Actemra® product overview

Katsunori Yoshizawa
Lifecycle Leader – Actemra
Chugai Pharmaceutical Co., Ltd.

ACTEMRA®
tocilizumab

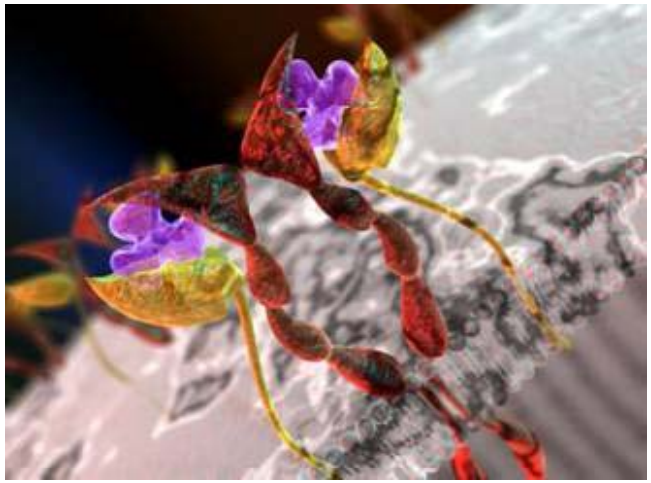
Forward looking statement

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

ACTEMRA® tocilizumab

Actemra®

- Humanized anti-human interleukin 6 (IL-6) monoclonal antibody approved globally
- Specifically inhibit IL-6 signaling
- First therapeutic monoclonal antibody originated from Japan
- Co-developed globally with F. Hoffmann-La Roche



ACTEMRA®
tocilizumab

Actemra® - Global approval status

Japan	•	**2005**	**Approved for multicentric Castleman's disease**
	•	**2008**	**Approved for RA (S&S and PJD), sJIA, pJIA**
EU	•	**2009**	**Approved for RA (S&S)**
	•	**2010**	**Approved for RA (PJD)**
US	•	**2010**	**Approved for RA (S&S)**
	•	**2010**	**PJD application is under review**

Actemra® (RoActemra®) has been approved in more than 90 countries

ACTEMRA® tocilizumab

Current Unmet Medial Needs in RA

- With current therapies, disease control is inadequate to retard disease progression in majority of patients[1-3]
- Definition of inadequate response (IR) needed - poor level of agreement among patients and physicians[4]
- Current licensed biologic therapies in monotherapy only comparable to non-biologic DMARD (MTX) monotherapy[3]
- Data supporting anti-tumour necrosis factor (anti-TNF) switching are limited and conflicting[5]
- Need for new therapies with novel mechanisms of action persists[2,3]

DMARD = disease-modifying anti-rheumatic drug;
MTX = methotrexate.

[1]Smolen J, *et al. Nat Rev Drug Disc* 2003; **2**:473–488.
[2]Smolen J, *et al. Arthritis Res Ther* 2006; **8 (Suppl. 2)**:S5.
[3]Smolen J, *et al. Lancet* 2007; **370**:1861–1874.
[4]Wolfe F & Michaud K. *J Rheumatol* 2009; **36**:27–33.
[5]Voll R and Kalden J, *Ann N Y Acad Sci* 2005; **1051**:799–810.

ACTEMRA® tocilizumab

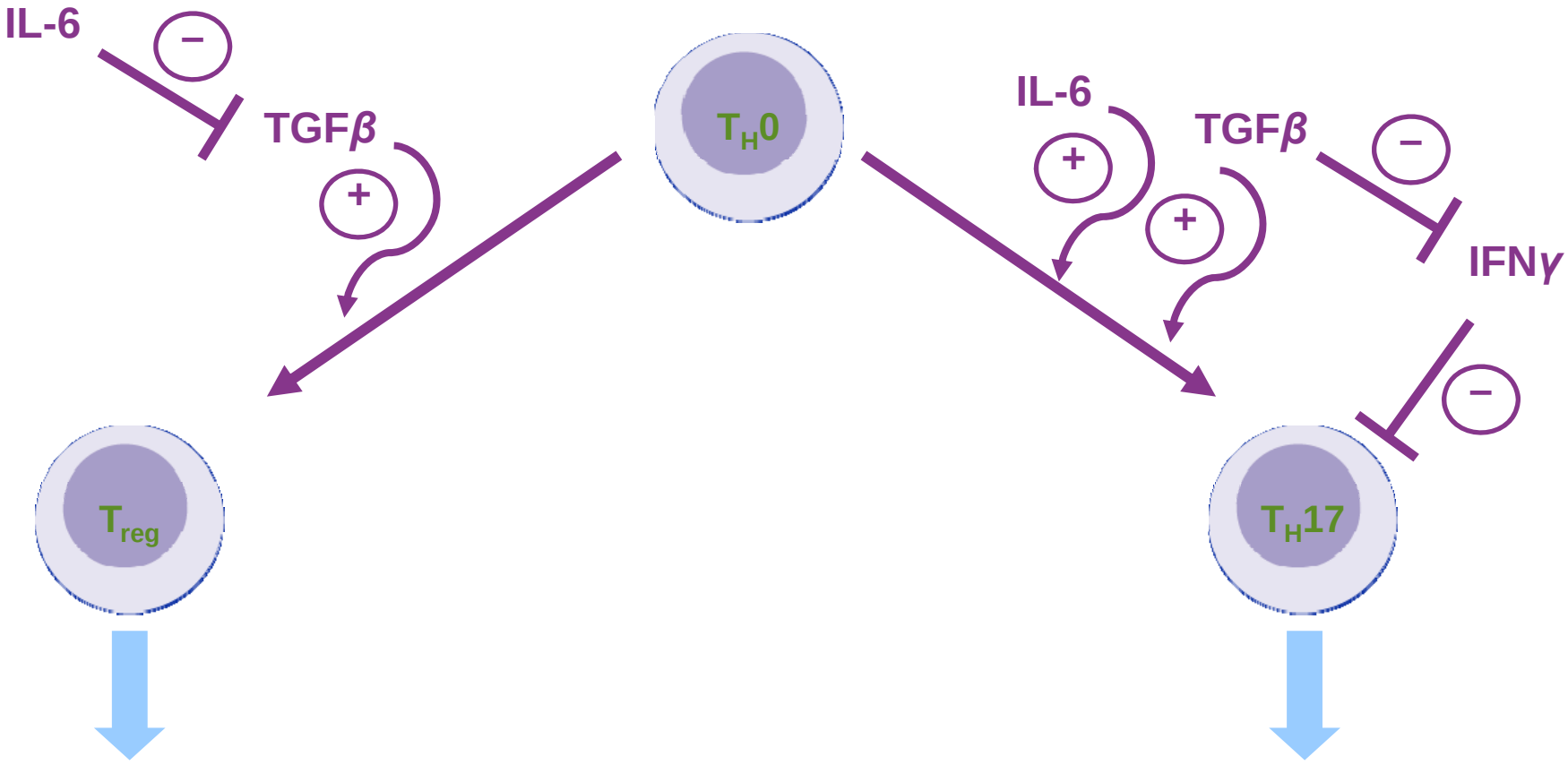
IL-6: Pivotal in inflammation and immunopathogenesis of RA

- Most abundant cytokine in joints and blood of RA patients (local/systemic effect)[1,2]
- Strong correlation between interleukin-6 (IL-6) levels and disease activity[3,4]
- Pivotal effect on autoimmunity
  - B-cell differentiation and antibody production[5], ↑ T_H17 cells (drives autoimmunity and perpetuates immune imbalance)[6,7]
- Unique systemic effects of IL-6 receptor (IL-6R) inhibition on:
  - C-reactive protein (CRP) production (inflammation)[2],Hepcidin (anaemia)[8,9], Osteoclasts/osteoblasts (osteoporosis/local joint destruction)[10], Hypothalamic–pituitary–adrenal axis (fatigue, pain, mood)[11–13]

[1]Madhok R, *et al. Ann Rheum Dis* 1993; **52**:232–234. [2]Choy E. *Rheum Dis Clin N Am* 2004; **30**:405–415. [3]Straub R, *et al. Br J Rheumatol* 1997; **36**:1298–1303. [4]Yoshizaki K, *et al. Springer Semin Immunopathol* 1998; **20**:247–259. [5]Youinou P and Jamin C. *J Autoimmun* 2009; **32**:206–210. [6]Fujimoto M, *et al. Arthritis Rheum* 2008; **58**:3710–3719. [7]Volpe E, *et al. Nat Immunol* 2008; **9**:650–657. [8]Andrews N. *J Clin Invest* 2004; **113**:1251–1253. [9]Nemeth E, *et al. J Clin Invest* 2004; **113**:1271–1276. [10]De Benedetti F, *et al. Arthritis Rheum* 2006; **54**:3551–3563. [11]Perlstein R, *et al. Endocrinology* 1993; **132**:946–952. [12]Chrousos G. *N Engl J Med* 1995; **332**:1351–1362. [13]Straub R and Cutolo M. *Arthritis Rheum* 2007; **56**:399–408.

ACTEMRA® tocilizumab

IL-6 controls balance between autoimmunity and self-tolerance - T_H17 cells/ T_{reg} cells



Bettelli E, *et al. Nature* 2006; **441**:235–238.

ACTEMRA® tocilizumab

Actemra® Clinical Development Program

JP program

N=691

>2,000 patient years

Global program

N=4,003

>10,000 patient years

One of the largest clinical program

J-PMS
[Interim Analysis]

N=3,881

≈1,900 patient years

Safety and efficacy profiles confirmed in the J-PMS, i.e. under real clinical practice were consistent with those identified in the Japanese and global clinical trials.

