg/day + MTX 10-20mg/wk (2) MTX 10-20mg/wk	61	CyA+MTX > MTX	45
1998	van den Borne et al.	R, DB, PC	24wk	(1) Clq 100-300mg/day (2) Clq 100-300mg/day + CyA 1.25mg/kg/day (3) Clq 100-300mg/day + CyA2.5mg/kg/day	88	CyA+Clq > Clq	44
1996	Bendix et al.	R, DB, PC	6mo	(1) CyA2.5-5mg/kg/day + i.m. gold 20-40mg (2) i.m. gold 20-40mg	40	NS	43
1995	Tugwell et al.	R, DB, PC	6mo	(1) CyA 2.5-5mg/day + MTX maximal tolerated dose (2) MTX maximal tolerated dose	148	CyA + MTX > MTX	42

O; open trial, R; randomized, DB; double blind, SB; single blind, PC; placebocontrolled
Clq ; chloroquine, CyA; cyclosporin A, HCQ; hydroxychloroquine, mPSL; methylprednisolone, MTX; methotrexate, SSZ; sulfasalazine
NS; not significant

(Kitahara K & Kawai S. *Curr Opin Rheumatol* 2007;19:238)

Tacrolimus

ACR20 & 50 Response Rates for Tacrolimus Therapy in American RA Patients



(Furst DE, et al. *Arthritis Rheum* 2002;46:2020)

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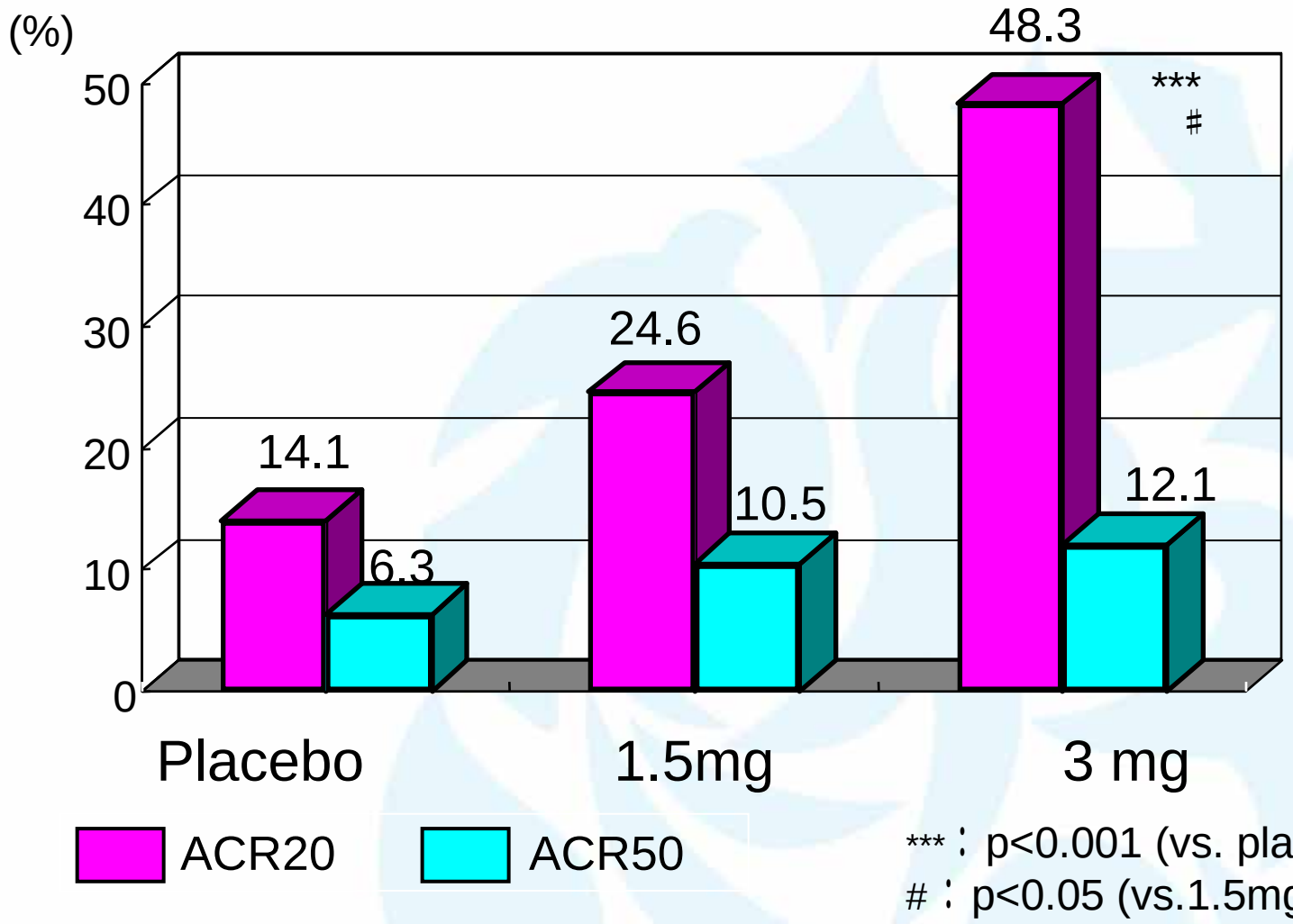
ACR20, 50, 70 Response Rates for Tacrolimus Therapy in American RA Patients

Treatment group	Response rate					
	ACR20		ACR50		ACR70	
	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*
Placebo (n = 157)	21 (13.4)	–	7 (4.5)	–	1 (0.6)	–
Tacrolimus 2 mg (n = 154)	33 (21.4)	0.0595	18 (11.7)	0.0228	8 (5.2)	0.0425
Tacrolimus 3 mg (n = 153)	49 (32.0)	0.0001	18 (11.8)	0.0228	5 (3.3)	0.1314

(Yocum DE, et al. *Arthritis Rheum* 2003;48:3328)

ACR20 & 50 Response Rates for Tacrolimus Therapy in Japanese RA Patients (4Mo)



*** : p<0.001 (vs. placebo)
# : p<0.05 (vs.1.5mg/day)

(Kondo Y, et al. *J Rheumatol* 2004;31:243)

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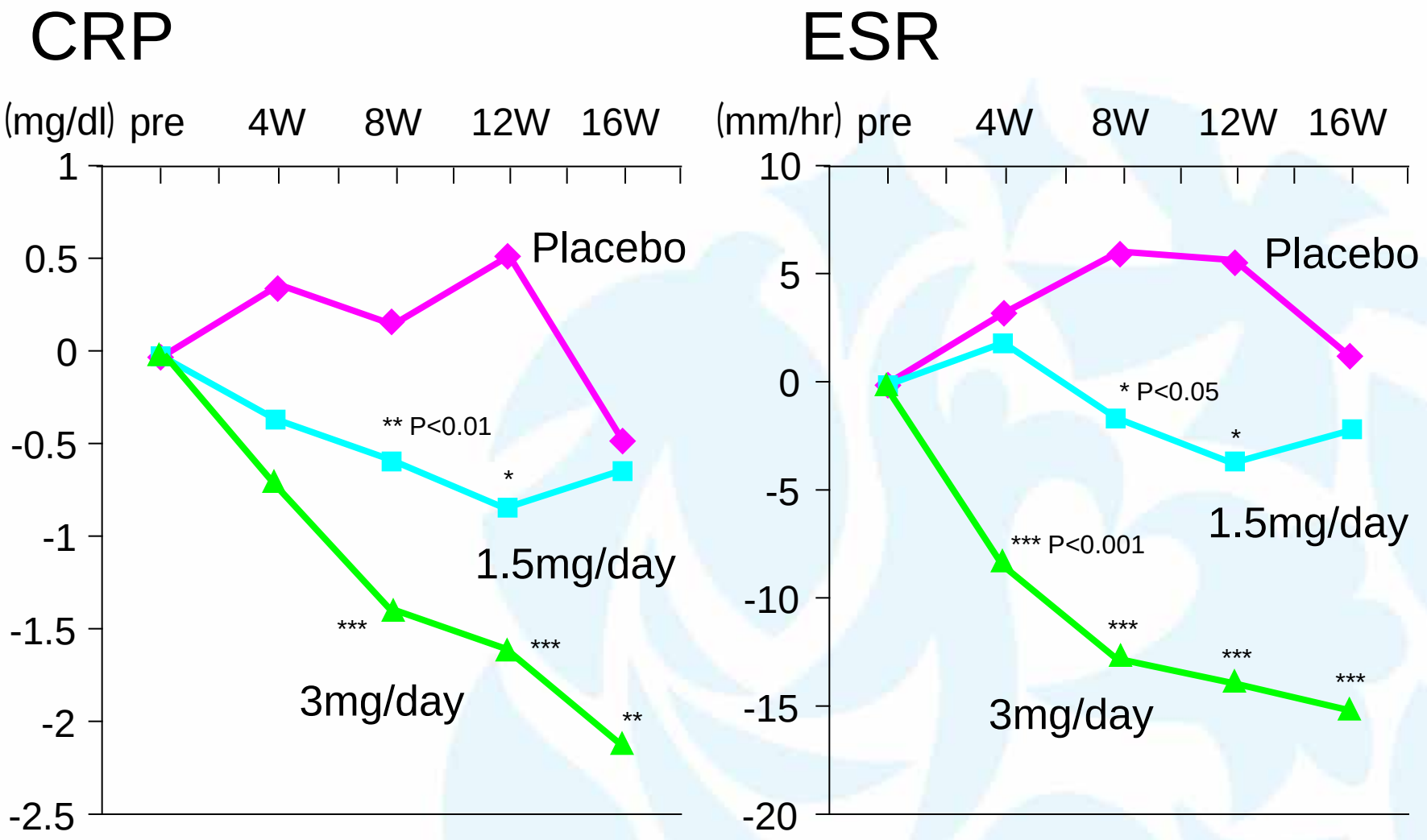
Effects of Tacrolimus on RA Patients



(Kondo Y, et al. *J Rheumatol* 2004;31:243)

