Predictors for Low Disease Activity and Remission in Rheumatoid Arthritis Patients Treated with Biological DMARDs

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Background: *Optimal outcome of treatment in rheumatoid arthritis (RA) is early clinical remission to delay joint damage. Therefore, severe RA patients with inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs) need high potency drug as biological DMARDs (bDMARDs). In general, one-third of RA patient could not get into disease remission with cDMARDs, and half of them are still suffering from severe arthritis. However, high cost of this agent is the major barrier for patient engagement, and it is affordable to only 5-10% of patients. We need a good strategy to distribute bDMARDs to patients, especially in limited resource situation.*

Objective: *We explored the characteristics of RA patients who were currently using biologic agents in Ramathibodi Hospital to determine the favorable treatment outcome.*

Material and Method: *The studied patients were RA patients classified according to ACR/EULAR 2010 criteria and using any biologic agents, between 2010 and 2012. Demographic data and treatment outcome (low disease activity and remission) were retrieved from patient records. Univariate analysis and generalized estimating equation (GEE) were used to analyze predicting factors to control disease at one year. Kaplan-Meier and log rank test were used to analyze time to disease remission or low disease activity.*

Results: *Patients treated with bDMARDs in Ramathibodi Hospital demonstrated long disease duration (mean 130.7 months) and severe disease activity (mean DAS28 5.37). At 1-year after treatment, 19.4% and 12.9% of patients achieved low disease activity (low DAS) and disease remission, respectively. At 3-years after treatment, 88.9% and 45.2% of patients attained low DAS and remission. Patients who started bDMARDs after 2010 had significantly shorter time to control disease when compared to patients who started bDMARDs before 2010 (10 months vs. 34 months). Moreover, we observed that patient who started bDMARDs after 2010 using more cDMARDs (2.5 vs. 1.7, p = 0.02) and higher dose of methotrexate (10.7 vs. 6.5, p = 0.03). There were no association between disease control status and treatment (methotrexate, prednisolone, biologic agent) or disease duration. However, the exposed status of biologic agent was associated with low DAS or remission at the first year of observation (p = 0.004 and 0.04, respectively).*

Conclusion: *Chance to control rheumatoid arthritis in the level of remission or low disease activity is predicted by time of bDAMRDs exposure. This result is mainly influenced by dose of methotrexate and number of cDMARDs.*

Keywords: *Biologic therapy, Efficacy, Rheumatoid arthritis (RA), Registry cohort*

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by severe joint inflammation and progressive joint damage, which are associated with increased disability and mortality[1]. Disease prevalence is 0.5 to 1% of population and increasing with age and female gender[2]. The primary goal of treatment is to control disease in low disease activity or remission stage to delay joint damage[3,4]. Several treatments are available, ranging from symptomatic drugs as non-steroidal anti-inflammatory drugs (NSAIDs) to disease modifying drugs as cDMARDs and bDMARDs such as antitumor necrosis factor-α [anti-TNFα], inlerleukin-6 receptor inhibitor and B-cell depleting antibodies[5].

Biologic DMARDs use has increased over the past 15 years and current recommendations support early use in patients with inadequate response to cDMARDs[3-6]. However, high cost of the biologic agents is still the major barrier for patient engagement. Accordingly, in 2010 Thai Rheumatism Association (TRA) has established the guideline for biological therapy in rheumatoid arthritis in favor of treatment standardization and cost-effectiveness[7]. In general, one-third of RA patient could not get into disease

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remission with cDMARDs, and more than half of them are still suffering from severe arthritis. Unfortunately, less than 10% of these patients can afford this therapy[8]. As such, in limited resource, we need a good strategy to distribute drug to patients. Likewise, we aim to study the characteristics of RA patients who are currently using biologic agents in Ramathibodi Hospital, and determine factors associated with the favorable treatment outcome, as well as the efficacy of the treatment.

Material and Method

Patients

Clinical data of RA patients fulfilling the classification criteria of the American college of rheumatology/European league against rheumatism (ACR/EULAR) 2010[9] were extracted from the medical record of Ramathibodi Hospital, Mahidol University. All patients using any biologic agents, either etanercept, infliximab or rituximab in January 2010 (year of established TRA biologic guideline) were enrolled in this retrospective cohort study.

Disease activity was assessed using the DAS28-ESR disease activity score. DAS28 values ≤2.6 were defined as remission and >2.6 to <3.2 were defined as low disease activity[10].

