



Review Article

Treatment trends of rheumatoid arthritis in Japan:  
Changes toward globalization and its unique  
innovation

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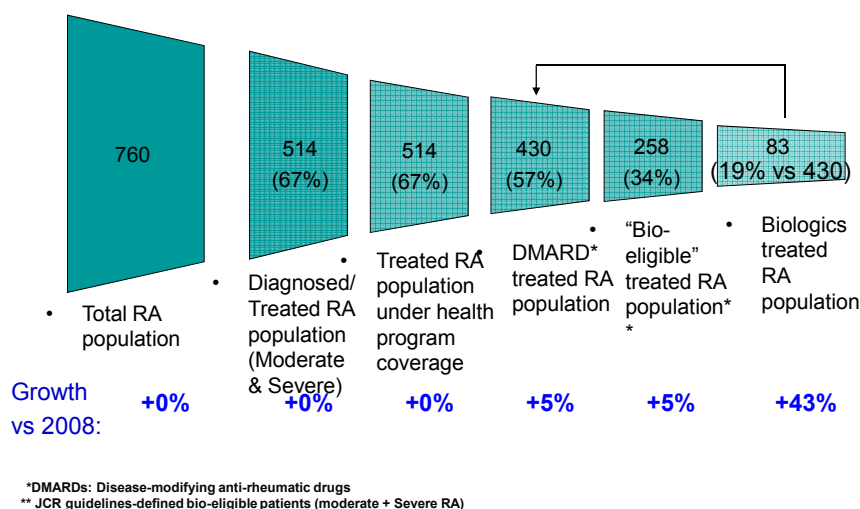
## Introduction

Rheumatoid arthritis (RA) is characterized by the inflammation and destruction of multiple joints. It can not only disturb quality of life but also shorten the lifespan of affected patients by causing comorbidities such as cardiovascular diseases<sup>1</sup>. Pathology includes new formation of blood vessels, inflammatory cell infiltration and synovial proliferation.

Abundant production of proteolytic enzymes such as metalloproteases, and inflammatory cytokines including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6) causes cartilage breakdown and bone destruction which lead to irreversible functional disability. In addition, chemokines produced in situ promotes recruitment of inflammatory cells in the joints.

### RA Patient Flow in Japan (2009)

#### • Number of RA patients – 760,000



**Figure 1**

**RA patient flow in 2009**

The ultimate goals in the treatment of RA are to prevent joint damage and restore normal life<sup>2</sup>. Nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) have been widely used in combination to control disease activity without complete success. Methotrexate (MTX), a folic acid antagonist that inhibits DNA and RNA synthesis, is the most potent, and commonly prescribed synthetic DMARD, and can retard joint destruction<sup>3,4</sup>. Treating RA early has been recommended<sup>5</sup>, however, the limitations of conventional DMARDs include insufficient capacity to prevent progression of damage and deterioration of physical function of the patients, and toxicities to the liver, the bone marrow and the lung<sup>6</sup>. Introduction of biologic DMARDs, i.e. biological agents which

inhibit multiple activities of inflammatory cytokines such as TNF- $\alpha$  and interleukin-6 (IL-6) have significantly altered the natural course of the disease and prevented joint destruction. Of note, TNF- $\alpha$  blocking agents have shown to be remarkably effective in preventing joint damage progression. Among them, infliximab and adalimumab are both anti-human TNF- $\alpha$  monoclonal antibodies<sup>7,8</sup>, and etanercept is a recombinant soluble p75 receptor for TNF- $\alpha$ , respectively<sup>9</sup>. Abatacept is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7<sup>10</sup>. It is currently used in RA patients who have had an inadequate response to one or more DMARDs including TNF- $\alpha$  blocking agents and also in patients with early stage disease. Rituximab, an anti-CD20 monoc-



lonal antibody is also effective in treating RA patients refractory to TNF- $\alpha$  blocking agents but has not been approved in Japan<sup>11</sup>). Furthermore, tocilizumab, a humanized anti-IL-6 receptor antibody originally developed in Japan, started to be widely used in Japan showing significant efficacy in treating RA patients refractory to conventional treatments<sup>12,13</sup>).

### Characteristics of Japanese patients with RA and physicians taking care of RA patients

There is speculated to be approximately 760,000 patients with RA in Japan, of which 67% are estimated to have moderate to severe in disease activity and are treated under various health insurance programs (Fig. 1). The male and female ratio of RA in Japan is expected to be 1:4, which is comparable to Caucasians. The average body weight of patients is approximately 50 to 55 kg, which is about 20kg less than counterparts in the United States and Europe. This difference should be taken into consideration when a

fixed dose of biologics is used, such as etanercept and adalimumab.