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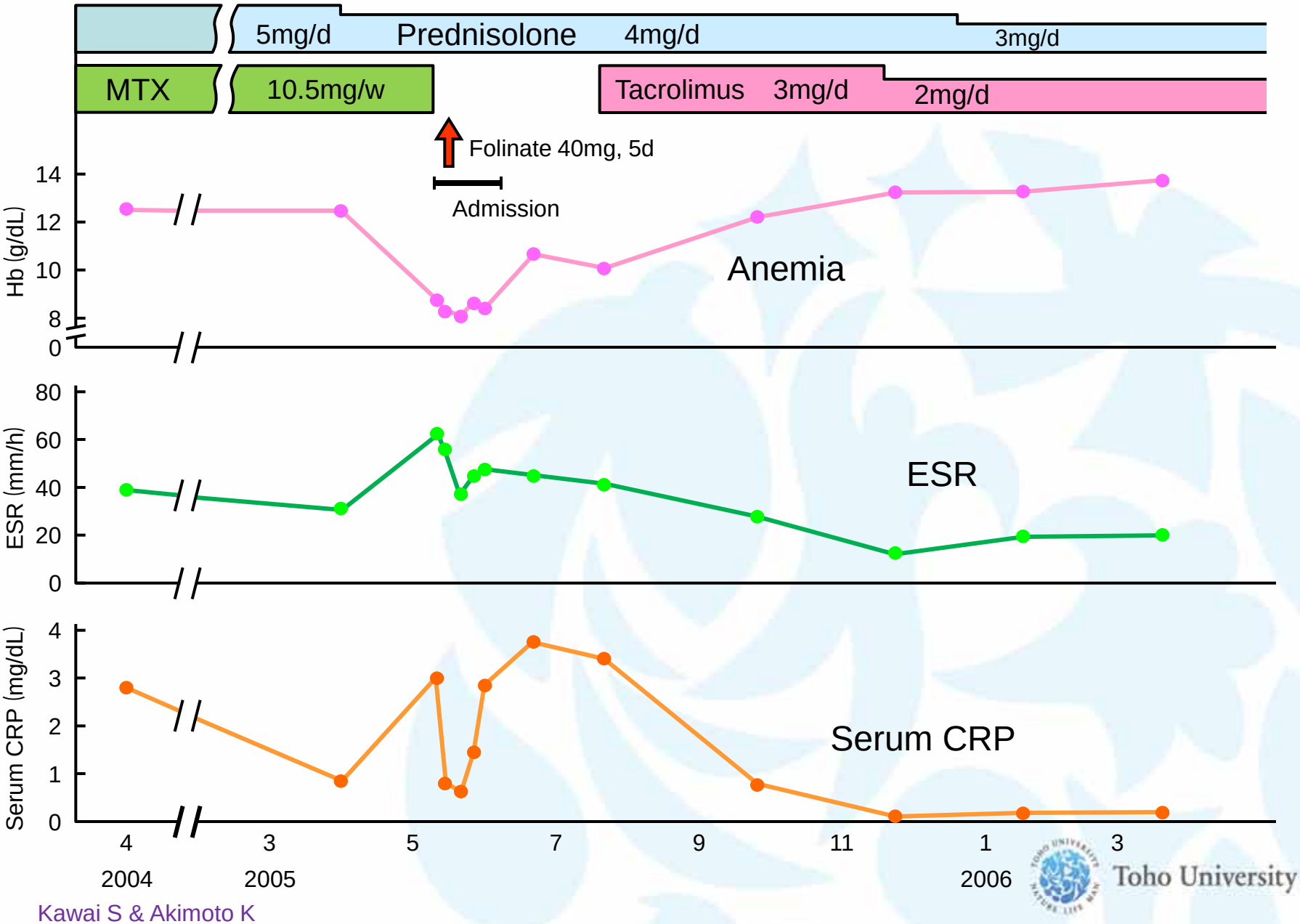
56y.o. Female Patient with RA



Kawai S & Akimoto K

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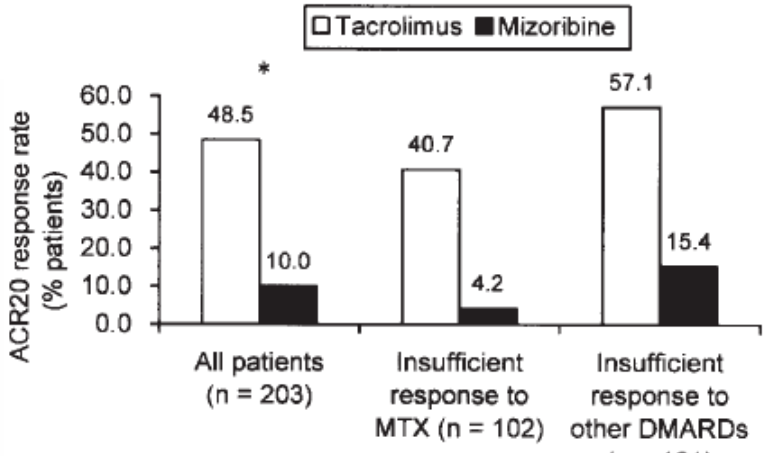
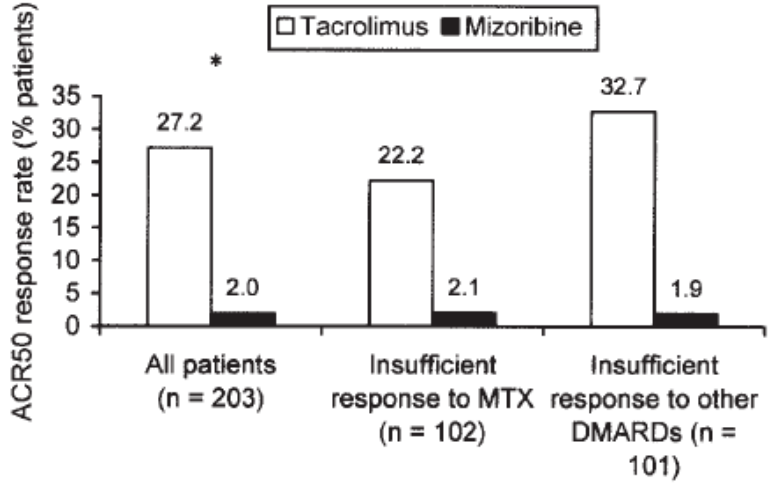
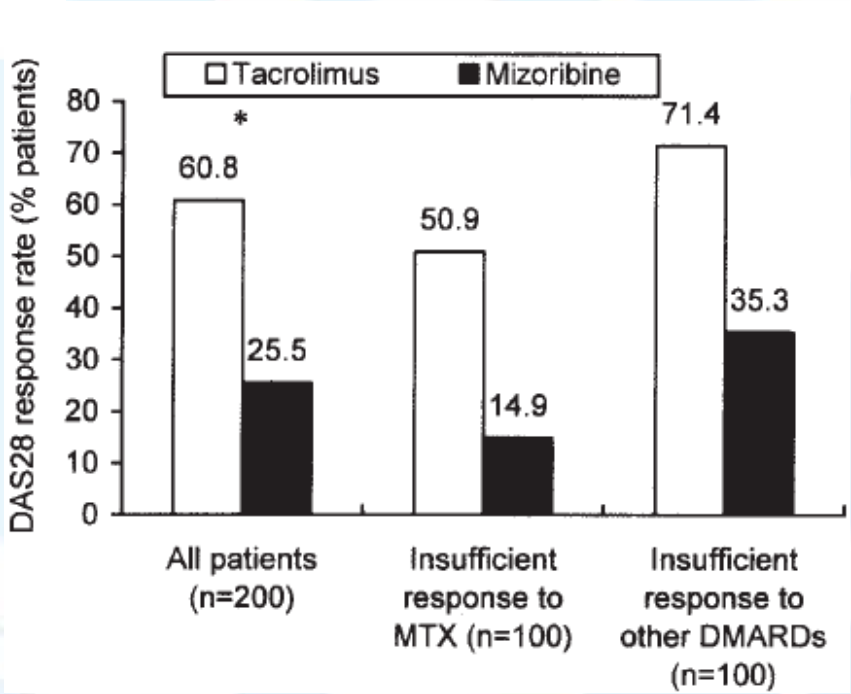
ACR20, 50, and DAS28 Response Rates for Tacrolimus and Mizoribine in Japanese RA Patients







(Kawai S, *et al. J Rheumatol* 2006;33:2153)

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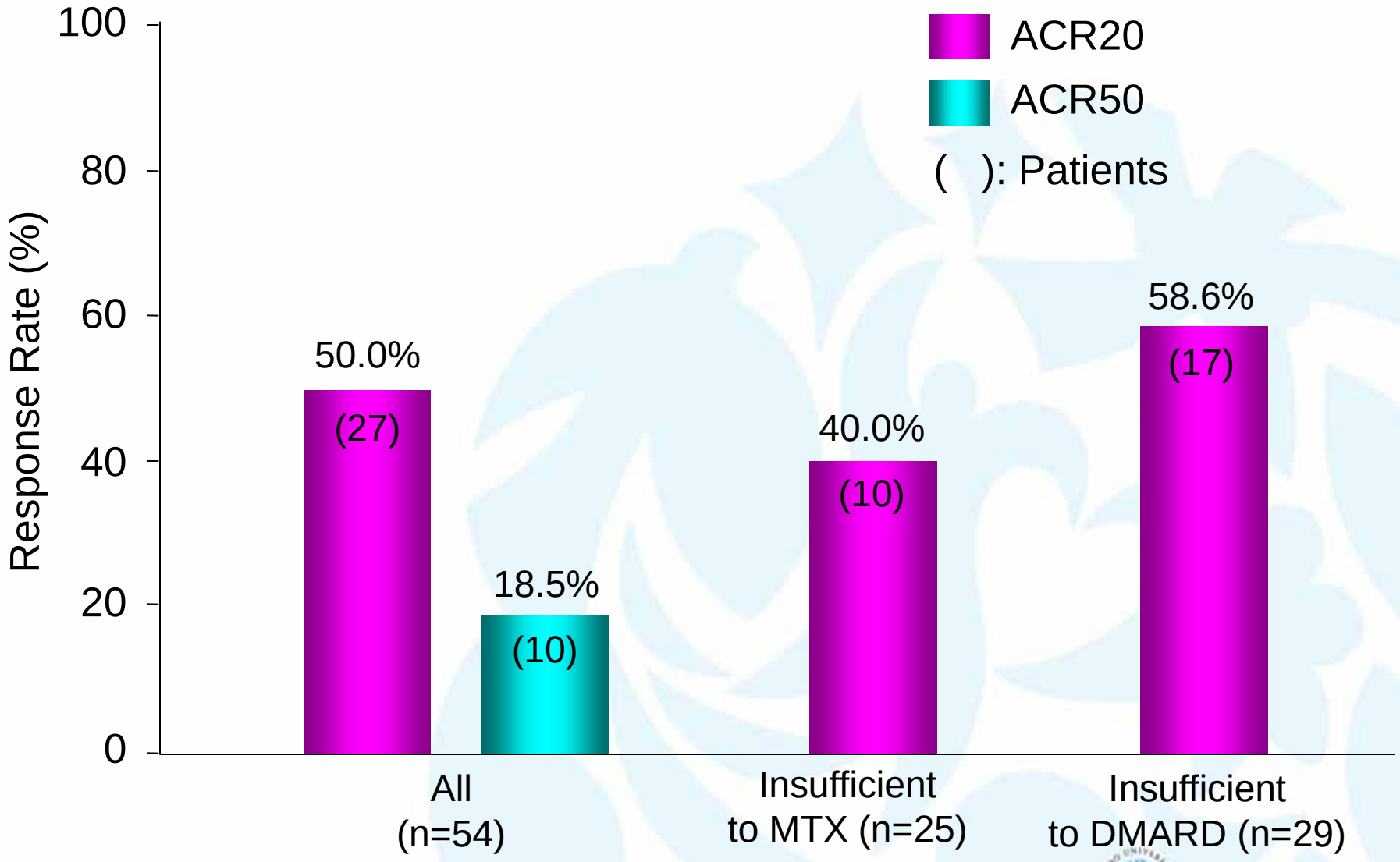
Open Study of Tacrolimus in the Elderly Japanese RA Patients



