Safety of Biologic Agents in Elderly Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To clarify the safety of biologics in elderly patients with rheumatoid arthritis.

Methods. Biologics were analyzed for safety in relation to age in 309 patients.

Results. Young (< 65 yrs old, n = 174), elderly (65–74 yrs old, n = 86), and older elderly patients (≥ 75 yrs old, n = 49) were enrolled. Although the incidence of adverse events causing treatment withdrawal was significantly higher in elderly and old elderly compared with young patients, no difference was found between elderly and older elderly patients. Pulmonary complications were independent risk factors.

Conclusion. Old patients require special attention, although the safety of biologics in those ≥ 75 years old and 65–74 was comparable. (First Release September 1 2016; J Rheumatol 2016;43:1984–8; doi:10.3899/jrheum.160012)

Key Indexing Terms:
ELDERLY PATIENT | RHEUMATOID ARTHRITIS | ADVERSE EVENTS
BIOLOGICAL THERAPY | SAFETY

The advent of biological agents has provoked a shift toward earlier and more aggressive intervention in the management of rheumatoid arthritis (RA), aimed at inducing rapid and sustained suppression of disease activity[1]. Biologic agents are recommended in patients with active RA with insufficient response to conventional disease-modifying antirheumatic drugs (DMARD) since the efficacy of biological DMARD has been established in a number of trials and cohort studies.

The safety of biological DMARD is acknowledged, but the risk of adverse events (AE) is also recognized. Although most clinical trials exclude elderly patients, large-scale registries or postmarketing surveillance reported that age over 60 or 65 years contributed to infection risk[2,3,4], suggesting that advanced age is a risk factor for AE of biological DMARD. When adjusting treatment, because physicians must take into account wide individual differences among elderly patients in the presence of complications or performance status, it is important to recognize the relevant factors associated with AE in elderly patients with RA receiving biological agents.

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Accepted for publication July 6, 2016.

The aims of our study were to clarify the safety of biologics in elderly patients with RA compared with younger patients and to identify risk factors related to AE.

MATERIALS AND METHODS

Consecutive patients in our institute with RA classified according to the 1987 American College of Rheumatology (ACR)[5] or the 2010 ACR/European League Against Rheumatology[6] classification criteria who started a biologic agent for the first time from January 2012 to December 2014 were enrolled in our retrospective single-center study. We divided the patients into 3 groups according to their ages based on the World Health Organization criteria, with modification: young, < 65 years old (y/o); elderly, 65–74 y/o; and older elderly, ≥ 75 y/o. We also enrolled age-matched elderly/older elderly patients with RA with conventional DMARD without biologic agents as a control. The Ethics Committee of Keio University, School of Medicine (20110136) approved the study, and all patients provided consent for data collection from their charts.

The patients were observed until the last administration of the biologic agents as of February 2015. We collected the following information from their charts at the start of biologic agent use: sex, age, disease duration, 28-joint Disease Activity Score (DAS28)[7], stage and class of Steinbrocker classification, Health Assessment Questionnaire-Disability Index (HAQ-DI)[8], estimated glomerular filtration rate (eGFR), smoking history, Brinkman index, concomitant DMARD, concomitant prednisolone (PSL), and the presence of pulmonary disease, cardiovascular (CV) disease, diabetes mellitus (DM), hypertension, and hyperlipidemia. AE including infections, malignancies, CV diseases, laboratory abnormalities, and infusion reactions leading to biologic agent withdrawal were gathered. We did not count an event as an AE that had obviously no causal relationship with the drugs, for example, an elective operation of joint replacement.

Comparing variables for mean values between the 2 groups was performed by the independent sample Student t test and for proportions by Pearson chi-square test, and comparing variables among 3 groups was performed by 1-way ANOVA with Tukey posthoc test. Changes in DAS28 were compared with dependent sample Student t test. The discontinuation rate was calculated by the Kaplan-Meier log-rank test. To identify relevant factors with discontinuation of biologic agents, multivariable logistic regression analysis was performed to the listings at a p value of more than 0.2 in precedent univariable analysis. All analyses were performed using

JMP version 11 Software (Statistical Discovery; SAS Institute Inc.). A p value < 0.05 was considered significant.