ACTEMRA®
tocilizumab

Actemra® Lifecycle Management

- **Builds superiority in RA**
  - **Head to Head with anti-TNF (Global)**
  - **REACTION study (JP)**
  - **Early RA (Global)**
- **Subcutaneous formulation**
  - **Ph-III in both Japan and global**
- **Extends RA**
  – IL-6 is involved with many disease, which will be extensively explored for the therapeutic application of Actemra®
  - **Pediatric indications (sJIA and pJIA) – US/EU**
  - **Other autoimmune/inflammatory diseases**
  - **Oncology**

ACTEMRA® tocilizumab

Removal of Conditions on Approval of Actemra® for Intravenous Infusion with All Patients Surveillance

CHUGAI PHARMACEUTICAL CO.,LTD.
Pharmacovigilance Manager
Shunji Yokoyama

2010.9.8

Approval History of Actemra

- Apr 2005 Obtained approval for
  - Multicentric Castleman's disease (MCD)
- Jun 2005 Launched for MCD
- Apr 2008 Approved for additional indications for
  - Rheumatoid arthritis (RA)
  - Polyarticular-course juvenile idiopathic arthritis (pJIA)
  - Systemic juvenile idiopathic arthritis (sJIA)
- Aug 2010 Conditions for approval regarding all patients surveillance removed with RA and pJIA indications

Conditions of Approval
(at the time of obtaining approval for additional indications)

◦MCD *(conditions at the time of obtaining initial approval)*

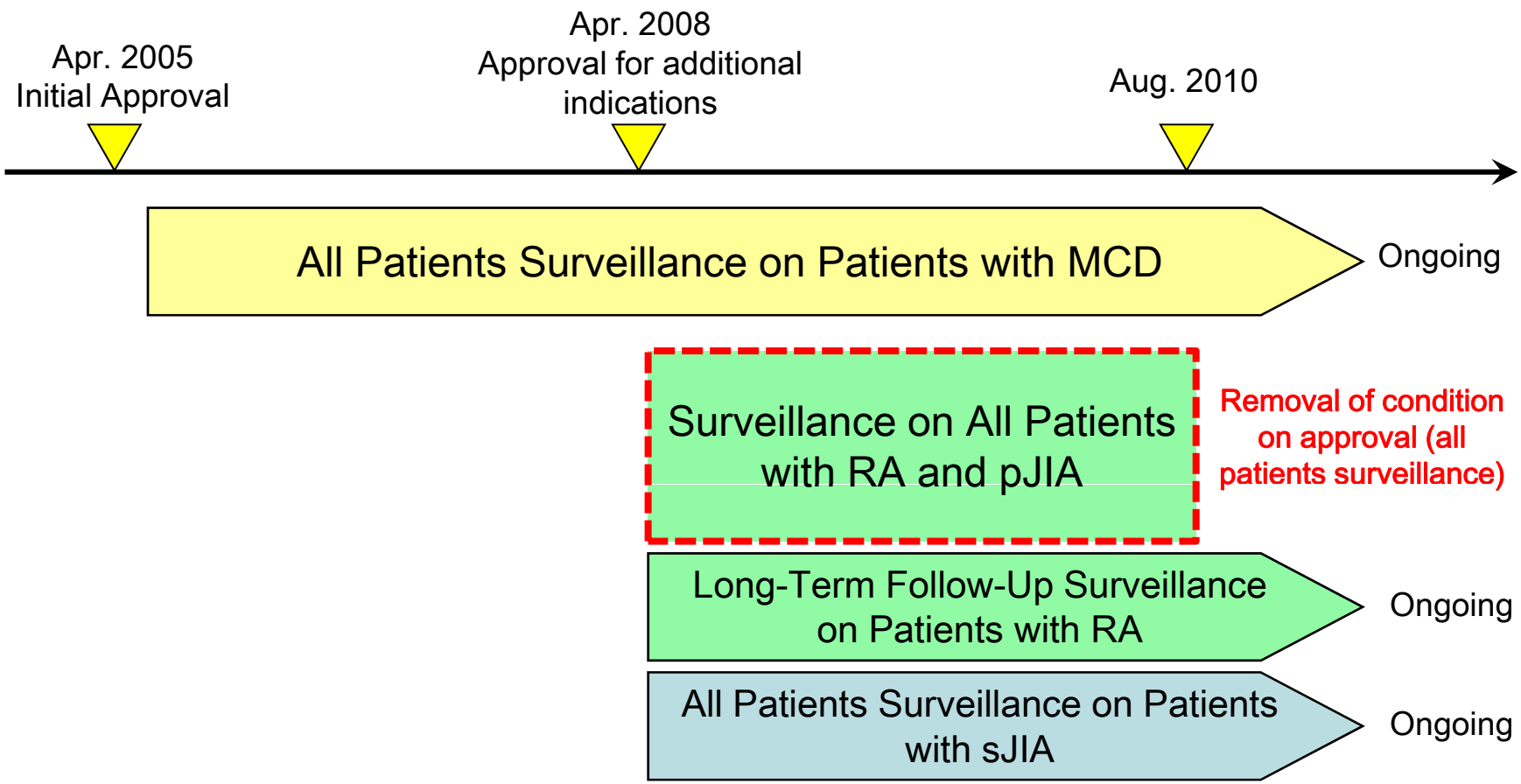
During the reexamination period, all patients treated with Actemra should be registered as subjects, and post-marketing surveillance of the efficacy and safety of Actemra including changes in lymph node swelling and effect on progression of complications should be conducted. At the same time, information about efficacy and safety of long-term treatment with Actemra should also be collected.

◦RA, pJIA, sJIA

(conditions added at the time of obtaining approval for additional indications)

1. After marketing, while data is being gathered for a fixed number of patients, safety and efficacy data for Actemra should be swiftly collected by conducting a drug use-results survey of all cases and necessary measures should be taken for the proper use of Actemra.
2. A large-scale post-marketing surveillance should be conducted with a comprehensive investigation of the safety of Actemra including the safety of long-term treatment and occurrence of infections, etc.

History of Post-Marketing Surveillance for Actemra



All surveillance studies are required as the post-approval commitments.

Summary of All Patients Surveillance for Patients with RA and pJIA

Objectives	To understand and evaluate the adverse drug reactions (ADRs) and factors which would influence safety and effectiveness of the drug in patients actually using Actemra	
Targeted patients	All patients with RA or pJIA who are administered Actemra	
Methods	Study method: central registration Number of prospective participants: undecided* Registration period: from date of approval to undecided day* Study period: from date of approval to undecided day* *When data is collected from 3,000 patients with RA, it will be analyzed and its result will be submitted to the authority. Post-marketing surveillance will be continued until final evaluation is conducted.	
Observation period	6 months from initiation of Actemra treatment	
Focuses of study	1. Infections 2. Gastrointestinal perforation 3. Cardiac function abnormalities 4. Malignant tumors	5. Anaphylactic shock / Anaphylactoid symptoms 6. Infusion reaction 7. Abnormal levels of lipids

Conditions on Approval (from Aug. 2010)

◦MCD *(no changes)*

During the reexamination period, all patients treated with Actemra should be registered as subjects, and post-marketing surveillance of the efficacy and safety of Actemra including changes in lymph node swelling and effect on progression of complications should be conducted. At the same time, information about efficacy and safety of long-term treatment with Actemra should also be collected.

◦RA, pJIA

A large-scale post-marketing surveillance should be conducted with a comprehensive investigation of the safety of Actemra including the safety of long-term treatment and occurrence of infections, etc.

◦sJIA *(no changes)*

1. After marketing, while data is being gathered for a fixed number of patients, safety and efficacy data for Actemra should be collected by conducting a drug use-results survey of all cases and necessary measures should be taken for the proper use of Actemra.
2. A large-scale post-marketing surveillance should be conducted with a comprehensive investigation of the safety of Actemra including the safety of long-term treatment and occurrence of infections, etc.

Safety Measures Up to Date and Future Actions

- Distribution management system
  - Prior confirmation on requirements of medical institutions and physicians, and prior explanation on delivery of the product to the medical institutions

  ⇒ *ongoing*

- Confirmation on prospective patients
  - Confirmation on eligibility of scheduled users with prior registration

  ⇒ *Conducted by medical representatives (MR)*

- Preparation of materials to promote proper use of Actemra (for medical professionals and patients)

  ⇒ *ongoing*

- Safety evaluation by external safety evaluation committee as well as Japan College of Rheumatology Post-Marketing Surveillance (PMS) Committee

  ⇒ *continued until final evaluation is conducted*

- Providing information via the company website

  ⇒ *Scheduled to post interim and final reports on the company website*

The ongoing safety measures will be continued for use of Actemra with MCD and sJIA patients.

Guide for Healthcare Professionals

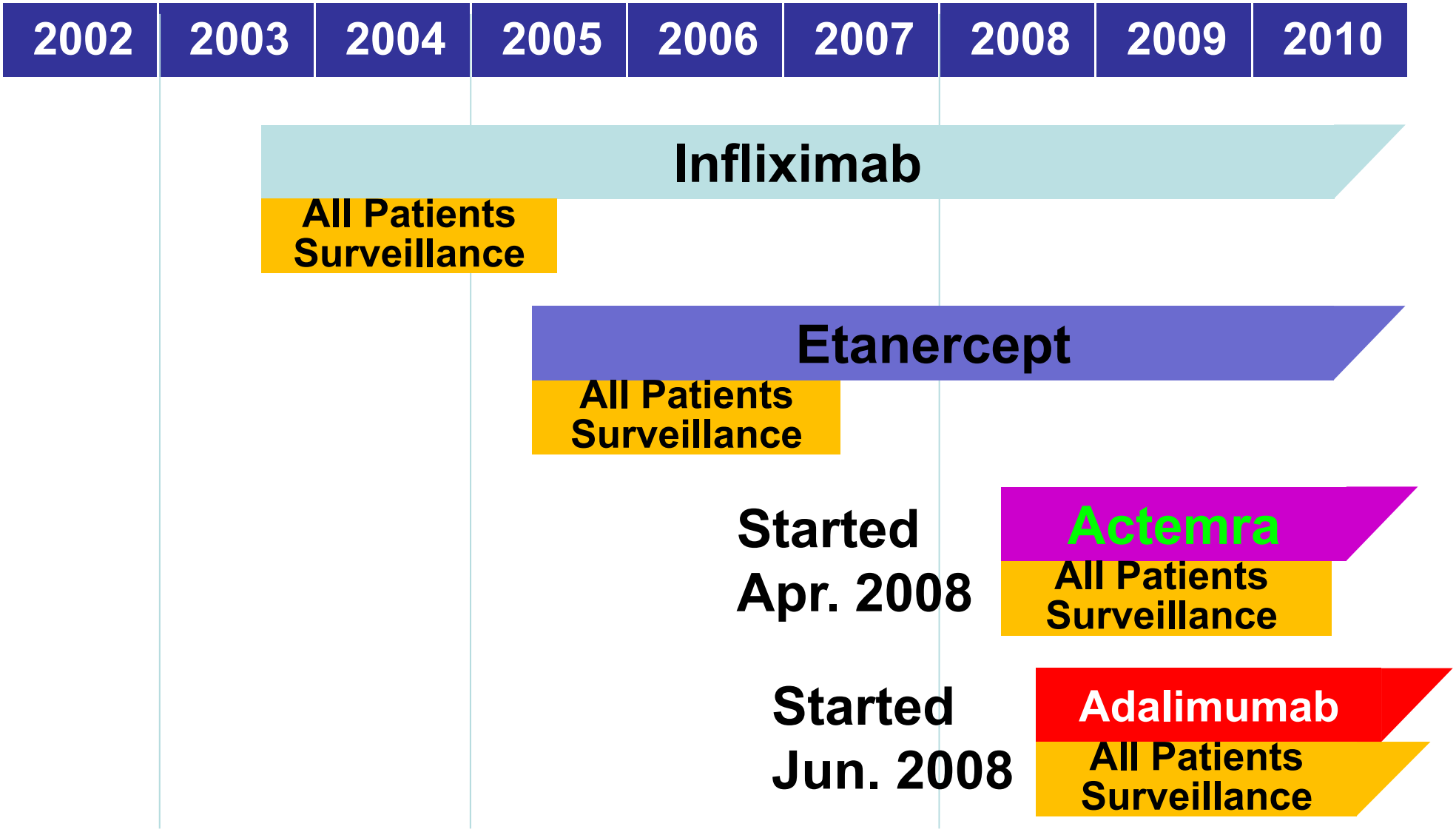
1. Prior explanation: We would explain to physicians, pharmacists and other medical professionals regarding, 1) proper use of Actemra (such as safety and efficacy, dosage and administration, prohibition on off-label use), and 2) safety measures taken by the company (such as distribution management system).
2. Distribution management system: Before the product is delivered to the medical institution, the following requirements have to be confirmed:
   - The medical institution has physicians who have sufficient knowledge and of Actemra experience with the treatment of RA or JIA.
   - The medical institution can cooperate with implementation of the safety measures for Actemra.
   - The medical institution can provide appropriate measurement including medications and emergency procedures if patients on Actemra urgently require them in cases of sudden changes in their conditions.
   - X-ray or CT scans can be conducted at the medical institutions for regular visits.