[Kawai S & Yamamoto K. *Rheumatology (Oxford)* 2006;45:441]

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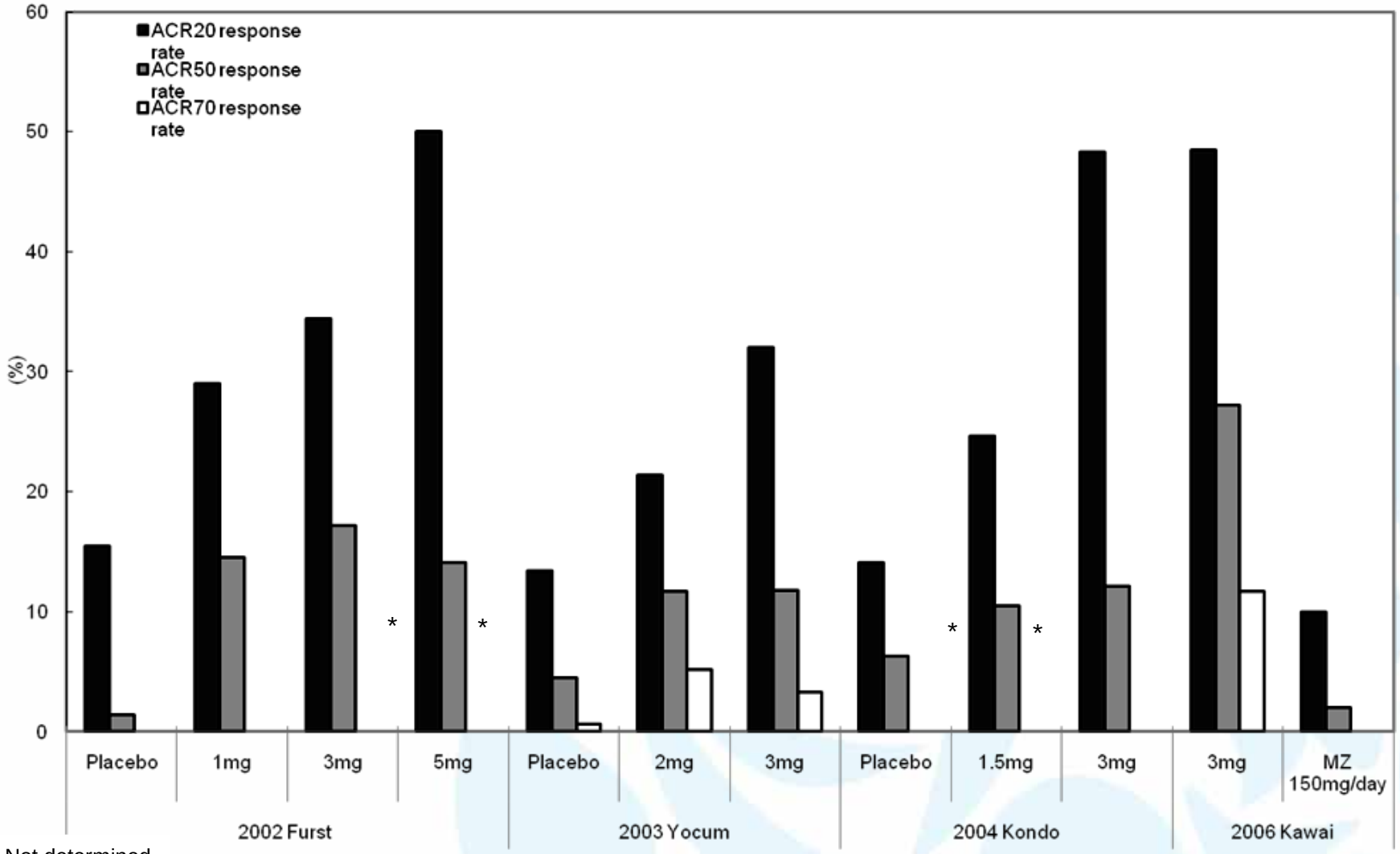
Comparison of ACR Response Rates to Tacrolimus in RCT for RA Patients



* Not determined

(Kitahara K & Kawai S. *Curr Opin Rheumatol* 2007;19:238)

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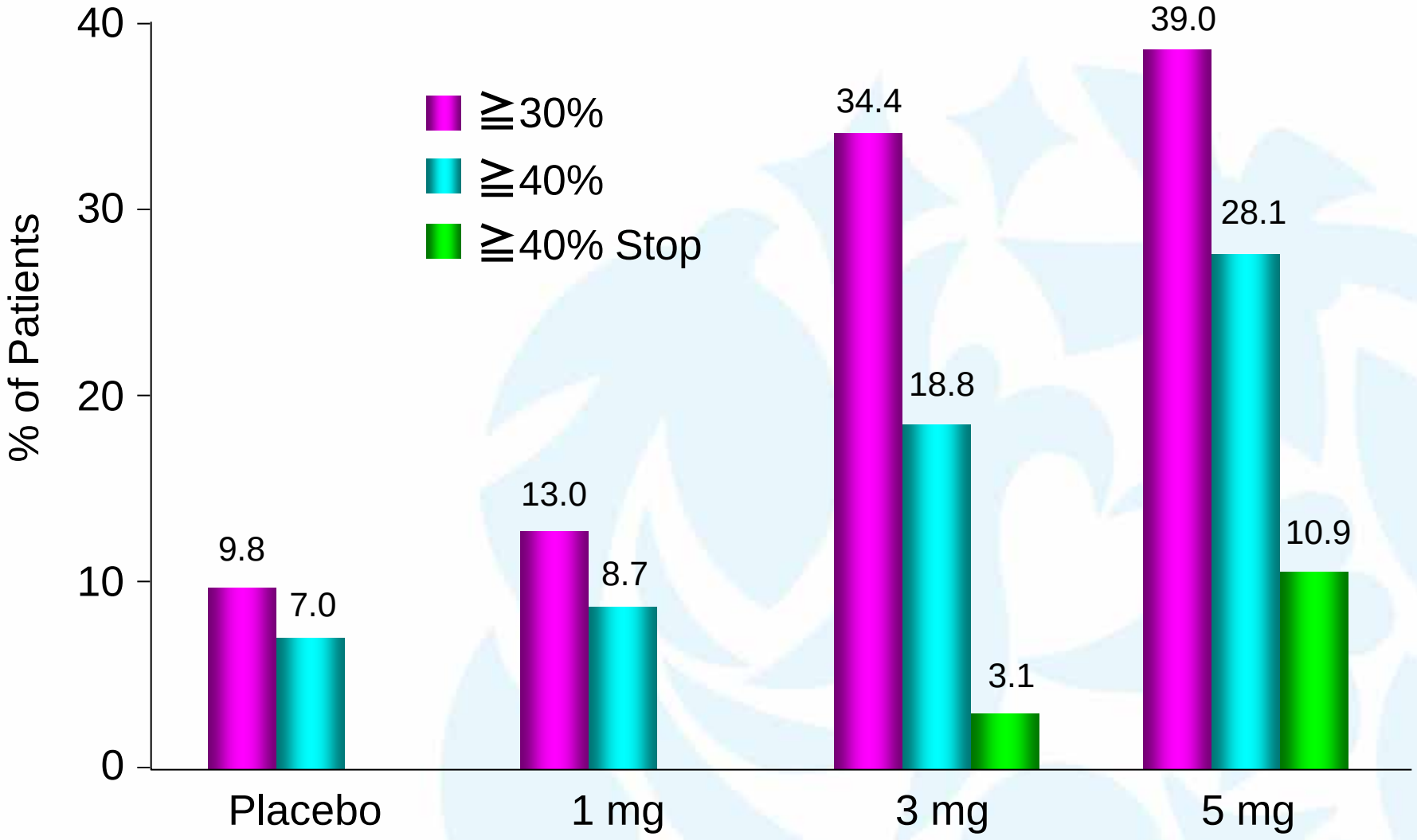
% of Patients with Increases in Serum Cr Levels Relative to Baseline



(Furst DE, et al. *Arthritis Rheum* 2002;46:2020)

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Increase in Serum Cr after Tacrolimus & MTX Therapy in American RA Patients