Previous bDMARDs exposure status was defined by RA patients who used any bDMARDs before January 2010 (year of established TRA biologic guideline) and was still using any bDMARDs at time of study, regardless of intermittent interrupted use.

Statistical analysis

Baseline characteristics of the patients comprised of age, gender, disease duration (before biologic agent exposure), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), levels of rheumatoid factor (RF) and anti-cyclic citrullinated protein 2 (anti-CCP2), methotrexate (MTX) dose and prednisolone dose, and DAS28 score, at the first registration period (Jan 2010) and every follow-up visit (ranging from 2 to 4 months).

These parameters were analyzed using descriptive statistics to demonstrate mean, median, quartile (25% and 75%) for the continuous variables and percentages for the categorical variables. Difference between groups was analyzed by Student t-test for normally distributed data and Mann-Withney U test for non-normally distributed data. Univariate analysis and generalized estimating equation (GEE) were used to analyze predicting factors for one-year disease remission or low disease activity. GEE is used to compensate for the variation of disease activity evaluation interval between patients. In the GEE model, we used low DAS or remission (DAS <3.2) at 1-year as a dependent variable. Variables from univariate analysis given p-value <0.1 were enrolled to the model and comprised of initial DAS28, exposure status of biologic agent, type of bDMARDs, number of cDMARDs, methotrexate (MTX) dose, including the interaction between methotrexate dose and prednisolone dose. Times to disease remission or low disease activity were analyzed by Kaplan-Meier test. Log rank test was used to estimate the influence of previous exposure effect of biologic agent before observation time.

Results

Demographic data

The demographic data of 31 patients were demonstrated in Table 1. All patients were women with mean age 66.8 years and disease duration 130.7 months. Initial DAS28 was 5.36, which was defined as high disease activity. Two-third of the patients (67.7%) had been using biologic agents before bDMARDs registration in 2010.

Predicting factors of one-year disease remission or low disease activity

From univariate analysis, exposure status of biologic agent was associated with low DAS or remission at the first year of observation (p = 0.004 and 0.04, respectively). However, there was no association between low DAS28/remission at one and three years after treatment and other variables such as MTX dose, prednisolone dose or type of biologic agent.

In the GEE model, only exposure status of bDMARDs predicted low DAS28 or remission at the first year of observation. RA patients who were never exposed to bDMARDs before observation time had higher chance of control disease, adjusted odd ratio was 1.88 (95% CI 1.46-2.42, p<0.001).

Time of treatment to attain low disease activity and remission

Median estimated time to control RA at low disease activity was 32 months (95% CI 27-37) and to achieve disease remission was 65 months (95% CI 25-105). After one year of treatment, 19.4% and 12.9% of the patients attained low disease activity and remission, respectively. At three years after treatment, 88.9% of patients could be controlled in low disease

Table 1. Demographic data

Characteristics (n = 31)	
% female	100
Age (years), mean (SD)	66.8 (12.4)
% RF positive	77.4
RF level (IU/ml), median (25^{th}, 75^{th})	191 (20.8, 670)
% anti-CCP positive	75
Anti-CCP level (u/ml), median (25^{th}, 75^{th})	155 (37.7, 353)
Disease duration (months), mean (SD)	130.7 (122.6)
ESR (mm/hour), mean (SD)	76.43 (28.1)
Initial DAS28, mean (SD)	5.36 (1.77)
Number cDMARDs, mean (SD)	1.97 (0.87)
MTX dose (mg/week), mean (SD)	7.9 (5.8)
SSZ dose (mg/day), mean (SD)	1,016 (1,084)
Prednisolone dose (mg/day), mean (SD)	4.6 (4.2)
Reasons of biologic used	
DMARDs inadequate response	25 (80.6%)
DMARDs intolerance	6 (19.6%)
Biologic exposure status	
Naïve	10 (32.3%)
Ever exposure	21 (67.7%)
Biologic agents	
Etanercept	11 (35.5%)
Infliximab	4 (12.9%)
Rituximab	16 (51.6%)

RF = rheumatoid factor; CCP = cyclic citrullinated peptides; ESR = erythrocyte sedimentation rate; DAS28 = disease activity score evaluated in 28 joints; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine

activity and 45.2% of patients achieve disease remission.

The influence of bDMARDs exposure status to time to control disease was shown in Fig. 1 and 2. Time to low disease activity was 10 months (95% CI 0.7-19) in RA patients who were never exposed to bDMARDs and 34 months (95% CI 30-37) in RA patients who were previously exposed to bDMARDs before January 2010, $p<0.001$. Time to disease remission was 28 months (95% CI 4.4-51.6) in RA patients who were never exposed to bDMARDs and 65 months (95% CI 20-110) in RA patients who were previously exposed to bDMARDs, $p = 0.003$.