Actemra®
Results of All Patients Surveillance and Its Position in RA treatment in Japan

Tsutomu Takeuchi, M.D. Ph.D.
Division of Rheumatology, School of Medicine
Keio University

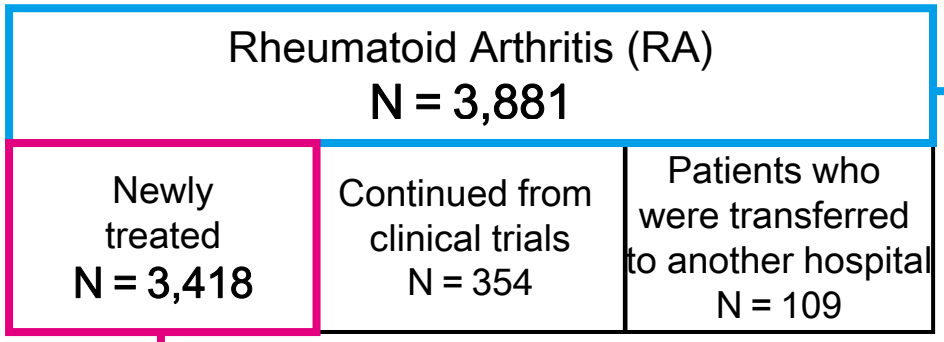
September 8, 2010

Biologics Approved for RA in Japan



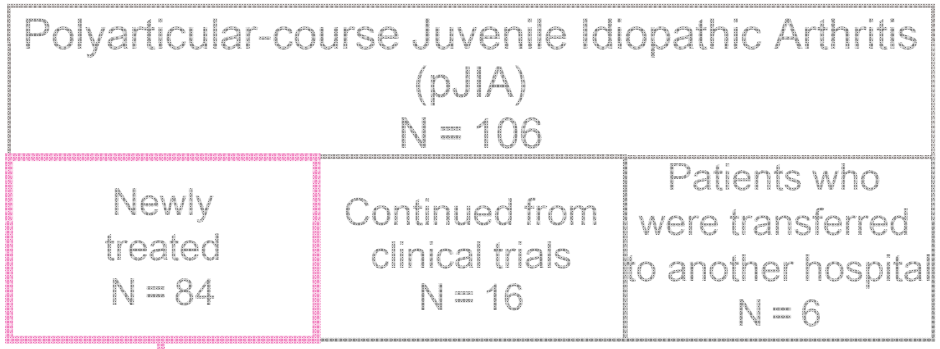
All Patients Surveillance

N=3,987
data collected by July 15, 2009



All RA patients enrolled (N=3,881) analyzed for:

- AEs of special interest
- Other events of interest
- Death cases



Newly treated patients analyzed for:

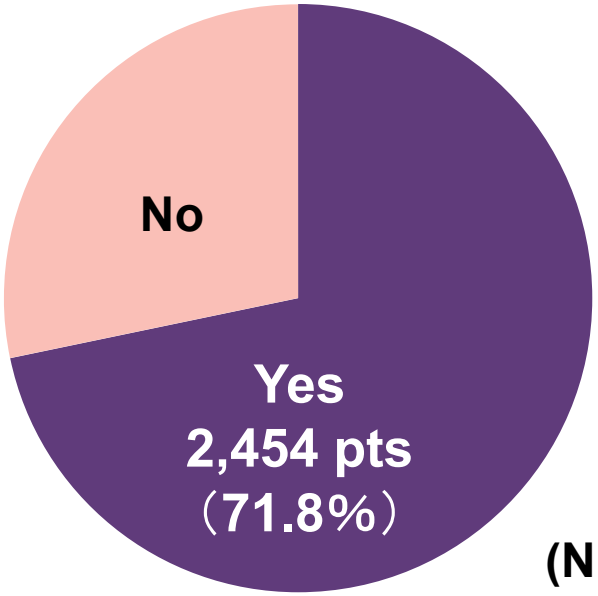
- Patient background
- Overall profiles of Adverse Drug Reactions
- Efficacy

Demographics and Baseline Clinical Characteristics

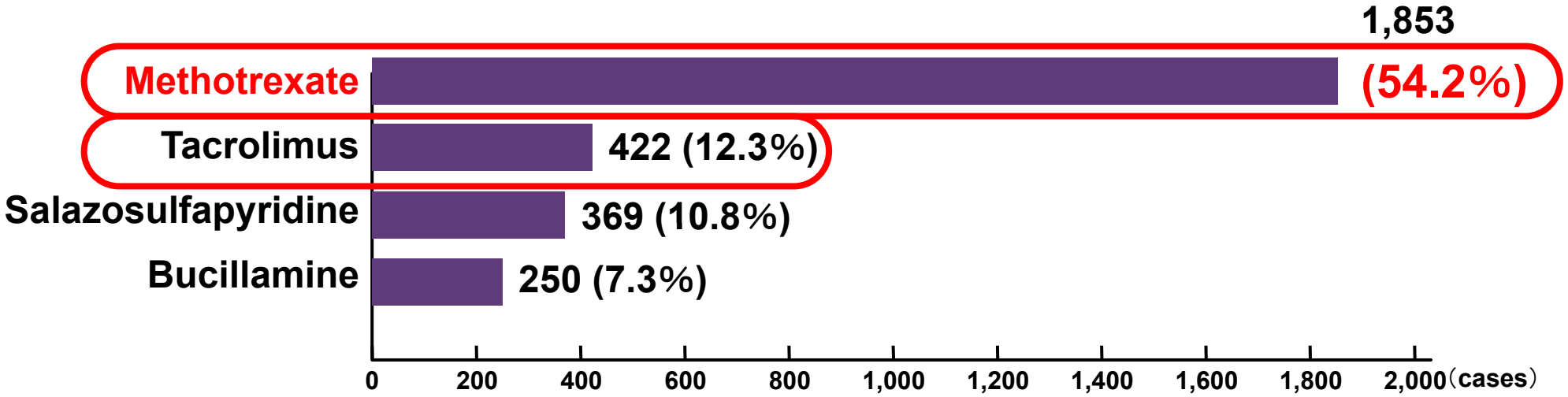
Demographics and Baseline Clinical Characteristics

	variables (Mean ± SD)
Total patient (newly treated)	3418
Age (years old)	58.8±12.9
Median (years, range)	60.0 (16.0-87.0)
% of >65 years old patients	37.1
Gender (% of female patients)	81.9
Body weight (kg)	52.9±10.3
Disease duration (years)	10.6±9.5
Median (years, range)	7.8 (0.0-71.4)
Concomitant DMARDs use (%)	71.8
Concomitant steroid use (%)	77.1
Previous biologics use (%)	68.1

Concomitant DMARDs

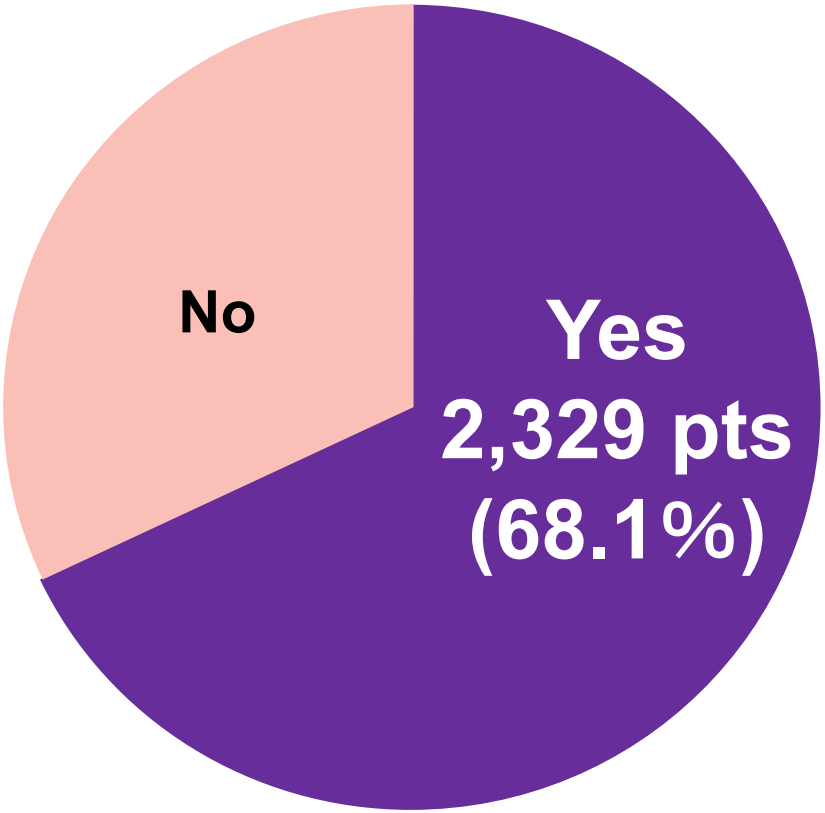


(N＝3,418)