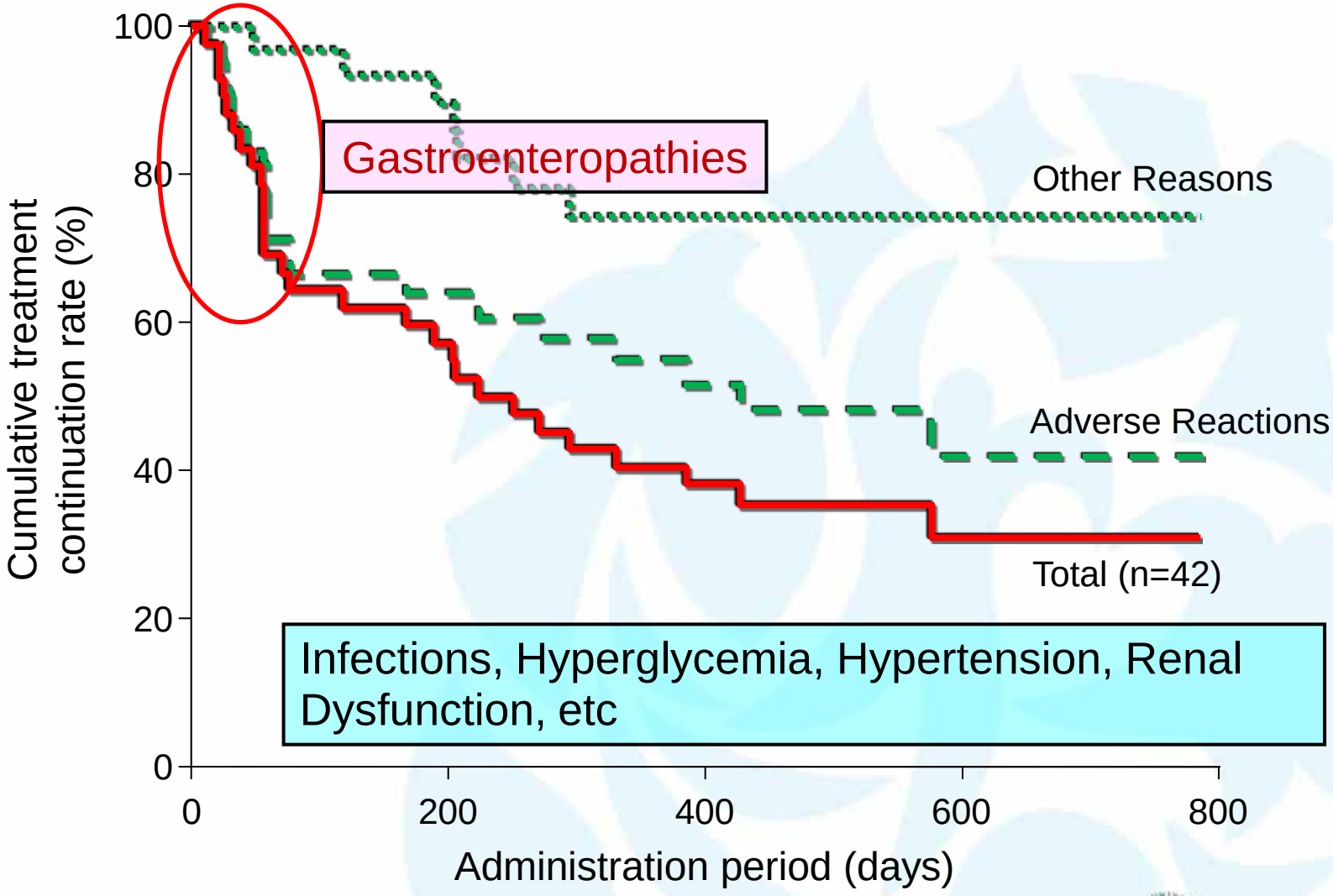
Table 2. Incidence of increase in serum creatinine (Cr) among patients who received at least one dose of study drug and for whom a baseline and at least one on-treatment Cr measurement were available*

Serum Cr	Tacrolimus 3 mg + MTX 5–12.5 mg/week (n = 35)	Tacrolimus 3 mg + MTX 15–20 mg/week (n = 45)	Total (n = 80)
% increase from baseline			
≥30% to <40%			
Maximum†	4 (11.4)	5 (11.1)	9 (11.3)
End of treatment	2 (5.7)	4 (8.9)	6 (7.5)
≥40%			
Maximum†	7 (20)	7 (15.6)	14 (17.5)
End of treatment	3 (8.6)	3 (6.7)	6 (7.5)
Maximum on-treatment value			
≥0.5 mg/dl to ≤1.4 mg/dl‡	34 (97.1)	43 (95.6)	77 (96.3)
>1.4 mg/dl to ≤1.8 mg/dl	1 (2.9)	2 (4.4)	3 (3.7)
>1.8 mg/dl	0	0	0

* Values are the number (percentage) of patients.
† Maximum increase during treatment, from baseline.
‡ Normal range.

(Kremer JM, et al. *Arthritis Rheum* 2003;48:2763)

Cumulative Treatment Cotinuation Rate to Tacrolimus Therapy for RA Patients



(Akimoto K, et al. *Clin Rheumatol,* 2008;27:1393)

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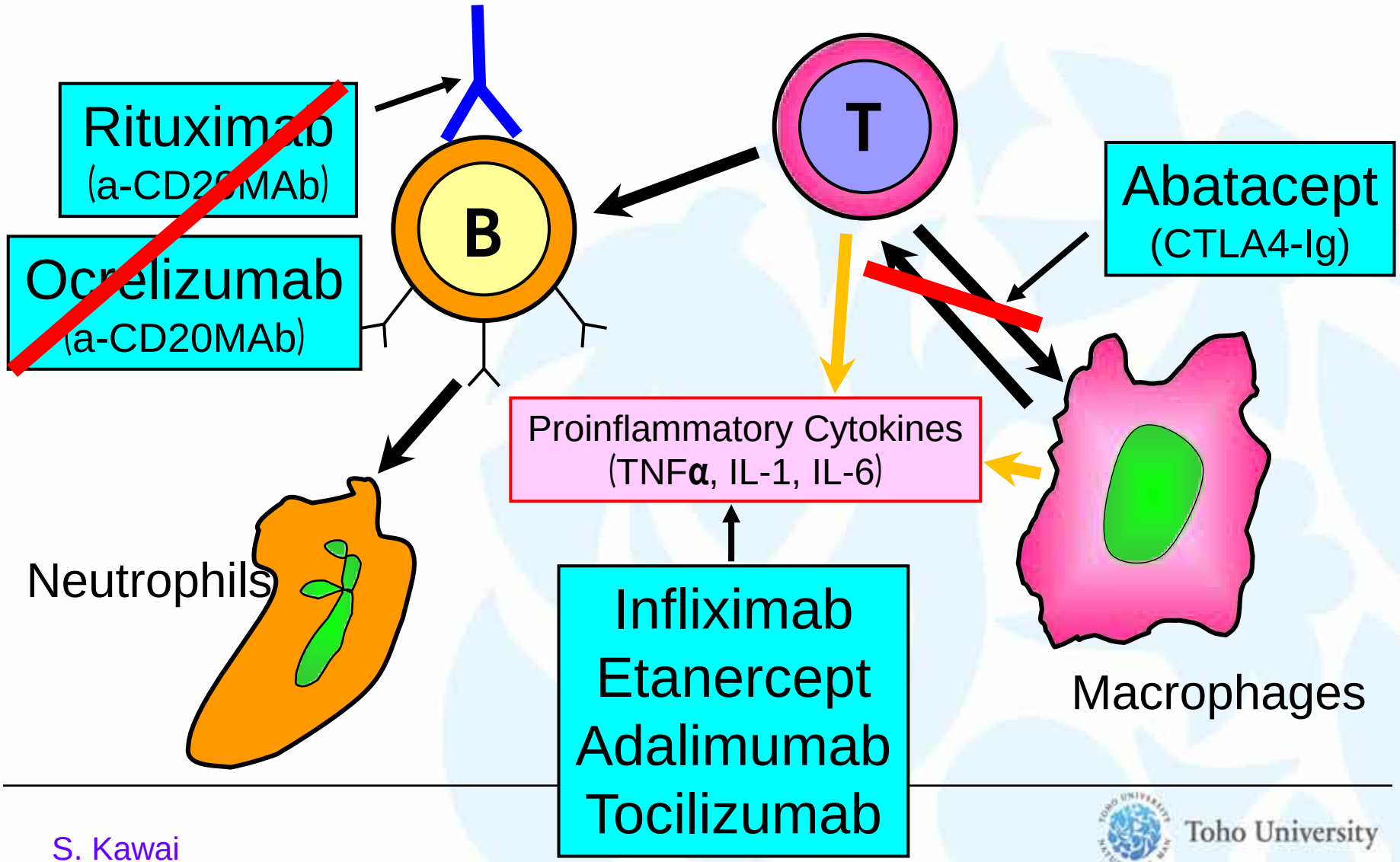
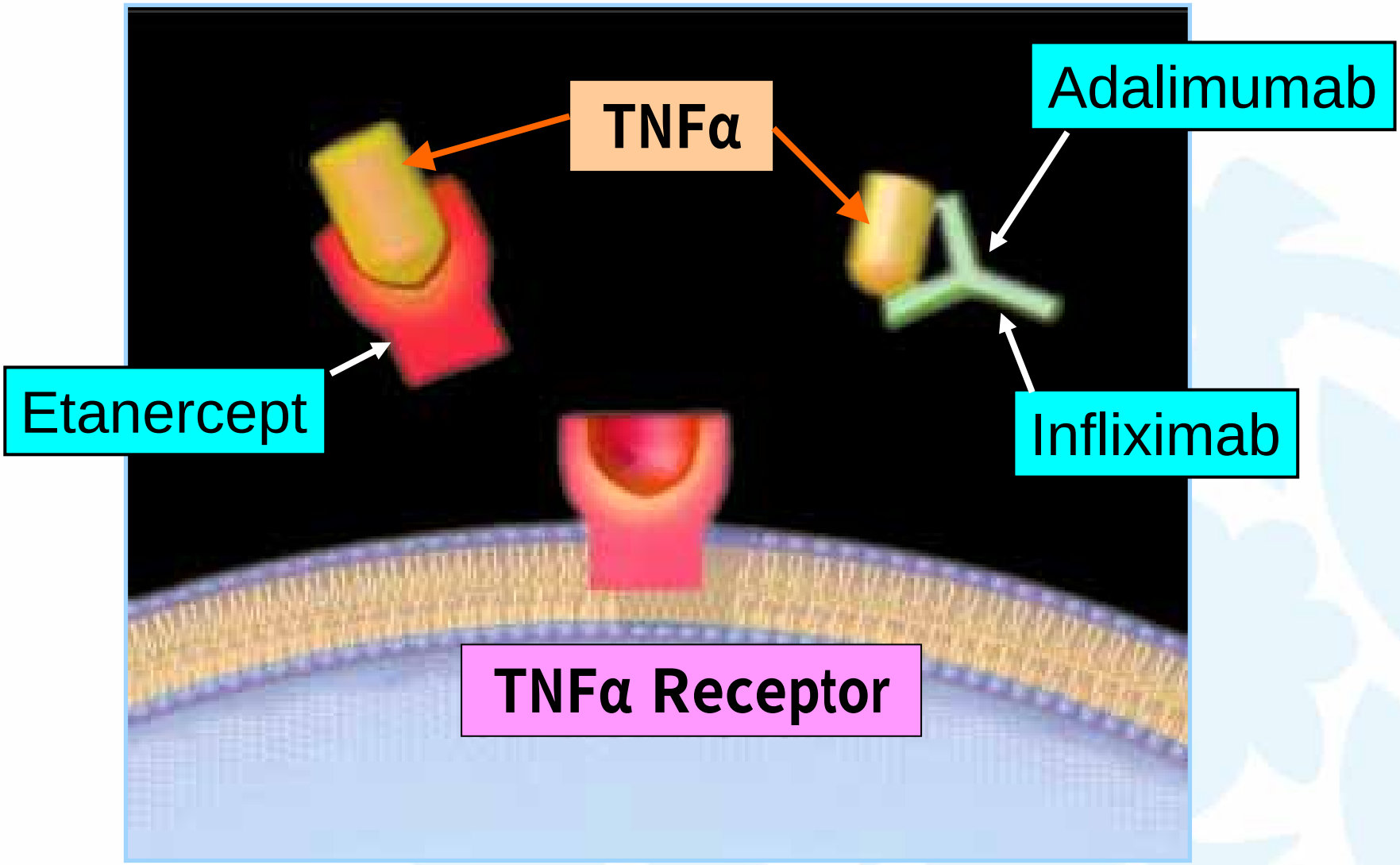
Biological Agents