The profile of physicians taking care of RA patients in Japan is unique when compared to those in the United States and Europe. Namely, physicians who take care of RA patients in Japan are divided into two populations in terms of their specialties; i.e. internists and orthopedic surgeons. Orthopedic surgeons used to take advantage of treating RA patients in Japan for many years since rehabilitation and reconstructive surgeries were the main treatment modalities for RA in addition to gold injection. However, rheumatologists trained in the field of internal medicine are growing rapidly in number with the introduction of synthetic DMARDs including methotrexate (MTX). Consequently, approximately half of the board members in the Japan College of Rheumatology (JCR) are internists at present. However, most of private physicians taking care of RA in daily practice are still orthopedic surgeons, which is a trend more prominent in the western part of Japan.

## DMARDs approved for RA in Japan and USA

<u>JAPAN</u>		<u>USA</u>	
oral gold		oral gold	
inject gold		inject gold	
sulfasalazine (max: 1000mg/d)		sulfasalazine	
D-penicillamine		D-penicillamine	
methotrexate (max: 8mg/w)		methotrexate	
lobenzarit		hydroxychloroquine	
bucillamine		azathiopurine	
mizoribine		minocycline	
actarit		staphylococcal protein A column	
tacrolimus (05)			
Domestic brands			
leflunomide	(03)	cyclosporine	
infliximab + MTX	(03)	leflunomide	(97)
etanercept	(05)	etanercept	(98)
adalimumab	(08)	infliximab + MTX	(99)
tocilizumab	(08)	anakinra	(01)
abatacept	(10)	adalimumab	(05)
		abatacept	(05)
		rituximab	(05)
		golimumab	(08)
		certolizumab	(09)