Previous Biologics Use

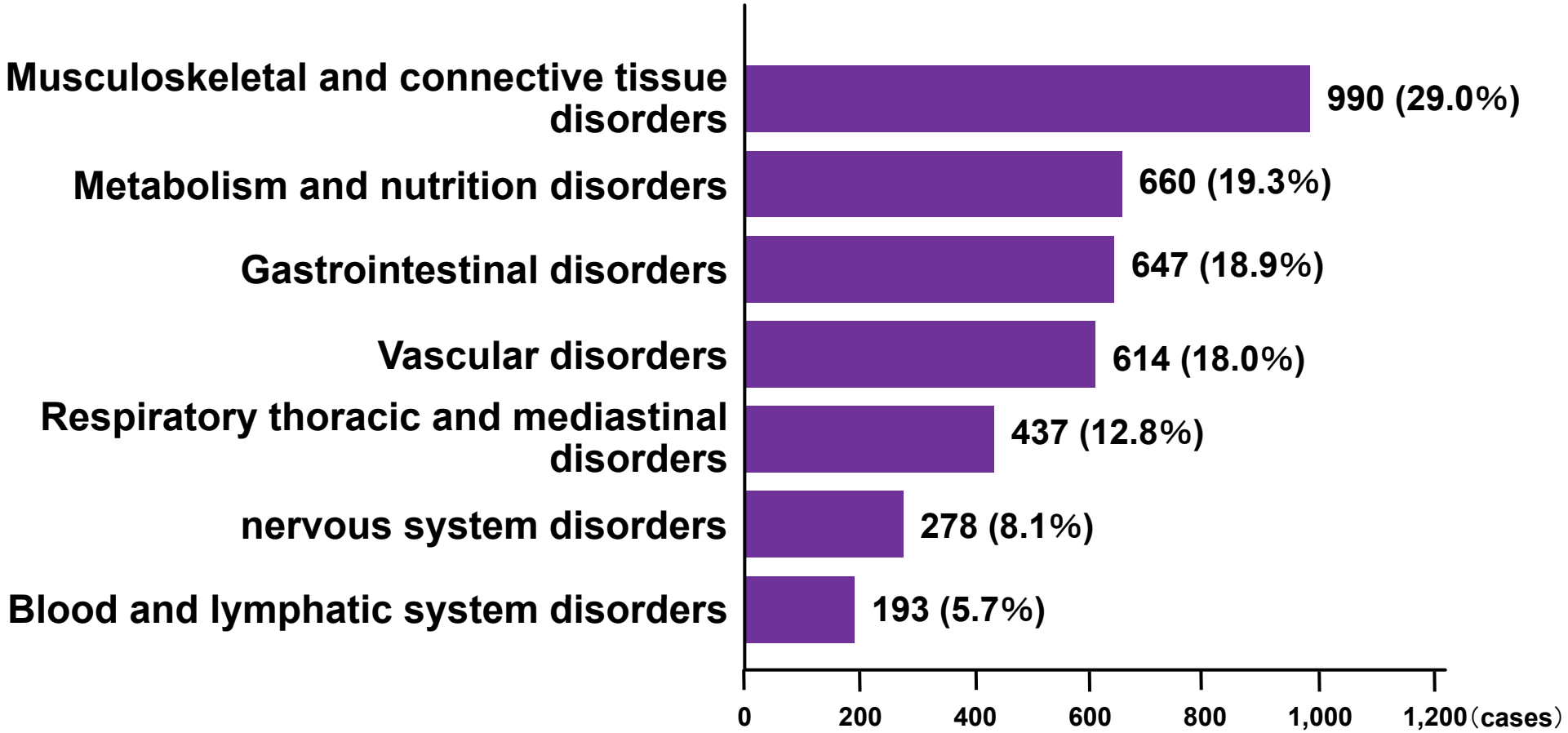
(N = 3,418)



	Previous Biologics		
	ETN	IFX	ADA
Number of patients	1,495	1,422	84
% (n=2,329)	64.2%	61.1%	3.6%

Comorbidities at Baseline

The proportion of patients with comorbidities = 64.6%



Comorbidities at Baseline

	tocilizumab (Actemra)	infliximab†
Total patients (n)	3,418	5,000
Hepatic disorder (%)	4.3	3.1
Cardiac disorder (%)	4.6	2.5
Diabetes mellitus (%)	9.9	9.4
Respiratory disorder(%)	12.8	4.7
Hematological disorder (%)	5.6	1.2
History of tuberculosis (%)	3.4	5.2

†;T takeuchi et al., *Ann Rheum Dis* 2008 67: 189-194

Comparisons of Patient Characteristics among Japanese PMS Programs

†; T Takeuchi et al., Ann Rheum Dis 2008 67: 189-194
‡; T Koike et al., JR 2009 36: 898-906

	tocilizumab (Actemra)	infliximab	etanercept
No. of cases in PMS	3,418	5,000	13,894
Approval date	2008.4	2003.7	2005.3
age (mean)	58.8	55.1	58.3
Disease duration	10.6	9.9	9.4
comorbidity	65%	38%	61%
concomitant MTX	54.2%	100%	49.8%
previous biologics	68.1%	0%	12.8%

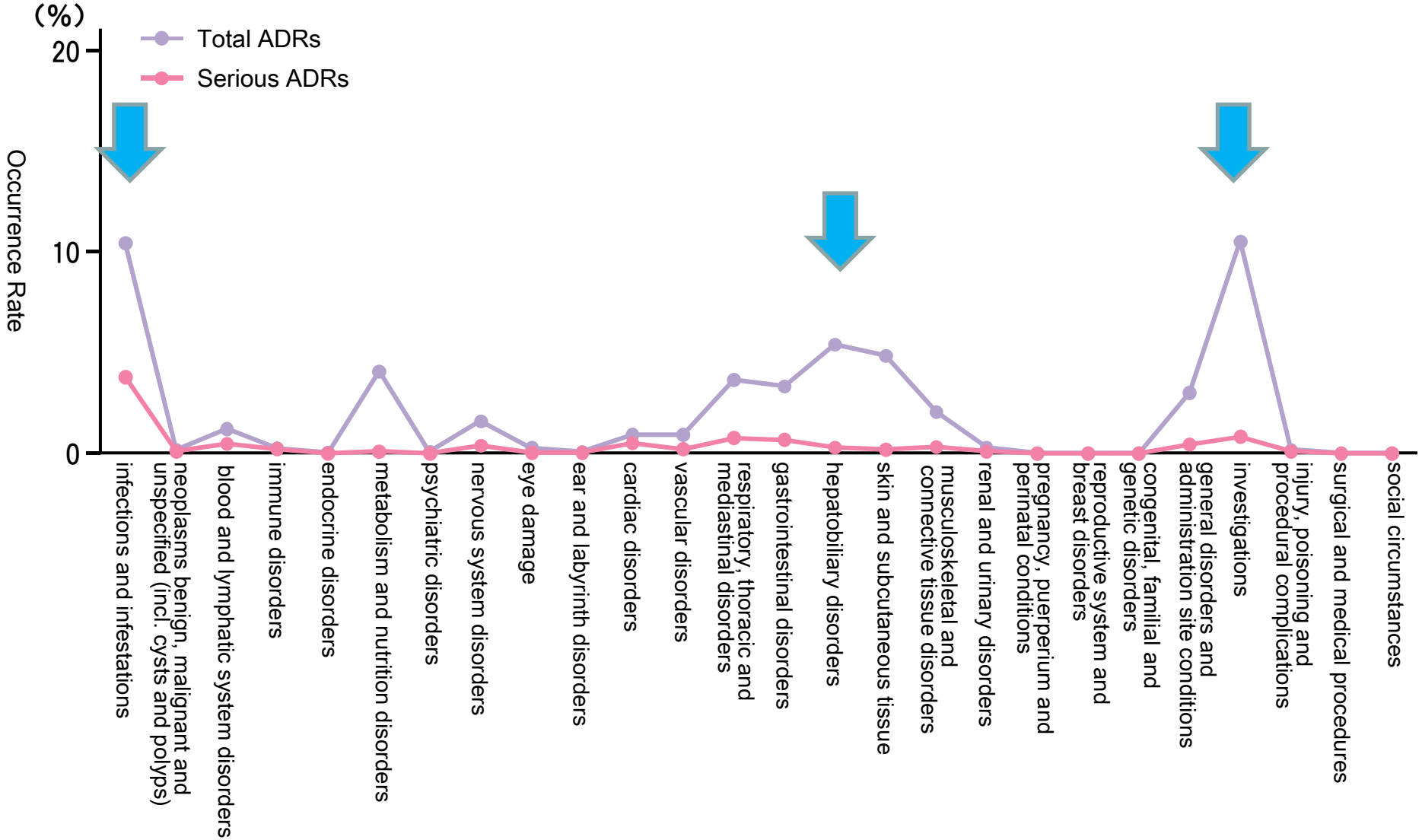
Adverse Drug Reactions

Incidences of Adverse Drug Reactions

	Actemra (n=3,418)
All ADRs (%)	37.9
Serious (%)	8.0
Non-serious (%)	32.6

ADRs by System Organ Class

The most frequent ADR is Clinical Laboratory Values(10.5%), followed by Infections and Infestations(10.4%), and hepatobiliary disorders(5.4%)



Common Adverse Drug Reactions (MedDRA PT)

category	subject	n (%)
infection (10.4%)	herpes zoster	50 (1.5%)
	nasopharyngitis	40 (1.2%)
	pneumonia	38 (1.1%)
	bronchitis	35 (1.0%)
laboratory abnormalities (10.5%)	white blood cell count decreased	115 (3.4%)
	blood cholesterol increased	62 (1.8%)
	platelet count decreased	51 (1.5%)
	blood triglycerides increased	38 (1.1%)
	alanine aminotransferase increased	36 (1.1%)
others	hepatic function abnormal	156 (4.6%)
	hyperlipidaemia	70 (2.1%)
	rash	59 (1.7%)
	hypercholesterolaemia	50 (1.5%)
	upper respiratory tract inflammation	46 (1.4%)

Infections

ADR	n (%)	Number of ADRs
Infections	389 (10.0%)	451
Serious infections	139 (3.6%)	154

Rate of infections by body region among 3,881 patients

Site of infections	n (%)
Respiratory infections	106 (2.7%)
Pneumonia	58 (1.5%)
Tuberculosis (pulmonary)	3 (0.1%)
Atypical mycobacteria infection	8 (0.2%)
Pneumocystis jiroveci pneumonia	6 (0.2%)
Urinary infections	24 (0.6%)
Skin infections	110 (2.8%)
Herpes zoster	52 (1.3%)
Cellulitis	34 (0.9%)
Sepsis	7 (0.2%)

Incidence of Pneumonia / Tuberculosis/PJP in Japanese PMS

Infections of interest	Japanese PMS
	Actemra (n=3881)
pneumonia	1.49% (n=58)
tuberculosis	0.1% (n=4)
Pneumocystis jirovecii pneumonia	0.2% (n=6)

Risk Factors for Serious Infections (139 pts)

– multiple logistic regression analysis

Adjustment factor	Control		Odds ratio	95% CI	P value
co-morbid or past history of respiratory disease	No	Yes	2.831	1.884-4.254	＜0.0001
age	＜ 65 years	≥ 65 years	1.712	1.148-2.552	0.0083
disease duration	＜10 years	≥ 10 years	1.582	1.055-2.370	0.0263
Steinbrocker Class	Class 1+2	Class 3+4	1.559	1.036-2.347	0.0332
daily dose of GCs at baseline	0 mg/day	≤ 5mg/day	1.039	0.593-1.819	0.8936
	0 mg/day	＞5mg/day	2.260	1.296-3.941	0.0040

All adjustment factors include gender, weight, existence infection and diabetes are included as modulators other than above

Risk factors for infections

- co-morbid or past history of respiratory disease
- elderly (age ≥ 65 years)
- disease duration ≥ 10 years
- Steinbrocker class 3 or 4
- Higher daily dose of GCs exceeding 5 mg/day

Interstitial Pneumonia

	Japanese PMS
	Actemra (n=3881)
number of pts	21
incidence (%)	0.54

Risk factors for interstitial pneumonia in TCZ (21 patients)
– multivariate logistic regression analysis

Adjustment factor	Control		Odds ratio	95% CI	P value
comorbid or past history of interstitial pneumonia	No	Yes	7.945	2.976-21.205	＜0.0001
age	< 65	≥65	5.128	1.650-15.936	0.0047
co-morbid infection	No	Yes	3.855	1.067-13.925	0.0395

All adjustment factors include history of smoking and concomitant use of MTX, other than above