Recent Biological Agents



TNFα Inhibitors for RA Patients



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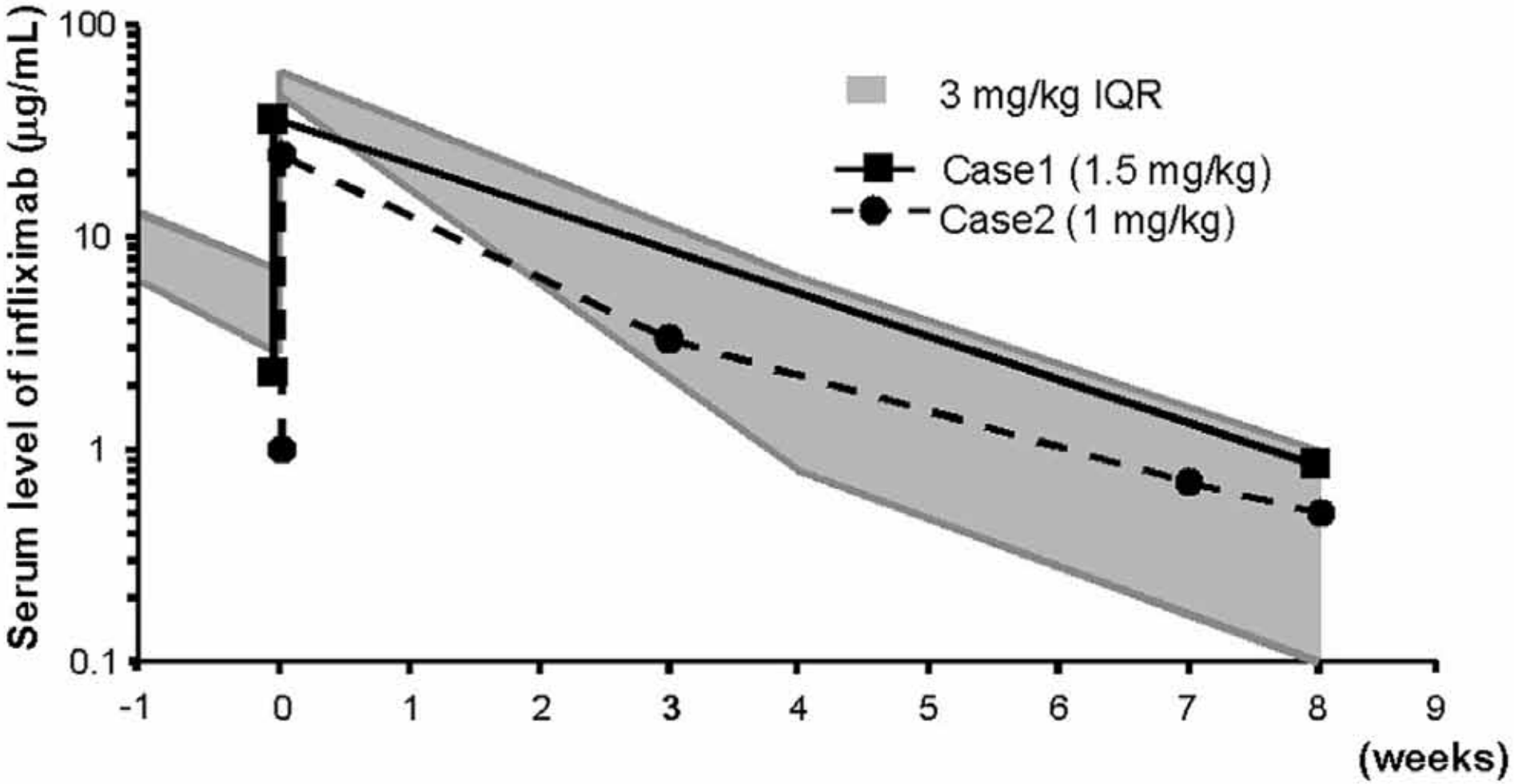
Various Biologic Drugs: TNF Antagonists

	Compound	
Approved		
Chimeric anti-TNF mAb (lgG1)	Infliximab	
TNF-receptor p75 lgG1 construct	Etanercept	
Fully human anti-TNF mAb (IgG1)	Adalimumab	
In late-stage development		
PEGylated humanized anti-TNF Fab fragment	CDP870	
TNF-receptor p55 PEG	PEG-sTNF-R1	

Human Mouse Synthetic element = Polyethylene glycol

Infliximab

Concentration versus Time Curves for Infliximab in Our RA Patients



(Nishio S, et al. *Mod Rheumatol* 2009;19:329)

PK Data for Our RA Patients and A Japanese Clinical Trial

	C1h (μg/mL)	Ctrough (μg/mL)	$t_{1/2}$ (hrs)
Patient 1 (1.5 mg/kg)	35.6	1.2	274.8
Patient 2 (1 mg/kg)	24.3	0.5	245.3
Trial median* (Interquartile range)	53.3 (46.7-60.5)	0.5 (<0.1-1.0)	159.5 (45.6-232.8)

(Nishio S, et al. *Mod Rheumatol* 2009;19:329)

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Fcg Receptor Gene Polymorphisms in Our RA Patients Controlled by Low-Dose Infliximab

	Patient 1	Patient 2
FcγRIIA	131H/H	131H/H
FcγRIIIA	176F/F	176F/F
FcγRIIIB	NA1/NA2	NA2/NA2

(Nishio S, et al. *Mod Rheumatol* 2009;19:329)

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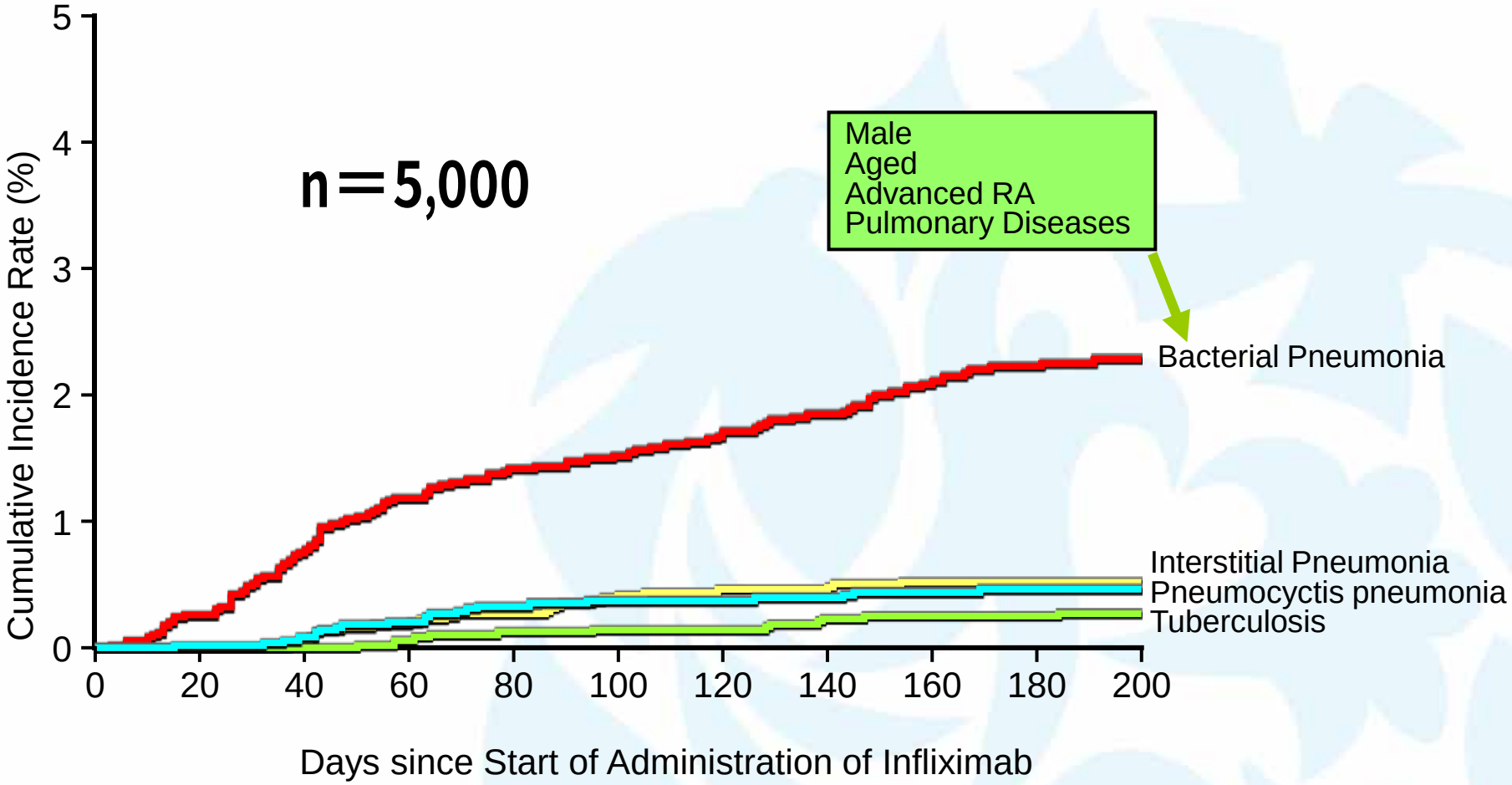
Cumulative Incidence Rate of Complications in RA Patients on Infliximab Therapy