Comparison of baseline characteristic between different status of bDMARDs exposure

As show in the Table 2, RA patients who were never exposed to bDMARDs before January 2010 have higher disease activity (DAS28 6.76 vs. 4.69, $p = 0.01$), used more cDMARDs (2.5 vs. 1.7, $p = 0.025$) and used higher dose of methotrexate (10.75 vs. 6.54, $p = 0.03$). There was no significant difference of prednisolone dose and disease duration.

Discussion

RA patients treated with bDMARDs in the early stage of disease could achieve very early and high remission rate. Data from BeSt study (Leiden, the Netherland) revealed that 32% of RA patients with disease duration <2 years can achieved clinical remission at 1-year[11]. Moreover, in DREAM study (Rotterdam, the Netherland), earlier and higher disease

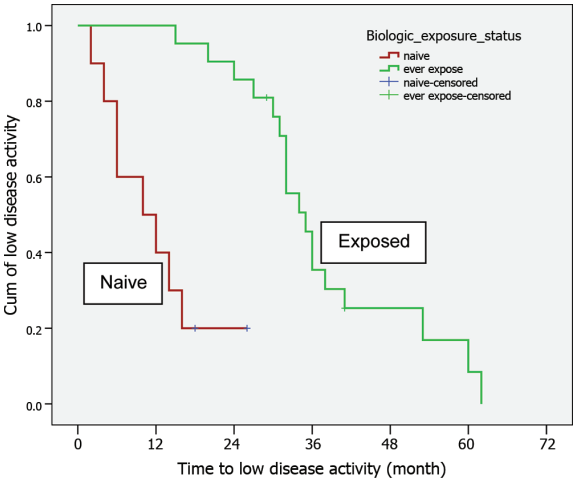

Fig. 1 Kaplan-Meier curve compares time to first low disease activity between patients which ever and never exposed to biologic agents.

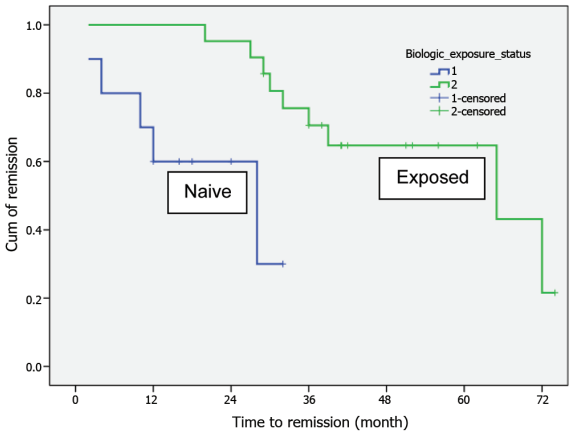

Fig. 2 Kaplan-Meier curve compares time to first remission between patients which ever and never exposed to biologic agents.

Table 2. Compare characteristics of RA patients who were previously exposed to biologic agents before 2010 and biologic agent naïve before 2010

	Biologic exposure	Mean	SD	*p*-value
Initial DAS28	Naïve	6.80	1.10	0.010
	Exposed	4.70	1.60	
Number DMARDs	Naïve	2.50	0.85	0.025
	Exposed	1.71	0.78	
MTX dose	Naïve	10.75	3.92	0.030
	Exposed	6.54	6.14	
Prednisolone dose	Naïve	6.75	3.92	0.079
	Exposed	3.63	4.03	
Disease duration	Naïve	82.30	56.20	0.287
	Exposed	153.70	139.30	

RA = rheumatoid arthriti

remission was shown in RA with disease duration <1 year (47% at 6 months and 58% at 1 year)[12]. The longer disease duration before bDMARDs exposure might influence rate of disease remission.

In clinical practice, RA patients are treated with bDMARDs when there is inadequate response to cDMARDs at longer disease duration than in early arthritis cohort. In German Biologics Register (RABBIT) and British Society for Rheumatology (BSR) Biologics Register, patients with disease duration 10-14 years had remission rate 8.6% at 6 months[13] and 22% after one year of treatment[14]. In the present study, RA patients also had long disease duration (10 years) and low remission rate at 12.9% after 1 year of treatment. However, with longer observation time, we observed higher rate of remission at 45.2% after three years of treatment.