Infusion Reaction

ADRs	Number of patients (%)
Total Infusion Reaction	135 (3.5%)
Urticaria	10 (0.3%)
Infusion-related reaction	10 (0.3%)
Blood pressure increased	10 (0.3%)
Headache	9 (0.2%)
Pyrexia	9 (0.2%)
Dizziness	8 (0.2%)
Anaphylactic shock	8 (0.2%)

Gastrointestinal Perforations

Subject	1	2	3	4	5	6	7
ADR term	Gastrointestinal perforation	Large intestine perforation	Small intestine perforation	Gastric perforation	Appendicitis perforated	Retroperitoneal abscess	Peritonitis
anatomical location of perforation	Small intestine	Large intestine	Small intestine	Stomach	Appendix	Unknown	Unknown
age/sex	53/Female	70/Female	55/Female	72/Male	60/Female	62/Male	73/Male
disease duration	9.9 years	28.9 years	13.9 years	11.9 years	6.4 years	1.5 years	20.4 years
stage	Stage IV	Stage IV	Stage IV	Stage II	Stage III	Stage II	Stage IV
class	Class4	Class3	Class4	Class1	Class2	Class2	Class3
number of infusion at development	1	4	1	5	5	5	5
outcome	Recovered	Improved	Recovered	Improved	Recovered	Recovered	Improved
concomitant GCs	Yes	Yes	Yes	Yes	Yes	Yes	No
Concomitant NSAID	No	No	Yes	Yes	Yes	Yes	No
confounding variable	Amyloidosis, colitis	Large bowel endoscopy procedure, salazosulfapyridine	foreign substance (fish bone)	(betamethasone phosphate 10 mg/day max.)	No	Methotrexate	Salazosulfapyridine

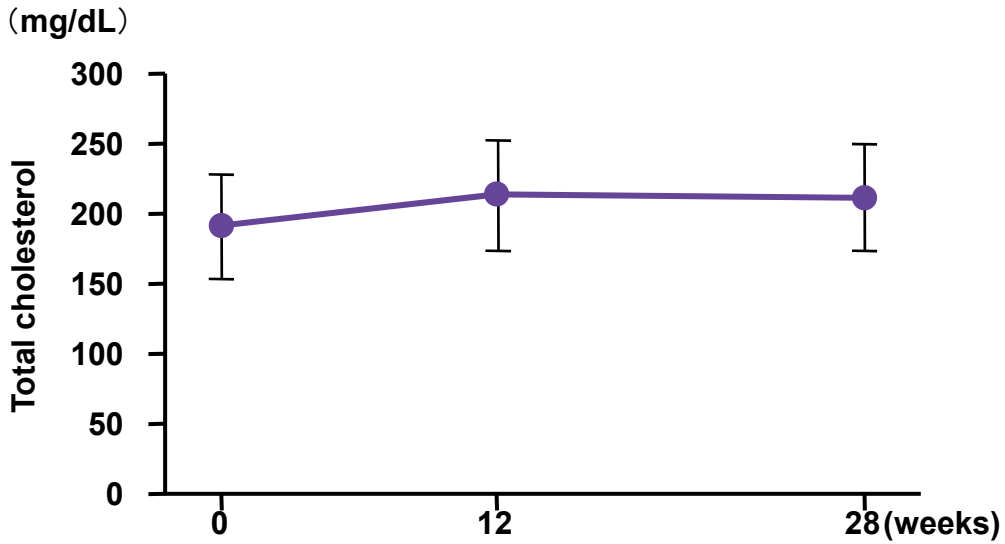
The incidence of GI perforation =0.2% (7/3,881)

Common Adverse Drug Reactions (MedDRA PT)

category	subject	n (%)
infection (10.4%)	herpes zoster	50 (1.5%)
	nasopharyngitis	40 (1.2%)
	pneumonia	38 (1.1%)
	bronchitis	35 (1.0%)
laboratory abnormalities (10.5%)	white blood cell count decreased	115 (3.4%)
	blood cholesterol increased	62 (1.8%)
	platelet count decreased	51 (1.5%)
	blood triglycerides increased	38 (1.1%)
	alanine aminotransferase increased	36 (1.1%)
others	hepatic function abnormal	156 (4.6%)
	hyperlipidaemia	70 (2.1%)
	rash	59 (1.7%)
	hypercholesterolaemia	50 (1.5%)
	upper respiratory tract inflammation	46 (1.4%)

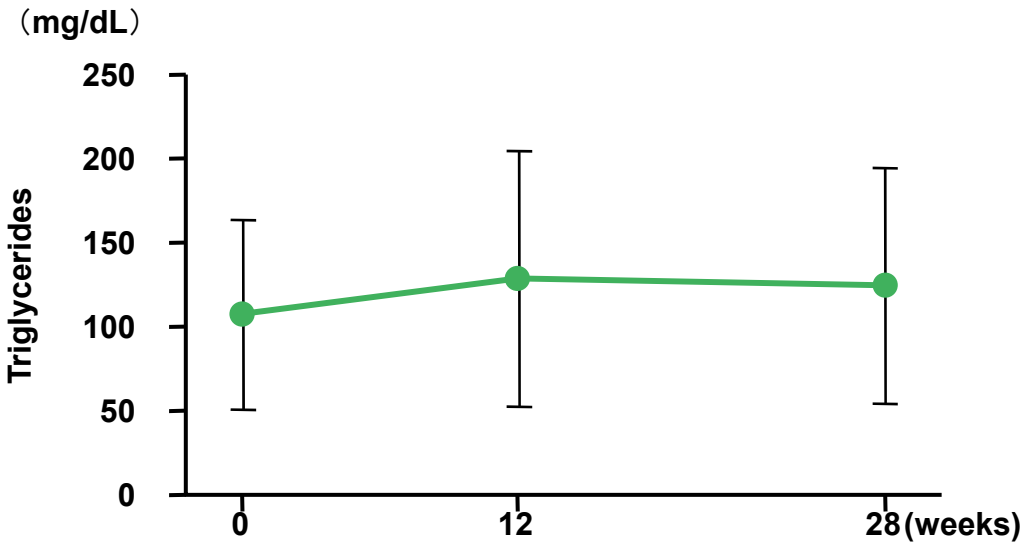
Lipid-Related Laboratory Abnormalities

Mean of total cholesterol



Time from treatment initiation

Mean triglycerides



Time from treatment initiation

- **Lipid-related abnormalities: 5.9% (230/3881 pts.)**
- **No cardiovascular events occurred in these 230 pts.**

Hepatic Function Disorder

The incidence of ADR = 6.6% (256/3,881)
The incidence of serious ADR =0.3% (10/3,881)

Risk factors for hepatic function disorder (256 patients)
– multivariate logistic regression analysis

Adjustment factor	Control		Odds ratio	95% CI	P value
Comorbid abnormal liver function	No	Yes	2.446	1.555-3.847	0.0001
Concomitant use of methotrexate	No	Yes	1.777	1.367-2.311	< 0.0001

All adjustment factors are shown above

Relationship between White Blood Cell Counts and Occurrence of Infection

	Grade*	Before Actemra treatment	Number of patients with infection	During Actemra treatment	Number of patients with infection
WBC count	Grade3;< 2,000-1,000/mm^3	No	No	18	No
	Grade4;< 1,000/mm^3	No		7	
Neutrophil count	Grade3;< 1,000-500/mm^3	2	No	67	No
	Grade4;< 500/mm^3	1		16	
Lymphocyte count	Grade3;< 500-200/mm^3	58	8	89	12
	Grade4;< 200/mm^3	4		14	

＊ CTCAE［Common Terminology Criteria for Adverse Events］（Ver.3.0）

Infection were reported in 8 patients who exhibited Grade 3 or 4 low lymphocyte count before Actemra treatment.
Actemra treatment should be avoided when low lymphocyte counts (e.g. <500/mm^3)

Key Messages -1-

- The adverse drug reactions (ADR) were reported in 37.9% of the 3,418 newly treated patients (1,296 / 3,418 pts)
- Serious ADRs were reported in 8.0% of the patients (275 / 3,418 pts)
- The common ADR were those categorized into “investigations”, “infections and infestations”, and “hepatobiliary disorders”.
- The most common infection was pneumonia and the incidence of pneumonia in the Actemra PMS was equivalent to those of other biologics.
- The risk factors of the serious infections were:
  - Comobidity and/or history of respiratory disorder
  - Concomitant use of high dose steroid exceeding 5mg/day
  - Eldery patients (65 years or older)
  - Long disease duration (10 years or more)
  - Class III or IV of Steinbrocker’s functional classification

Key Messages -2-

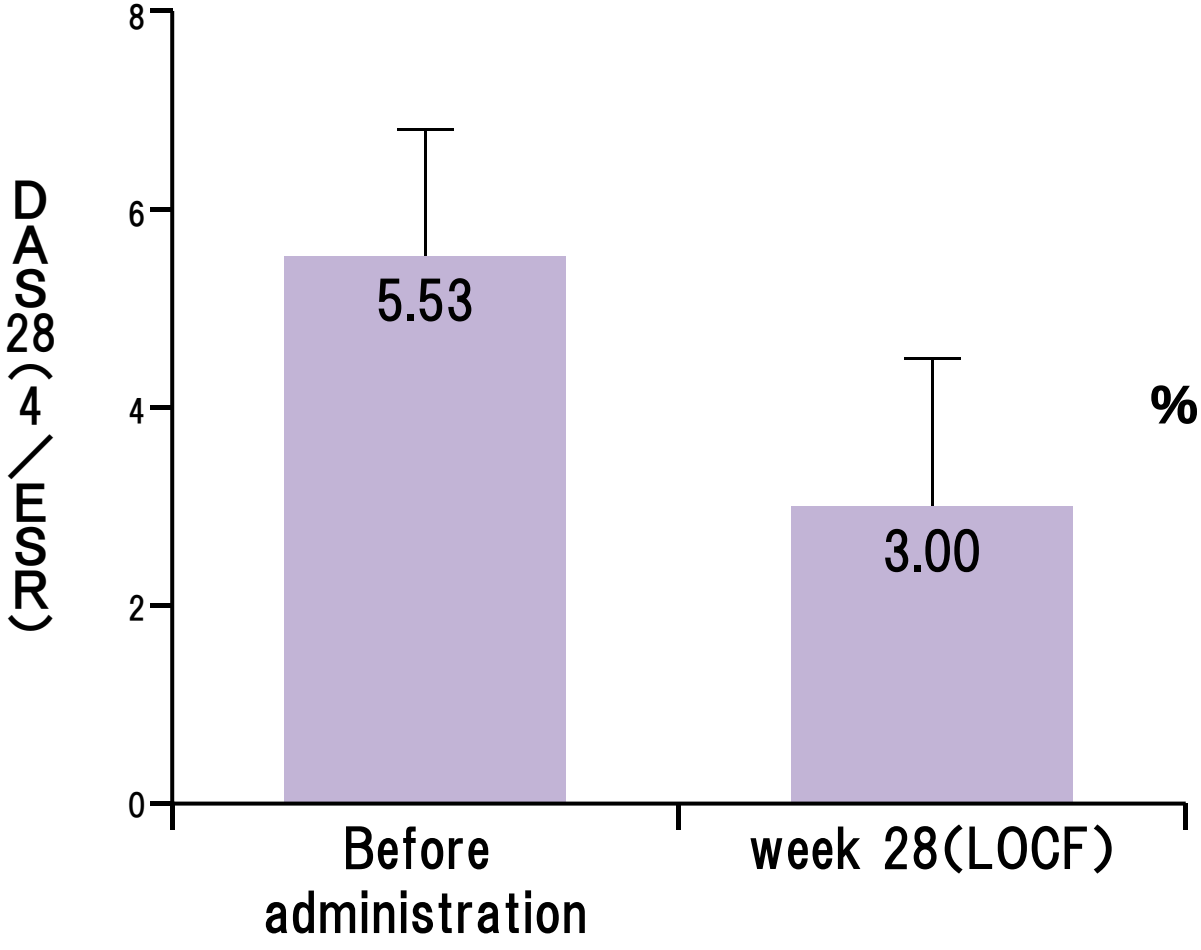
- Gastrointestinal perforation were reported in seven pts and six of them recovered with appropriate measures at the time of report.
- Although ADRs categorized into lipid abnormalities were reported in 230 (5.9%) patients, no cardiovascular disorder were reported in these patients.
- ADRs categorized into hepatic function disorders were reported in 6.6% of the patients.