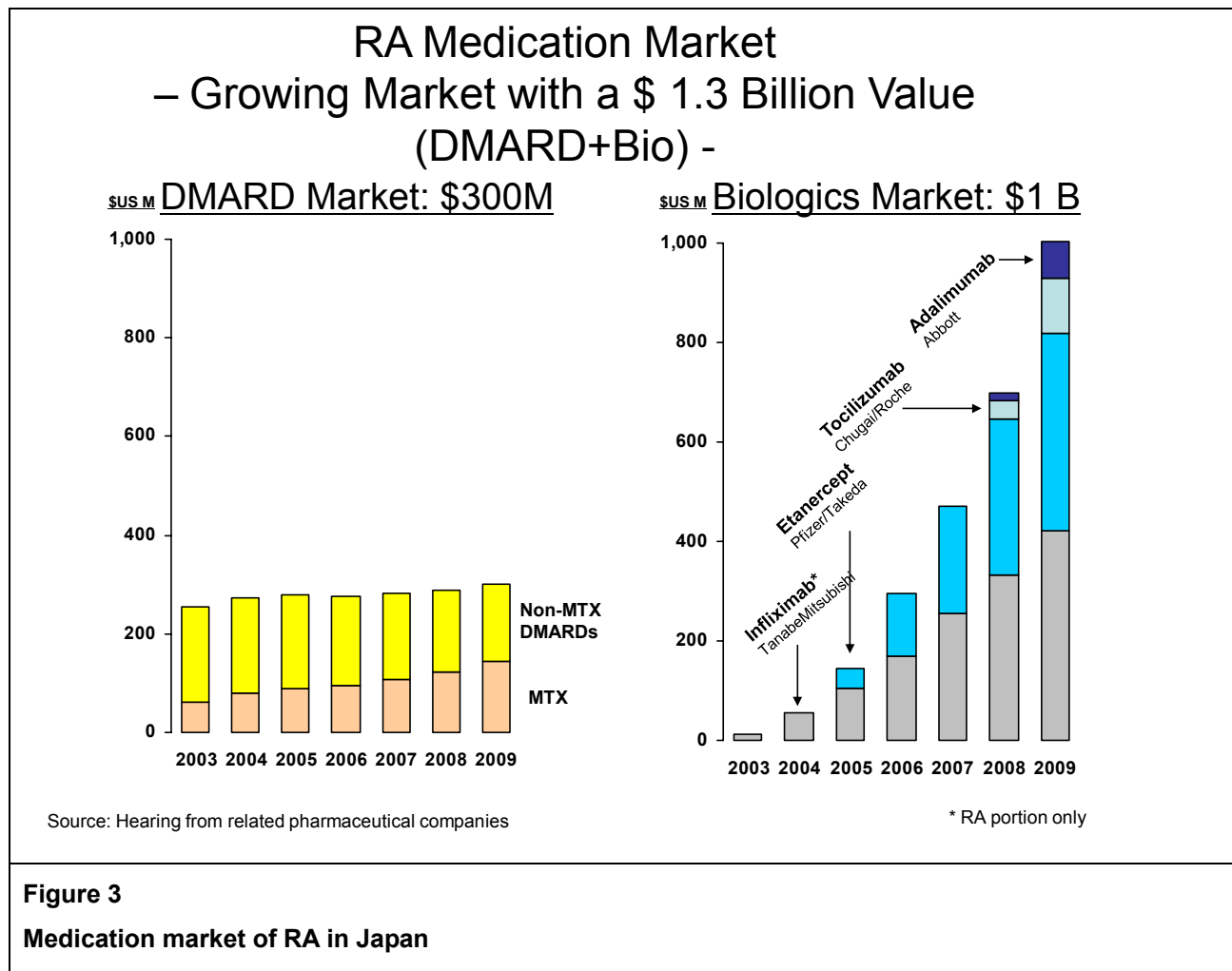
Figure 2

DMARDs approved in Japan



There is approximated to be 36,000 physicians in Japan who prescribe synthetic DMARDs, of which, 3,700 are board-certified rheumatologists by JCR. In addition, there are approximately 5,000 orthopedic rheumatologists certified by the Japanese Orthopedic Association and 4,000 physicians are enrolled as 'registered rheumatologists' by the Japan Rheumatism Foundation. Some overlap with

JCR-registered rheumatologists. This turmoil creates confusion among RA patients and also results in concerns of inappropriate use of synthetic and biologic DMARDs. Board-certified rheumatologists should therefore be unified in Japan in the near future to improve their quality and clarify their accountability.



## Characteristics in treatment modalities in Japan

Among these 760,000 patients, 430,000 (57%) are considered to be treated with DMARDs, of which about 83,000 (11%) are treated with biologics as of the end of 2009. DMARDs approved in Japan are illustrated in Figure 2. Although DMARDs are the first choice of RA treatment in Japan, there are several synthetic DMARDs mostly approved in Japan, such as bucillamine, actarit and mizoribine. Although most of them lack discrete evidences in haltering joint destruction