(Takeuchi T, et al. *Ann Rheum Dis* 2008;67:189)

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Comparisons between PMS of Infliximab and Etanercept in Japanese RA Patients

	Infliximab	Etanercept
Duration	2003.7 - 2005.8.	2005.3 - 2007.4
Patient Number	5,000	7,091
Adverse Event	1,401 (28.0%)	2,173 (30.6%)
Severe A.E.	308 (6.2%)	403 (5.7%)
Pneumonia	108 (2.2%)	102 (1.4%)
Tuberculosis	14 (0.28%)	10 (0.14%)
PCP	25 (0.50%)	16 (0.23%)
Int. Pneumonia	22 (0.44%)	44 (0.62%)

PCP= Pneumocystis Pneumonia

(Takeuchi T, et al. *Ann Rheum Dis* 2008;67:189)
(Koike T, et al. *J Rheumatol.* 2009;36:898)

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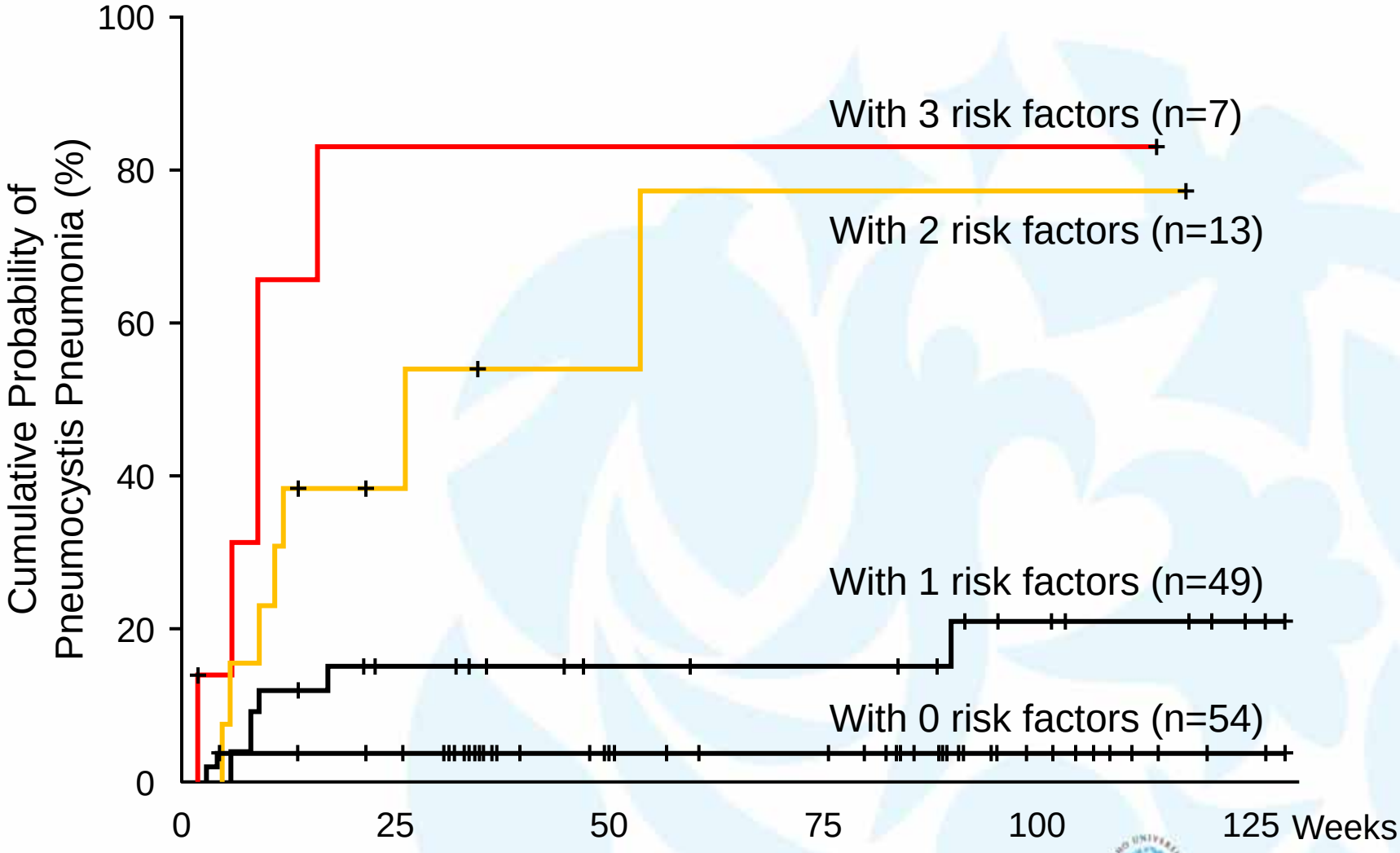
Cumulative Probability of Pneumocystis Pneumonia in RA Patients on Infliximab Therapy

(Risk Factors: Elderly; >6mg Prednisolone; Pulmonary Diseases)



(Harigai M, et al. *N Engl J Med* 2007; 357:1874)