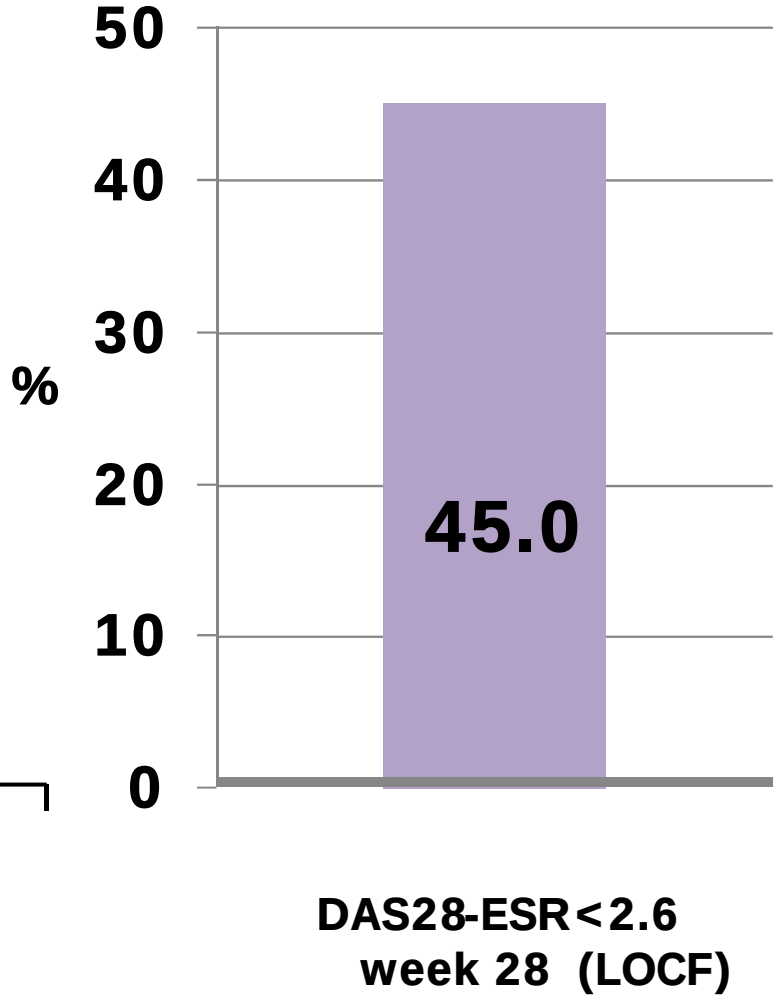
- better know the risks!
- carefully monitor the risks!
- promptly manage the risks!

Efficacy

Efficacy

DAS28-ESR and remission at week 28 n=2,072





1) Actemra interim report on all patient surveillance

REACTION Study

- Retrospective Actemra Investigation for Optimal Needs of RA Patients
- Analysis of efficacy of Actemra in multiple medical institutions under the daily clinical practice
- Data of 229 patients for six months were collected and analyzed from three medical institutions that initiated administration of Actemra by end of March 2009
  - Institute of Rheumatology, Tokyo Women's Medical University
  - The first department of internal medicine, school of medicine, University of Occupational and Environmental Health
  - Division of Rheumatology and clinical immunology, Department of internal medicine, Saitama Medical Center, Saitama Medical University
- Members
  - Drs. Hisashi Yamanaka, Daisuke Hoshi, Eisuke Inoue, Institute of Rheumatology, Tokyo Women's Medical University
  - Drs. Yoshia Tanaka, Kazuyoshi Saito, The first department of internal medicine, school of medicine, University of Occupational and Environmental Health
  - Drs. Kouichi Amano, Hideto Kameda, Division of Rheumatology and clinical immunology, Department of internal medicine, Saitama Medical Center, Saitama Medical University
  - Dr. Tsutomu Takeuchi, Division of Rheumatology, school of medicine, Keio University

REACTION Study –Summary-

- Efficacy observed in all RA patients treated with Actemra in three medical institutions under the daily clinical practice were evaluated.
- Over six-month treatment, 88% of patients achieved equal or better than “moderate” of EULAR response, and 40% of patients achieved DAS28 remission.
- Efficacy were higher in patients who were on Actemra in combination with MTX, than those with Actemra monotherapy.
- There was no difference in efficacy depending on the previous usage of anti-TNFs.
- Continuation rate at six months was 80%.

Efficacy of Actemra was confirmed under daily clinical practice

H Yamanaka et al., Modern Rheum revised

The Latest RA Treatment Target and Effective Use of Actemra

RA Treatment
-Dramatic Advance in Recent Years

- Revised RA classification /diagnosis criteria (09')
- Introduction of RA treatment goal(clinical remission) (09'-10')
- Innovative treatment strategy for patients with RA (ACR 08', EULAR 09')
- Revision of dosage and administration of the currently licenced drugs (Japan)
  - infliximab: approval of increased dosage and shortening of period (7/7, 09')
  - MTX: preparing to file "NDA based on evidence in the public domain" to increased dosage (JCR, Japan RA Patient Group)
- Approval/filing of novel treatments
  - Global: TNF inhibitors : certolizumab, golimumab (not yet approved in Japan)
  - Japan: TNF inhibitors (adalimumab), anti IL-6 receptor monoclonal antibody (Actemra/tocilizumab), and T-Cell co-stimulation modulator (abatacept)in 2010
- Development of new drugs with novel target
  - Cytokines (IL-6, IL-17A, IL-22, BAFF/R, GM-CSF-R, Jak, Syk)
  - Cell-surface molecules (CD20, CD22, CD44, RANKL)

Treatment Goal Has Changed!
- Higher and clearer target -

and…..

How to manage the treatment strategy to achieve higher goal?

- Tight Control -

Treatment Recommendation of European League Against Rheumatism

Recommendation	Scientific perspective		Economic perspective	
Treatment start	Level	State	Level	State
Therapy with synthetic DMARDs should be started as soon as the *diagnosis* of RA is made	1a	A	NA	NA
Treat-to-target	Level	State	Level	State
Treatment should be aimed at reaching a target of *remission* or *low disease activity* as *soon as possible* in *every* patient; as long as the target has not been reached, adjustment of the treatment should be done by *frequent** and *strict* monitoring *Once per 1-3 months	1a	A	1b	A
Strategies	Level	State	Level	State
Intensive medication strategies should be considered in every patient, patients with bad prognostic factors have *more to gain*	1b	A	NA	NA

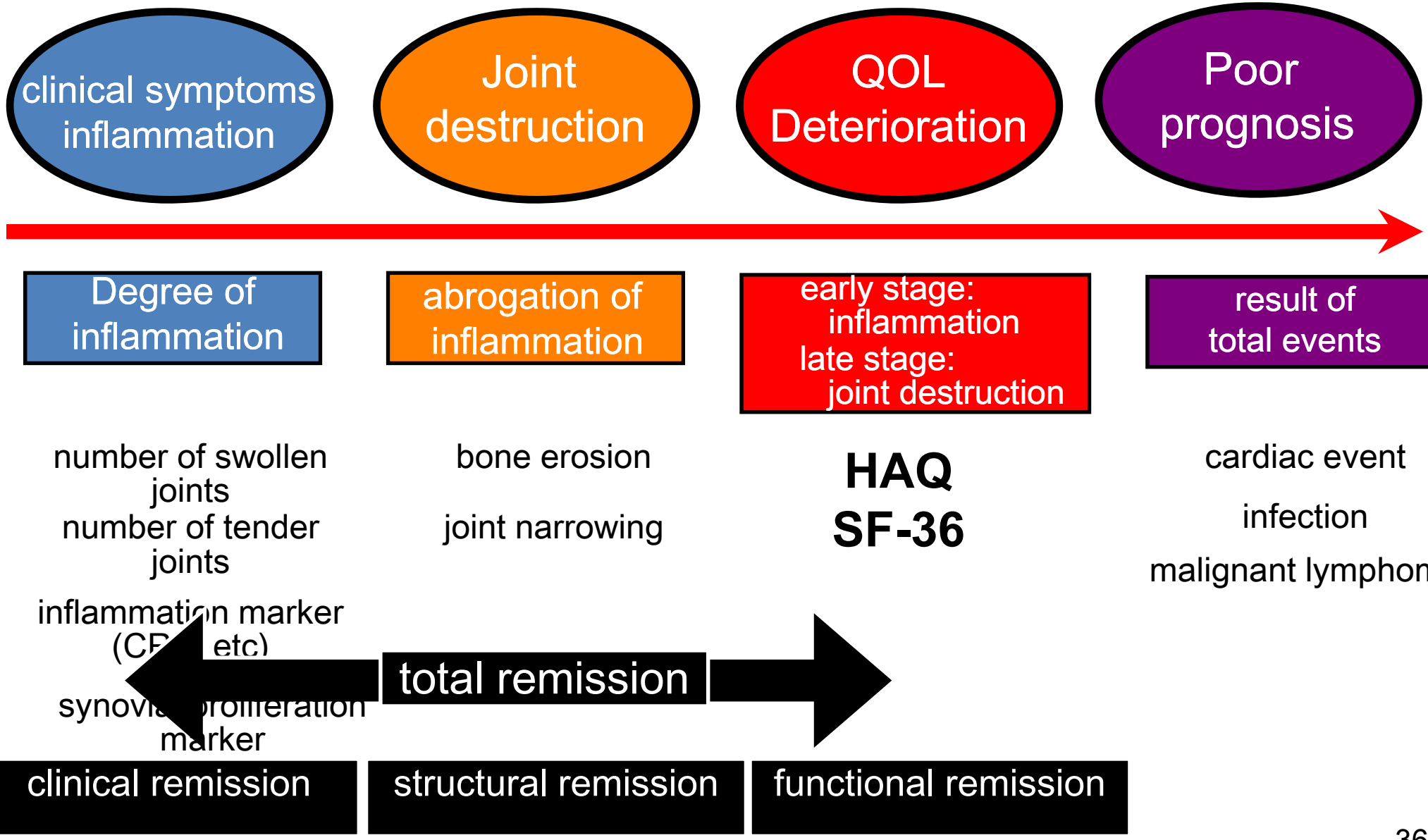
“Treat to Target, T2T”
- Overarching Principles-

A.	The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.
B.	The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation.
C.	Abrogation of inflammation is the most important way to achieve these goals.
D.	Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis.