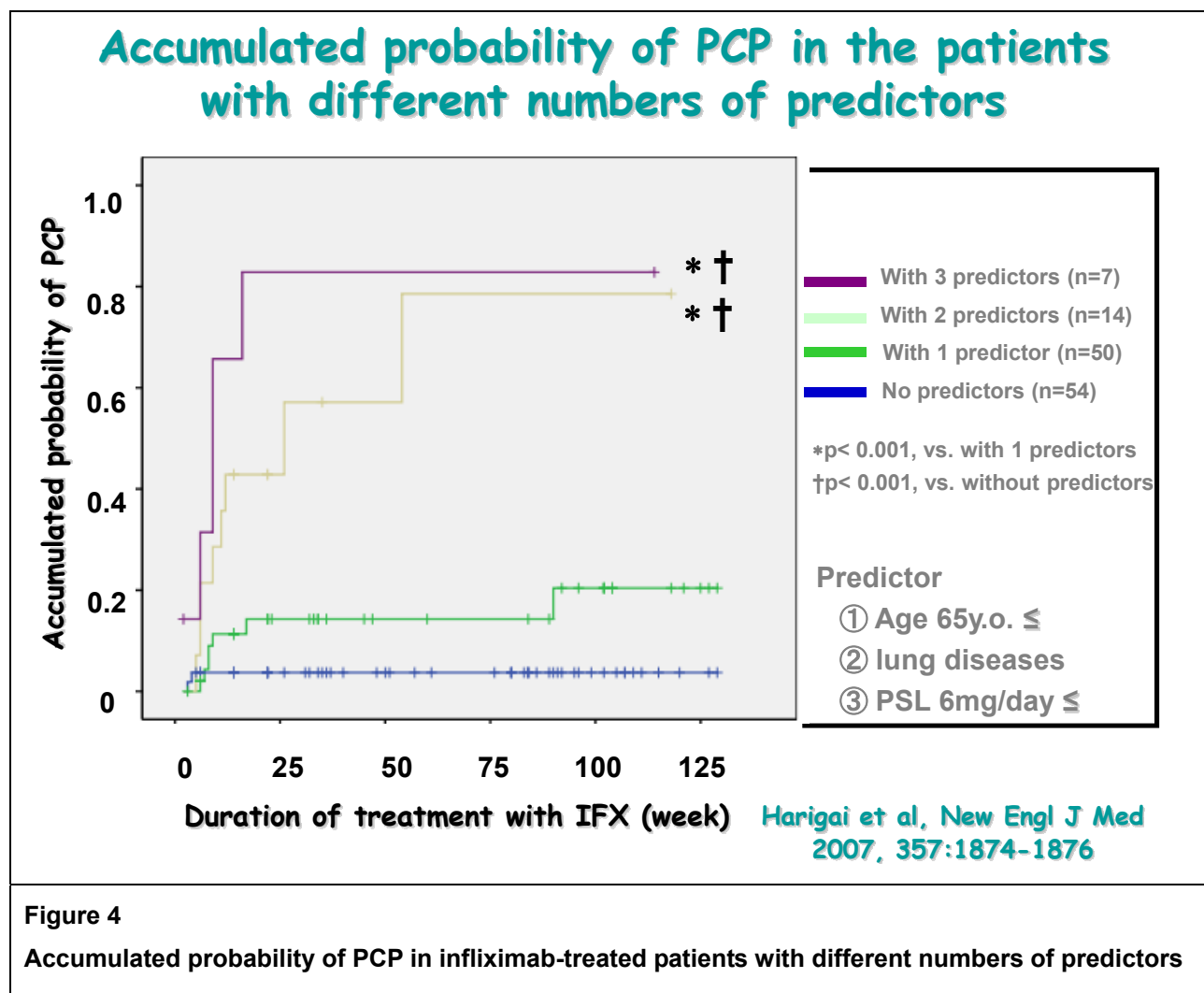
in RA but they tend to be administered by private physicians because of fewer adverse effects. Tacrolimus was also approved for RA patients only in Japan showing a significant anti-rheumatic effect<sup>14</sup>). However, it does not have robust evidence of preventing joint destruction.

MTX has become an anchor drugs in RA treatment globally, however, it is not a first-choice DMARD in Japan because of the package insert as of the end of 2010. Furthermore, there is a dosing restriction when using MTX, i.e. 8mg/week, which is far below any approved doses in foreign countries, since higher rates of adverse effects using



over 8mg/week without concomitant use of folic acid has been observed in Japanese clinical trials conducted back in the 1990's. However, JCR performed an extensive survey using four different cohorts on the efficacy and safety of MTX when used with doses over 8 mg/week, and concluded that MTX up to 16 mg/week can be used effectively and safely in Japanese RA patients with an 'on demand'

use of folic acid<sup>15)</sup>. Application for higher dose of MTX was submitted by Pfizer Japan Inc. in 2010 using these data in addition to the worldwide clinical data available, and is currently being reviewed by the approving agency. Approval of up to 16mg/week of MTX in adult RA patients and its first-line use are expected in early spring of 2011.



### Biological agents and their postmarketing surveillance (PMS) programs in Japan

The pharmaceutical market of DMARDs in Japan is calculated to be \$300 million and there is an increasing tendency to prescribe MTX among Japanese physicians every year reaching approximately 50% as of the end of 2009, although this figure is still lower compared with the United States and Europe. In contrast, that of biological DMARDs is increasing more rapidly reaching to \$1 billion

(Fig. 3). Most of the biologics prescribed in Japan used to be TNF- $\alpha$  blocking agents, i.e., infliximab and etanercept, since they were the first two biologics approved in Japan. However, tocilizumab and adalimumab are now expanding every year due to their high efficacy and safety. Of note, tocilizumab, an anti-IL-6 receptor monoclonal antibody, has been shown to be effective even in a majority of incomplete responders to TNF- $\alpha$  blocking agents and has just finished a postmarketing surveillance (PMS) program to prove its safety.