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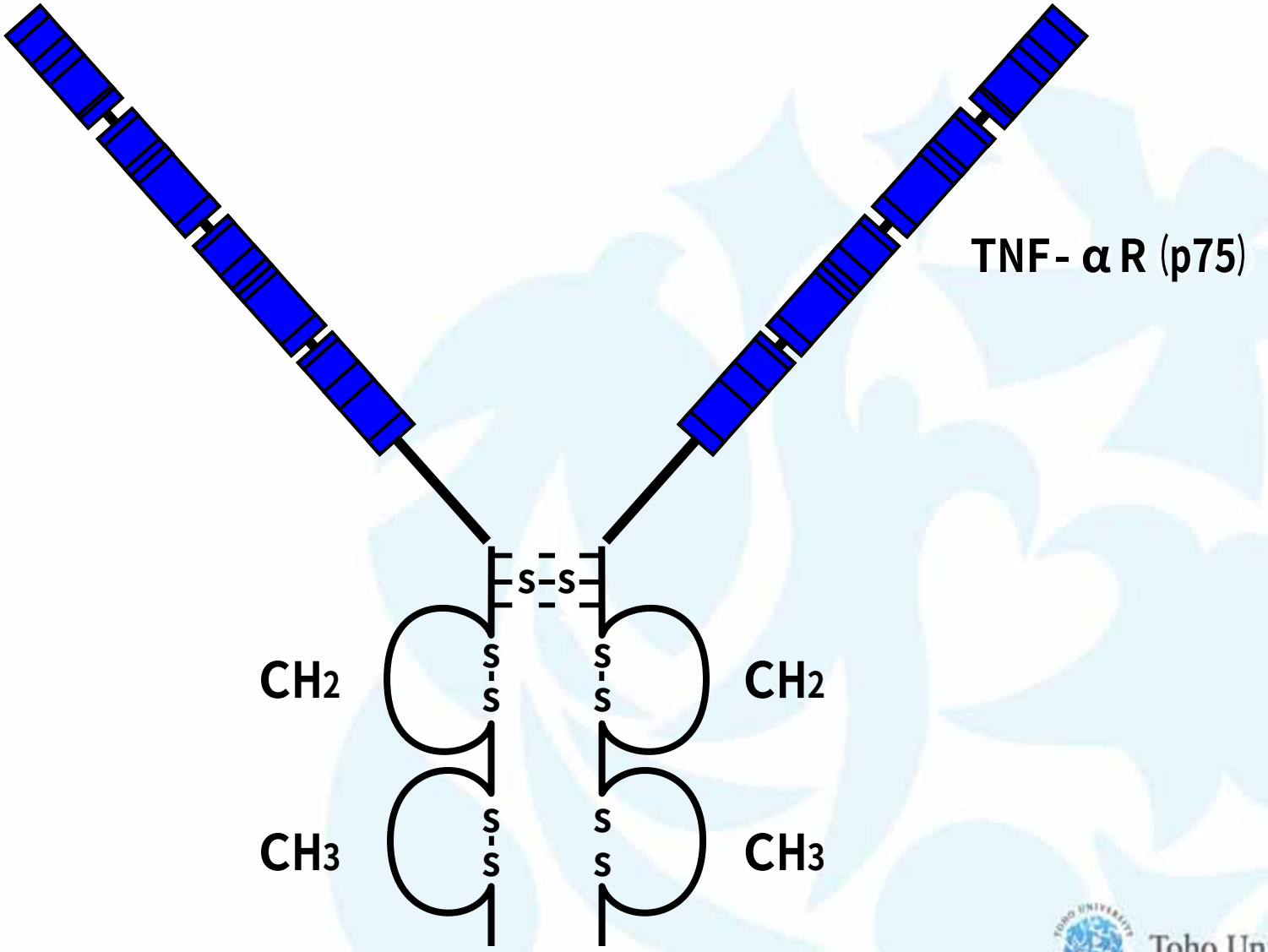
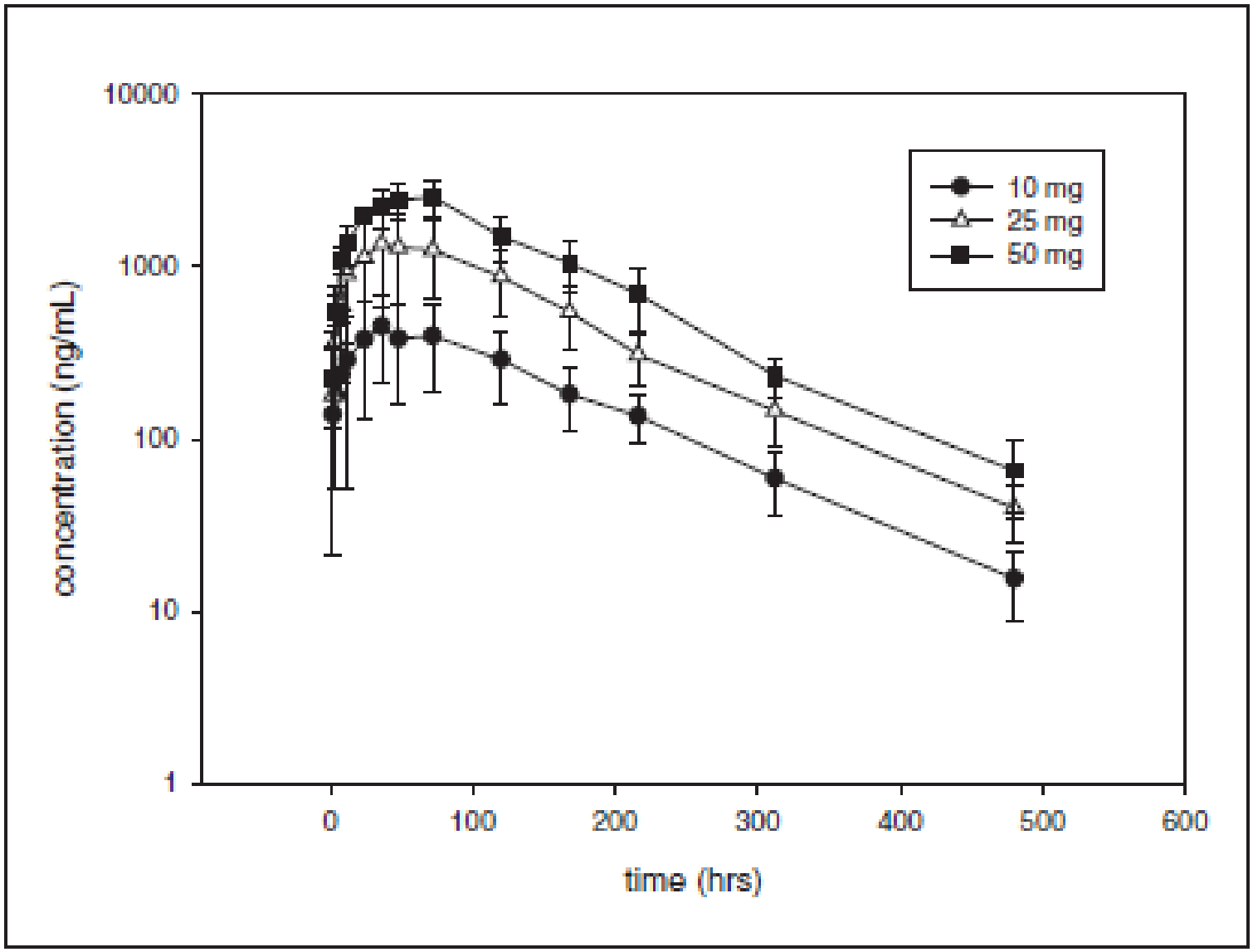
Etanercept

Structure of Etanercept



Serum Etanercept in Japanese Volunteers



(Kawai S, et al. *J Clin Pharmacol* 2006;46:418)

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Comparison of PK of Etanercept between Japanese & American Volunteers

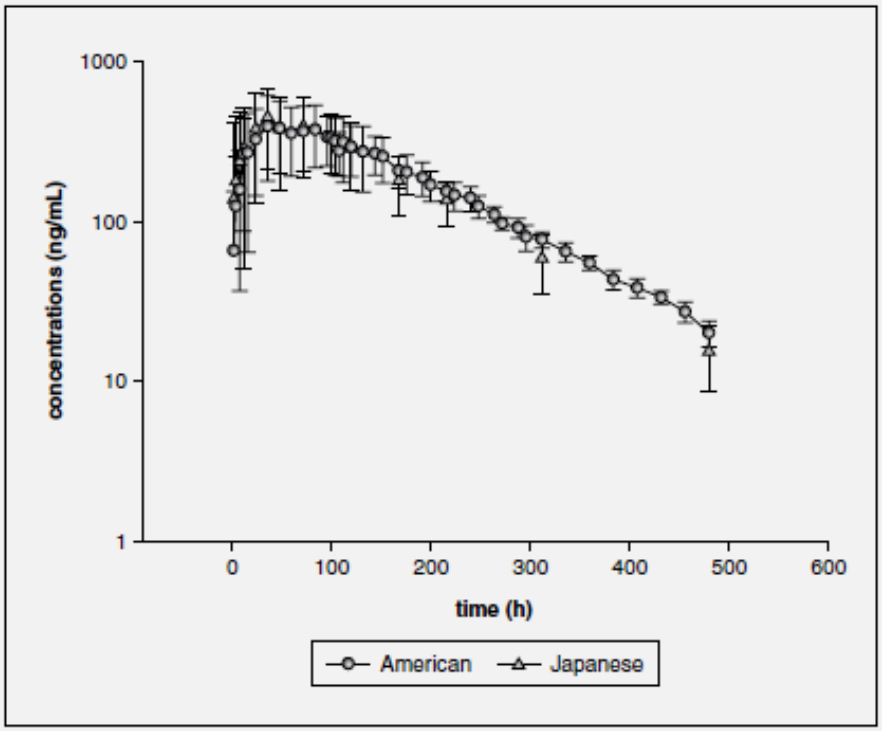

Figure 2. Mean ± SD serum etanercept concentrations after single 10-mg doses.

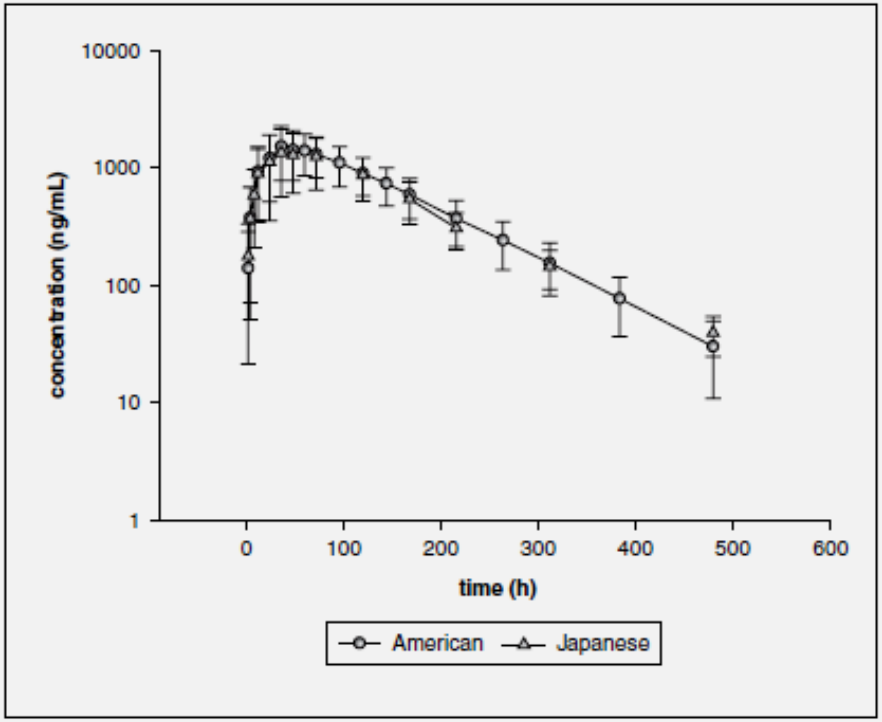

Figure 3. Mean ± SD serum etancercept concentrations after single 25-mg doses.

(Kawai S, et al. *J Clin Pharmacol* 2006;46:418)