TREAT TO TARGET

Smolen JS, et al. Ann Rheum Dis.2010.69:631-637

Clinical Condition and Evaluation in RA



Treat to Target (T2T)

-Recommendation Based on Evidence and Opinions of Professionals

1.	The primary target for treatment of rheumatoid arthritis should be a state of clinical remission
2.	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
3.	While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease
4.	Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
5.	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.

Smolen JS, et al. Ann Rheum Dis.2010.69:631-637

Treat to Target (T2T)

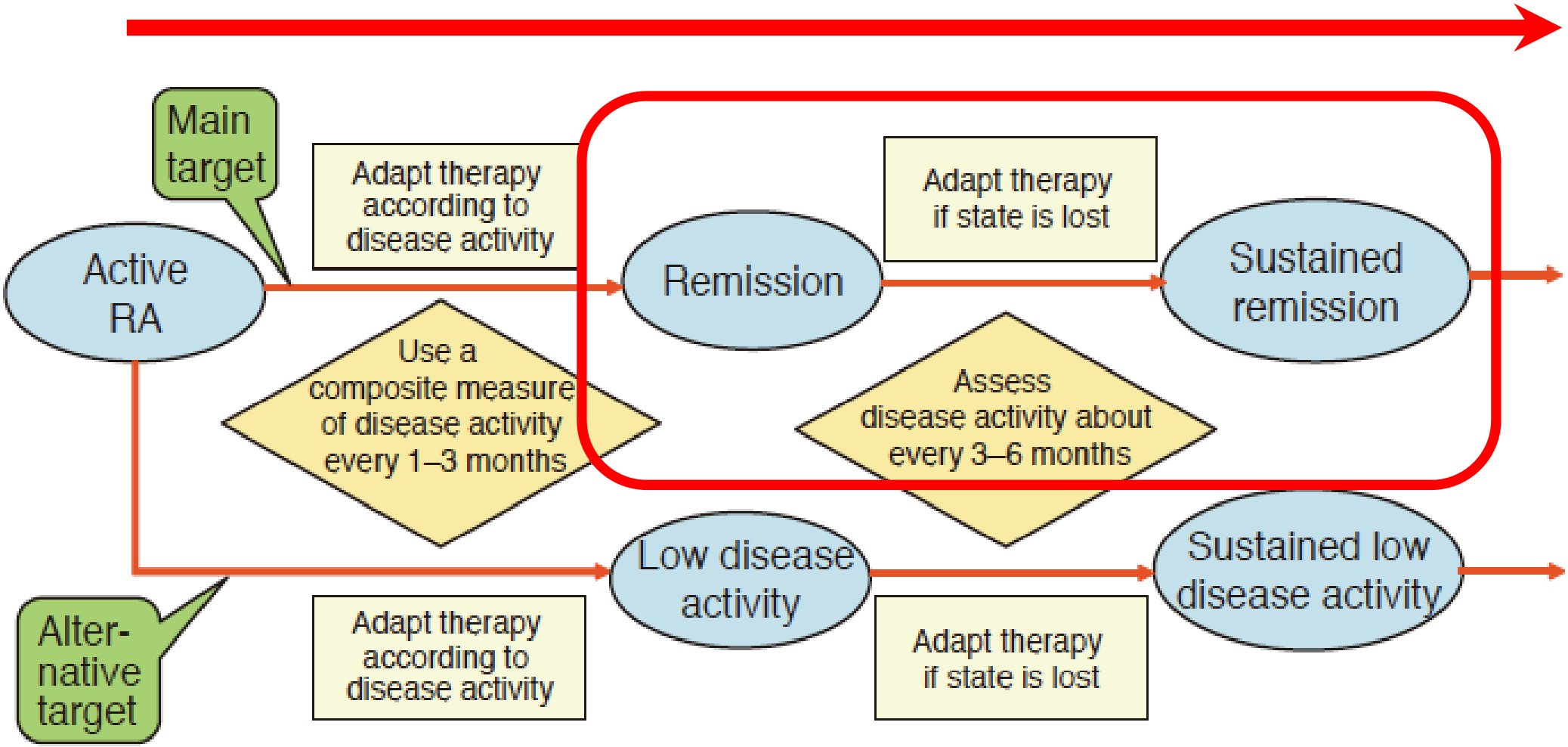
-Recommendation Based on Evidence and Opinions of Professionals

6.	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
7.	Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity
8.	The desired treatment target should be maintained throughout the remaining course of the disease.
9.	The choice of the (composite) measure of disease activity and the level of the target value may be infl uenced by consideration of co-morbidities, patient factors and drug-related risks.
10.	The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

Smolen JS, et al. Ann Rheum Dis.2010.69:631-637

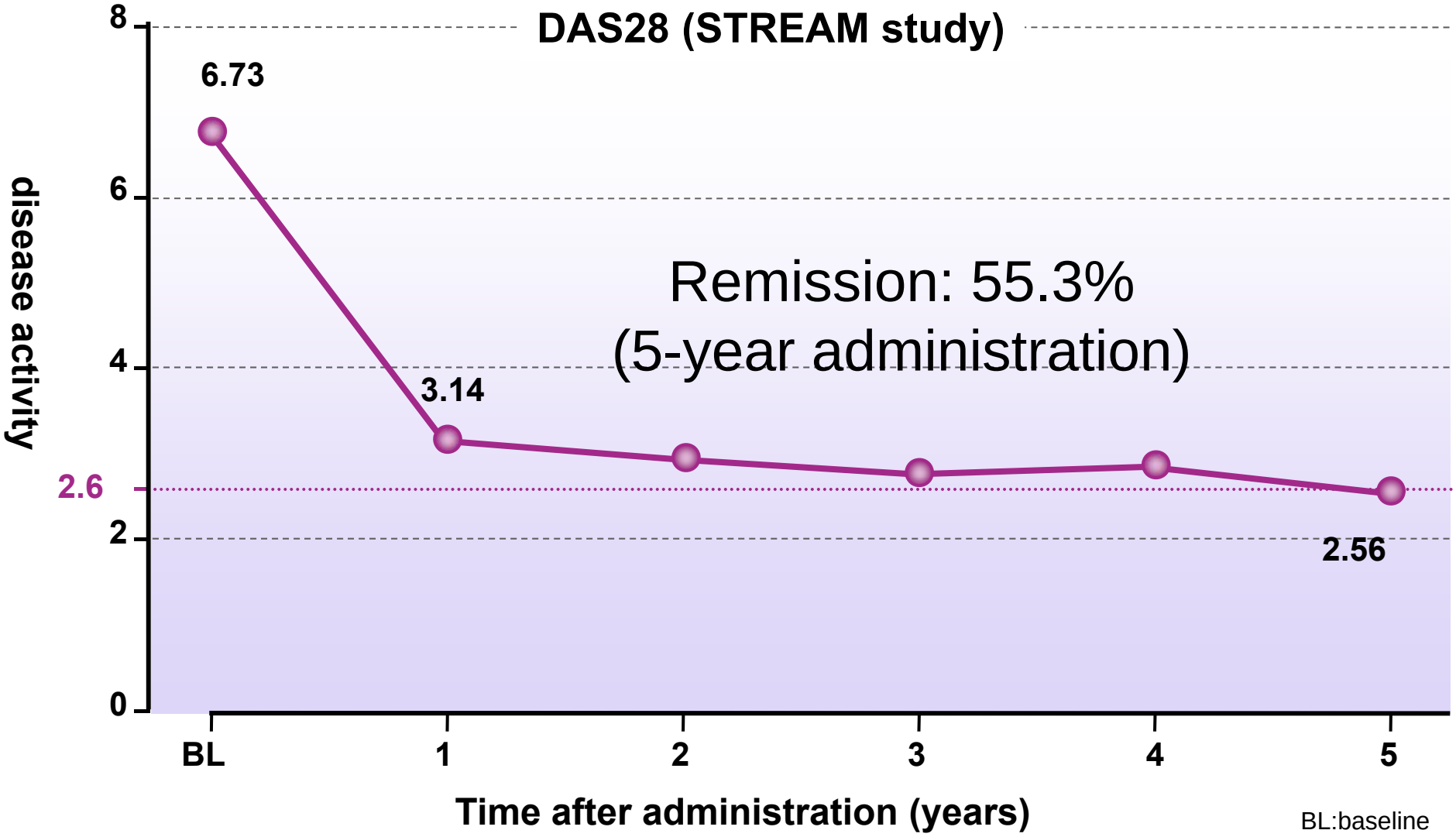
Algorithm for treating RA to target

Smolen JS, et al. *ARD March 9th, 2010*



Actemra Clinical Response (Japan)