In the present study, patients who were treated with bDMARDs might gain some efficacy before registration in 2010. Therefore, baseline DAS28 at register was lower than in naïve group. Nonetheless, we still observed pronounce treatment efficacy in new case. Since patients treated with bDMARDs after 2010 (new case of registry) had shorter time to low disease activity and remission, 10 and 28 months compared to patients with previous bDMARDs exposure, 34 and 65 months. However, the treatment outcome might be indirectly influenced by dose of methotrexate and number of cDMARDs. Since concurrent methotrexate use was identified as the predicting factor of clinical remission in response to bDMARDs[13,15]. Further study with larger sample size, as a national cohort, might enlighten the question regarding to the predicting factor of bDMARDs response in Thailand.

Mean initial DAS28 of this population was 5.37 in according to criteria of TRA biologic guideline. However, the mean number of cDMARDs was 1.97, which was lower than criteria in the guideline that should be 3 cDMARDs and mean dose of methotrexate was 7.9 mg/week, which was lower than mean dose in non-biologics early RA cohort of Ramathibodi Hospital (10 mg/week)[16]. This might be the consequence of cDMARDs intolerance in 19.6% of the study population. However, due to retrospective study design, the definition of DMARDs inadequate response at baseline of registration might be not clear. For instant, some patients used adequate number of cDMARDs, but with low dose (e.g. MTX 7.5 mg/week) due to high dose intolerance might be defined at registration as cDMARDs inadequate response, instead of cDMARDs intolerance.

Since it was shown that shorter time to remission was related to sustainability of remission[17]. Therefore, adequate dose of methotrexate and adequate number of cDMARDs might be critical concerns to get better treatment outcome of bDMARDs. As shown in Swefot study that patients treated with combination of cDMARDs could attain clinical response at two years as same as in patients treated with bDMARDs (EULAR good response 31% vs. 38%, $p = 0.204$)[18]. In addition, the present study supported the efficacy of methotrexate as the main cDMARDs for rheumatoid arthritis, even in combination with biologic DMARDs[19]. In addition, using methotrexate or other cDMARDs with bDMARDs could reduce chance to develop anti-drug antibodies against bDMARDs which might influence its efficacy in long-term use[20].

Conclusion

Chance to control rheumatoid arthritis in the level of remission or low disease activity is predicted by exposed status of biologic agents according to TRA biologic guideline. This result is mainly influenced by dose of methotrexate and number of cDMARDs.

What is already known on this topic?

Current therapies in rheumatoid arthritis could minimize disease activity and lead to achievement of treatment goals, including pain control, prevention of joint damage and loss of function[3,4]. Several treatment options are available, ranging from symptom relief through non-steroidal anti-inflammatory drugs (NSAIDs) to disease-modifying anti-rheumatic drugs

(DMARDs) and biological DMARDs (antitumor necrosis factor-α [anti-TNFα], interleukin-1 or -6 inhibitors, B-cell depleting antibodies and others)[5]. Use of biologic DMARDs (bDMARDs) has increased over the past 15 years and current recommendations support early use of biologic agents in patients with inadequate response to initial conventional DMARDs (cDMARDs) therapy[3-6]. Accordingly, Thai Rheumatism Association (TRA) has established the guideline for biological therapy in rheumatoid arthritis in favor of treatment standardization and cost-effectiveness[7].

What this study adds?

In most of the biologics registry cohorts, providing data were archived from patients initially using biologic agents per protocol of guidelines. Only eligible patients were enrolled to use biologic agents. Therefore, they could not show the clear benefit of registry system. In the present study, we explored the efficacy of biologic therapy in RA patients who were treated with biologic agents before and after the Thai rheumatism association (TRA) guideline was applied in 2010. Then we could address the benefit of using protocol according to guideline that could shorten time to control disease (10 months vs. 34 months). Consequently, using this strategy will reduce cost of treatment and increase quality of life in severe RA patients.

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Potential conflicts of interest

None.