Clinical trials revealed higher response



rates to some biologics including infliximab, etanercept and tocilizumab<sup>16)</sup>. Treatment guidelines for TNF- $\alpha$  blocking agents in Japan were firstly published by JCR in 2005<sup>17)</sup>. Strict guidance in the selection of the target patient population was carried out to avoid “over-use” of biologics since safety information was limited in Japanese clinical trials. Furthermore, all-patient PMS programs have been imposed on all biologics approved in Japan as a condition of regulatory approval. Collection of safety data includes informations regarding serious infections, such as pneumonia and tuberculosis, including the onset, frequency and severity, and details of other adverse events and factors considered to affect the safety of the drug. Special qualifications for each treating physician and clinical site were required and participation of this program was limited to about 400-1,000 out of 25,000 estimated RA treating sites in Japan for all biological agent. Sample population was closely monitored for 24 weeks, the first 5,000 cases on infliximab<sup>18)</sup> and 13,894 on etanercept<sup>19)</sup>. The incidence of total and serious adverse reactions with infliximab were 28.0% and 6.2%, respectively. Bacterial pneumonia developed in 2.2%, tuberculosis in 0.3%, *Pneumocystis jirovecii* pneumonia in 0.4%. Identified risk factors for bacterial pneumonia were male gender, older age and advanced stage of RA and comorbid respiratory diseases.

### **Complication of *Pneumocystis jirovecii* pneumonia (PCP) among Japanese RA patients using biological agents**

Strict PMS of infliximab and etanercept revealed that incidences of PCP in Japanese RA patients were higher (0.4% and 0.2%, respectively) than those in Western countries<sup>20)</sup>. The corresponding incidence in the United States is ~0.01%<sup>21)</sup>. A multicenter, case-control study of PCP in RA patients receiving infliximab treatment was therefore carried out. Cox proportional-hazards regression analysis found that the hazard ratio for an age of at least 65 years was 3.77 (95% confidence interval (CI), 1.54 to 9.25), that for a daily dose of prednisolone of at least 6mg was 3.76(95% CI, 1.37 to 10.3), and that for the presence of coexisting pulmonary disease was 2.54 (95% CI, 1.00 to 6.46). PCP developed more frequently in patients with two or three

of the risk factors than in the other patients (Fig. 4). A further study from Japan demonstrated that the median length of time from the first infliximab infusion to the development of PCP was 8.5 weeks<sup>22)</sup>. At the onset of PCP, the median dosages of prednisolone and MTX were 7.5 mg/day and 8 mg/week, respectively. The patients with PCP had significantly lower serum albumin levels ( $P<0.001$ ) and lower serum IgG levels ( $P<0.001$ ) than the patients without PCP. Sixteen of the 21 patients with PCP developed acute respiratory failure, but all survived. Of note, there was no development of PCP when prophylactic administration of trimethoprim/sulfamethoxazole (TMP/SMX) was given. These studies showed that PCP is a serious and unique complication that may occur early in the course of infliximab treatment in Japanese patients with RA.

Possible explanations for the difference include; 1) anti-TNF therapy may more severely affect host defenses in Japanese patients with RA due to genetic or environmental differences, 2) Japanese patients with RA may have a higher prevalence of prolonged colonization of *Pneumocystis jirovecii*, or 3) the incidence of PCP in patients with RA receiving anti-TNF therapy in Western countries may be underestimated due to the voluntary reporting system for adverse events. Further study will be needed to clarify this finding.

### **Conclusion**

The treatment of RA in Japan is now changing rapidly. The treatment target is getting tighter with clinical remission or at least low disease activity with MTX being the realistic goal in concordance with global trends. The three types of remission, i.e. clinical, radiographic, and functional remission, have started to be recognized among Japanese rheumatologists. Use of biologics is recommended in the revised treatment guidelines for moderate disease patients<sup>23)</sup>. Furthermore, treatment guidelines have been continuously revised based on new findings from PMS programs.

A recent study by Tanaka Y et al.<sup>24)</sup> clearly indicated that after attaining low disease activity with infliximab, 55% of treated patients discontinued infliximab for more than 1 year without progression of radiological joint destruction. Further clinical trials





aimed at “biologic-free” remission are being conducted for several biologics as the next treatment goal in Japan. These trials again suggest scientific and clinical uniqueness of Japanese rheumatologists.

It is obvious that we are entering ‘Biologics era’ with 5 biological agents in Japan. With over 100,000 patients estimated on any of biologic agents at the end of 2010, they are no longer seen as ‘investigational treatments’ and become essential to prevent joint destruction in RA. Clinical data generated from PMS programs for biological agents in Japan are robust and considered to be the highest levels of clinical evidence in the world. Japan is now expected to play an important role in providing “state-of-the art” evidence to other countries, rather than learning from others.

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