High remission rate was sustained as long as five years

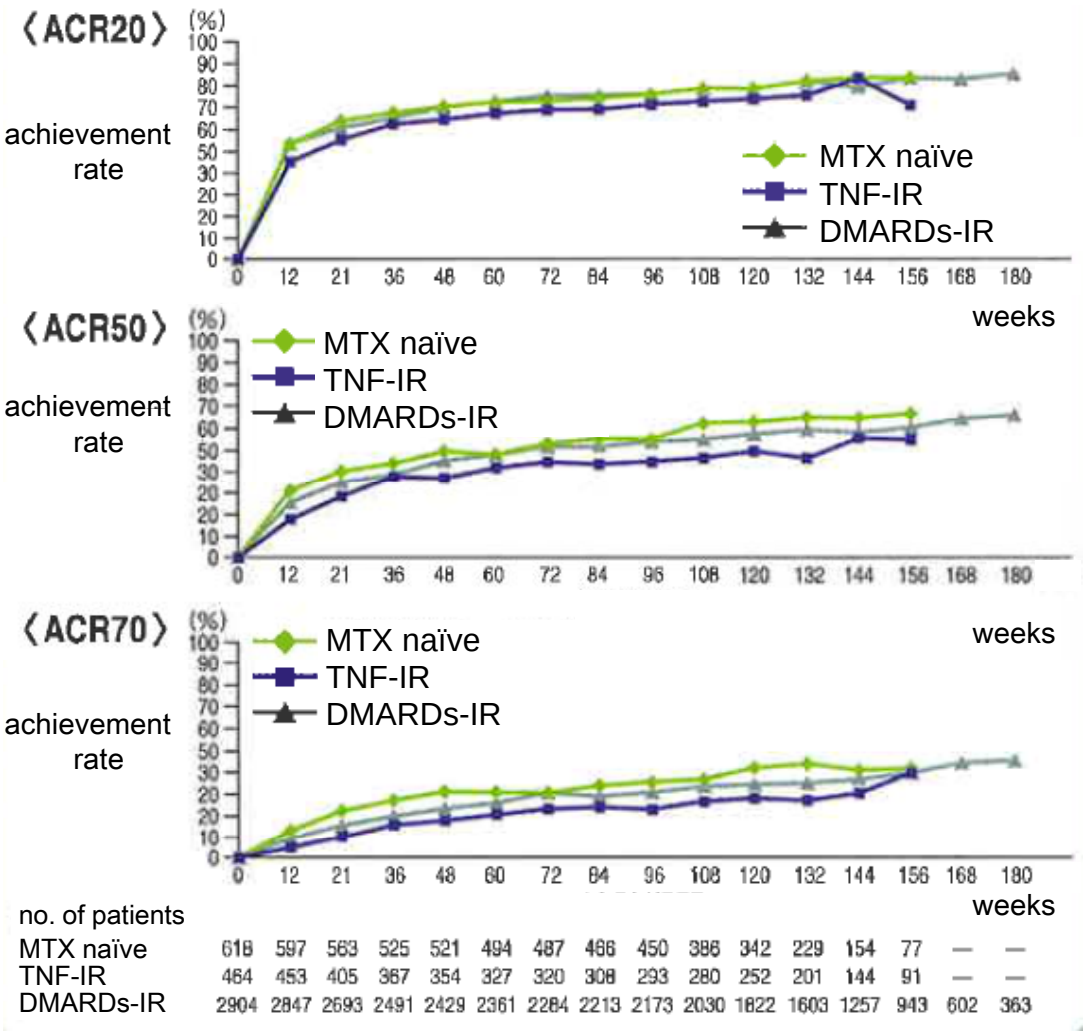


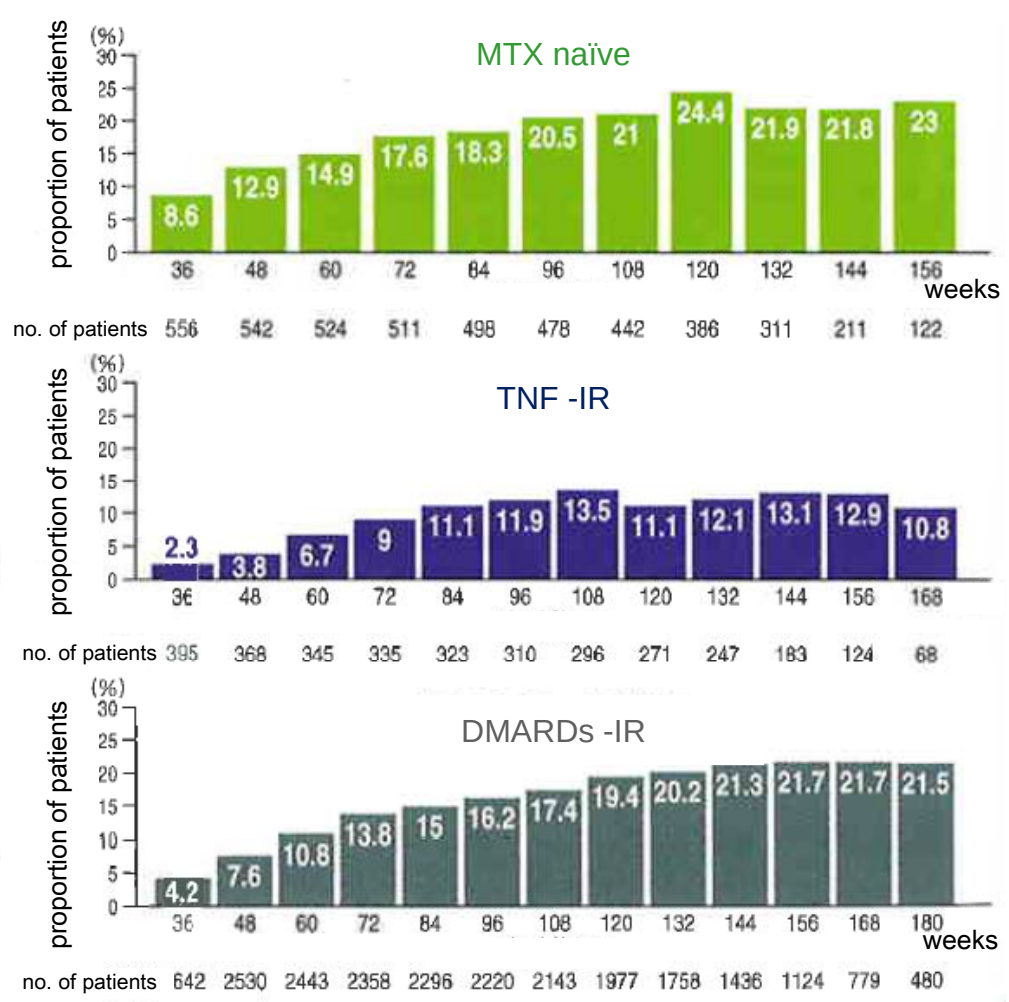
BL:baseline

Nishimoto N., et al. Ann. Rheum. Dis., 2009; 68:1580-1584

Actemra Clinical Efficacy (Overseas)

Improvement in ACR50 score for more than three years





*Pooled DMARD-IR: DMARD-IR from OPTION and TOWARD study

*MTX naive or 6 months no use of MTX prior to group allocation

Smolen J, et al., ACR 2009; Poster 413.

How to use Actemra to achieve higher treatment goals?

What to Do with Drugs?

- **select the “right” agent**
- **for the “right” patient**
- **at the “right” time.**

Bathon A&R 59: 757, 2008

Total Remission with Actemra

	Clinical Remission	Structural Remission	Functional Remission
DAS28	●		
HAQ	●	●	●
MTX dosage ↑	●		
PSL dosage ↓	●	●	

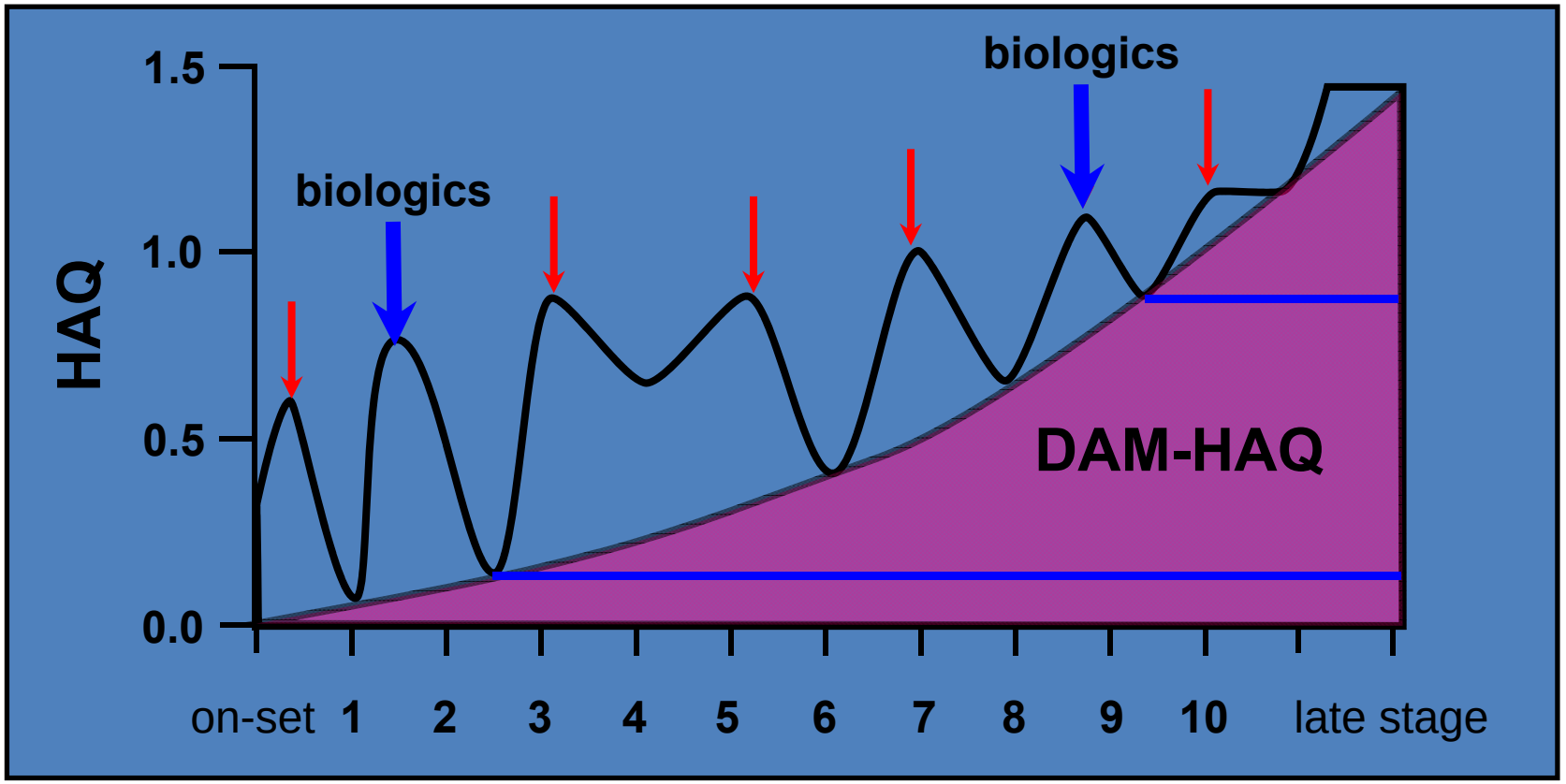
Control disease activity with Actemra before HAQ is deteriorated.

Clinical efficacy of Actemra does not depend on the prior use of anti-TNFs.

Use MTX to control disease activity before administration of Actemra.

There are Two Elements to HAQ: ACT-HAQ とDAM-HAQ

Igaku-no-Ayumi, vol.234 No.1 1-5 2010 revised



- HAQ worsens by 0.1 with TSS10 progression!
- To achieve HAQ=0.5 or below, the goal is TSS=50 or below!

If yearly progression is 10-25, 2-5 years from on-set!

How to Use Actemra Better

- 50% achieved clinical remission with patients who have inadequate response to anti-TNFs and high disease activity
- Need to consider the impact of disease duration, disease activity, HAQ and age on efficacy of Actemra.
- Infections needs to be carefully monitored together with potentially small changes in CRP values when experiencing infections.

Contacts : Corporate Communications Dept.

Corporate Communications Group

Tel: +81 (0)3-3273-0881 Fax: +81 (0)3-3281-6607
e-mail: pr@chugai-pharm.co.jp

Masayuki Yamada, Shinichi Hirose, Hiroshi Araki, Kae Miyata

Investor Relations Group

Tel: +81 (0)3-3273-0554 Fax: +81 (0)3-3281-6607
e-mail: ir@chugai-pharm.co.jp

Mac Uchida, Yumiko Watanabe, Yusuke Tokita, Chisato Kitamura