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ปัจจัยพยากรณ์ประสิทธิภาพการรักษาโรคข้ออักเสบรูมาตอยด์ด้วยยากลุ่มสารชีวภาพ

ปธาวุฒิ วัชราภรณินทร์, ปารวี สุวรรณาลัย

ภูมิหลัง: การรักษาโรคข้ออักเสบรูมาตอยด์ในปัจจุบันมีเป้าหมายให้โรคเข้าสู่ระยะโรคสงบโดยเร็วและไม่ให้เกิดการทำลายข้อ โดยในรายที่ไม่ตอบสนองต่อการรักษาด้วยยาต้านรูมาติกที่ปรับเปลี่ยนการดำเนินโรคชนิดดั้งเดิม ต้องได้รับยากลุ่มสารชีวภาพ แต่ด้วยข้อจำกัดด้านราคาที่สูงทำให้ผู้ที่เข้าถึงยากลุ่มนี้มีน้อย การจัดการทรัพยากรที่จำกัดเพื่อให้เข้าถึงผู้ที่ต้องการจึงเป็นสิ่งจำเป็น

วัตถุประสงค์: ผู้นิพนธ์ศึกษาปัจจัยที่พยากรณ์ผลการรักษาที่ดีในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ของโรงพยาบาลรามาธิบดี ที่ได้รับการรักษาด้วยยากลุ่มสารชีวภาพ

วัสดุและวิธีการ: กลุ่มตัวอย่างเป็นผู้ป่วยโรคข้ออักเสบรูมาตอยด์ที่ได้รับการวินิจฉัยตามตามเกณฑ์ของสมาคมโรคข้อของประเทศสหรัฐอเมริกาและกลุ่มประเทศยุโรป พ.ศ. 2553 และได้รับยาในกลุ่มสารชีวภาพระหว่าง พ.ศ. 2553 ถึง พ.ศ. 2555 โดยรวบรวมข้อมูลจากเวชระเบียนทั้งลักษณะพื้นฐานของผู้ป่วยและการตอบสนองต่อการรักษา ปัจจัยที่สัมพันธ์กับการเข้าสู่ระยะควบคุมโรคได้ภายในเวลา 1 ปี ได้รับการวิเคราะห์ด้วยวิธี univariate analysis และ generalized estimating equation (GEE) ระยะเวลาในการรักษาจนเข้าสู่ระยะควบคุมโรคได้ได้รับการวิเคราะห์ด้วยวิธี Kaplan-Meier และ log rank test

ผลการศึกษา: ผู้ป่วยที่ได้รับการรักษาด้วยยากลุ่มสารชีวภาพในโรงพยาบาลรามาธิบดีมีระยะเวลาการเป็นโรคนานก่อนเริ่มการรักษา (ค่าเฉลี่ย 130.7 เดือน) และมีความรุนแรงของโรคสูง โดยค่าเฉลี่ยความรุนแรงโรค หรือ disease activity score 28 (DAS28) เท่ากับ 5.37 หลังการรักษา 1 ปี ผู้ป่วยเข้าสู่ภาวะควบคุมโรคได้ร้อยละ 19.4 และเข้าสู่ภาวะโรคสงบร้อยละ 12.9 หลังการรักษา 3 ปี ผู้ป่วยเข้าสู่ภาวะควบคุมโรคได้ร้อยละ 88.9 และเข้าสู่ภาวะโรคสงบร้อยละ 45.2 ผู้ป่วยที่เริ่มใช้ยากลุ่มสารชีวภาพหลัง พ.ศ. 2553 ใช้เวลารักษาเพื่อควบคุมโรคสั้นกว่ากลุ่มที่เคยได้รับยากลุ่มสารชีวภาพมาก่อนอย่างมีนัยสำคัญทางสถิติ (10 เดือน และ 34 เดือน) โดยพบว่าผู้ป่วยที่เริ่มการรักษาด้วยยากลุ่มสารชีวภาพหลัง พ.ศ. 2553 ได้รับยาต้านรูมาติกที่ปรับเปลี่ยนการดำเนินโรคชนิดดั้งเดิมหลายชนิดกว่าและได้รับยา methotrexate ขนาดสูงกว่า อย่างไรก็ตามหลังจากวิเคราะห์ด้วย univariate analysis และ GEE พบว่าการได้รับการรักษาด้วยยากลุ่มสารชีวภาพก่อน พ.ศ. 2553 เท่านั้นที่สัมพันธ์กับการเข้าสู่ภาวะควบคุมโรคได้

สรุป: โดยสรุป โอกาสในการรักษาโรคข้ออักเสบรูมาตอยด์ให้เข้าสู่ระยะควบคุมโรคได้ สัมพันธ์กับการได้รับการรักษาด้วยยากลุ่มสารชีวภาพในระยะก่อนหรือหลังมีแนวทางการรักษาของประเทศไทย ใน พ.ศ. 2553 ซึ่งเป็นผลจากการรักษาด้วยยาต้านรูมาติกที่ปรับเปลี่ยนการดำเนินโรคชนิดดั้งเดิมต่างกัน ทั้งจำนวนชนิดยาและขนาดของยา methotrexate