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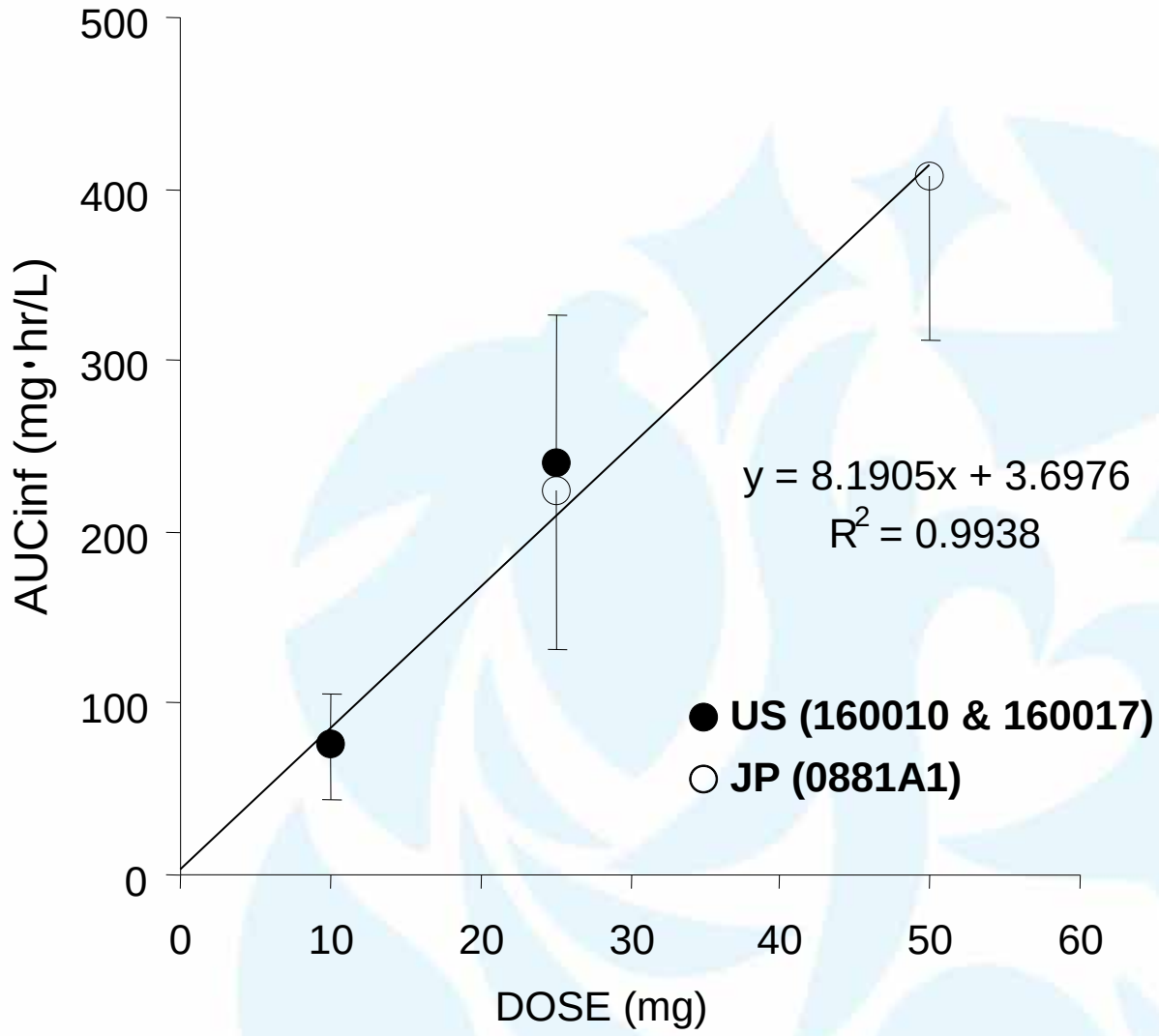
Relationship between $AUC_{0-\infty}$ and Dose of Etanercept in Japanese & American Healthy Subjects



(Calculated from Kawai S, et al. *J Clin Pharmacol* 2006;46:418)

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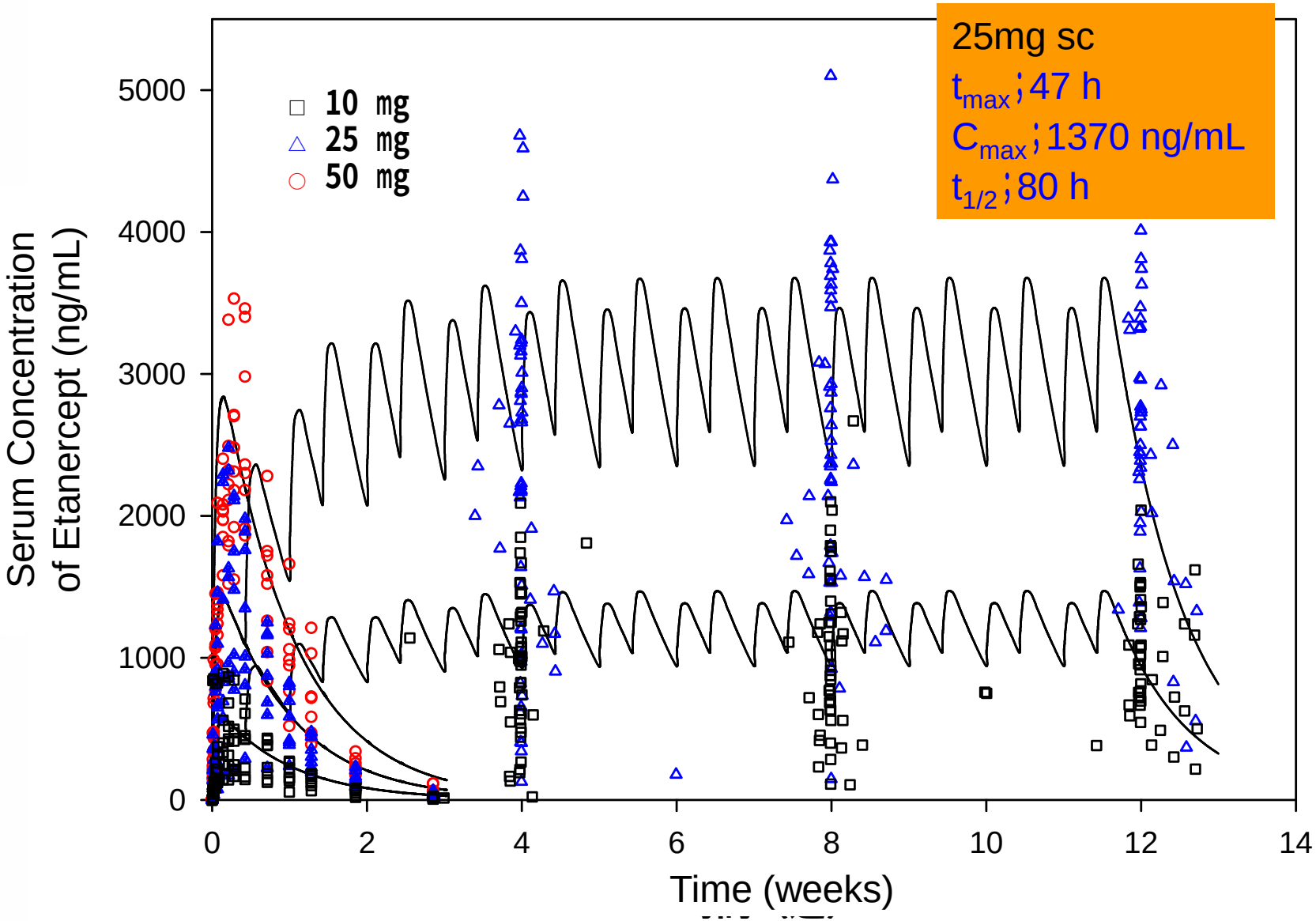
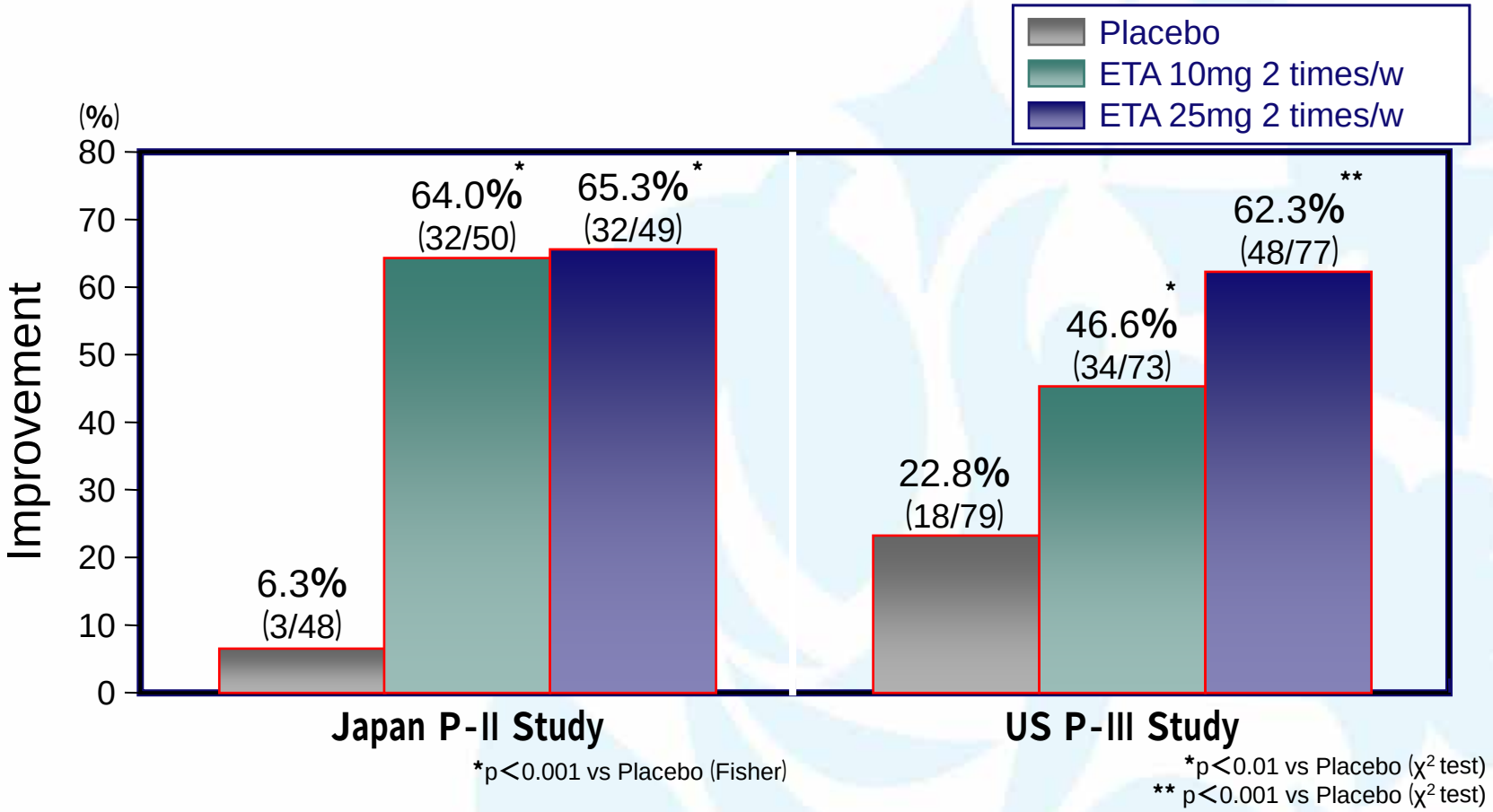
Simulation of Serum Etanercept Concentration



(Calculated from Kawai S, et al. *J Clin Pharmacol* 2006;46:418)

Comparison of PD of Etanercept between Japanese & American Patients



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