RESULTS

Patient characteristics and followup. Of the 309 patients enrolled in our study, 166 started treatment with a tumor necrosis factor inhibitor (TNFi; infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), 92 tocilizumab, and 51 abatacept; 174 patients were < 65 y/o (young group), 86 patients were 65–74 y/o (elderly group), and 49 patients were ≥ 75 y/o (older elderly group).

Table 1 summarizes the patients' baseline characteristics. The lowest proportion of current smokers was in the old elderly group. The prevalence of complications was higher in the elderly and the older elderly groups than in the young group, but comparable between the elderly and the older elderly.

Discontinuation because of AE. Of the 309 patients, 49 (15.9%) were lost to followup, 19 (6.1%) stopped receiving the biologic agent after achieving remission, and 31 (10.0%) switched the initial biologic agent to another one because of insufficient effectiveness. The switch pattern was not different between the groups. Among 14 patients in the young group and 7 in the elderly and older elderly groups who had initiated TNFi, 10 (71.4%) and 6 (85.6%), respectively, switched to non-TNF biologic agents (p = 0.49). Overall, 37 patients (12.0%) discontinued the biologic agent because of AE. All groups responded well to biologic agents. However, older elderly patients who discontinued biologic agents because of AE did not improve (Supplementary Table 1, available online at jrheum.org).

The incidences of AE leading to drug discontinuation were 53, 154, and 164 per 1000 patient-years in the young, elderly, and older elderly, respectively. Kaplan-Meier analysis revealed that drug discontinuation caused by AE was more frequent in the elderly and the older elderly than the young, but no difference was found between the elderly and the older elderly (Figure 1). Infection, one of the most worrisome AE, was not frequently observed: 1 nail candidiasis in the young, 1 bronchitis and 1 pneumocystis pneumonia in the elderly, and 1 purulent arthritis and 1 bacterial pneumonia in the older elderly. All AE leading to discontinuation are shown in Supplementary Table 2 (available online at jrheum.org).

Table 1. Patient background.

Characteristics	Total, n = 309	Young, n = 174	Elderly n = 86	Older Elderly, n = 49	ANOVA p	Student t Test		
						< 65 vs 65–74 y/o	< 65 vs ≥ 75 y/o	65–74 vs ≥ 75 y/o
Age, yrs, mean ± SD	59.7 ± 14.9	49.4 ± 11.5	69.7 ± 2.9	78.3 ± 3.1				
Disease duration, weeks, mean ± SD	398.9 ± 527.2	298.0 ± 382.3	422.8 ± 558.4	715.2 ± 751.1				
Female, %	82.8	86.8	79.1	83.7				
DAS28-ESR, mean ± SD	4.9 ± 4.9	4.7 ± 1.4	5.2 ± 1.3	5.2 ± 1.5	**< 0.01**	**0.02**	**< 0.01**	0.41
Stage 1/2/3/4, (n)	104/114/18/71	76/63/9/26	19/40/5/20	9/11/4/25				
Class 1/2/3/4, (n)	71/188/33/0	59/98/10/0	7/62/10/0	5/28/13/0				
HAQ-DI	1.07	0.86	1.18	1.63	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**
Current smoking, n (%)	74 (24.1)	40 (23.3)	29 (33.7)	5 (10.2)	**0.03**	0.17	0.26	**0.02**
Brinkman index	131.0	82.3	237.2	115.7	**< 0.01**	**< 0.01**	**0.03**	**0.02**
MTX usage, n (%)	262 (84.8)	155 (89.1)	71 (82.6)	36 (73.5)				
Dose, mg/week	8.7	9.6	7.4	7.1	**< 0.01**	**< 0.01**	**< 0.01**	0.60
Total amount, mg	999.2	920.7	876.6	1575.8	0.11			
PSL usage, n (%)	98 (31.7)	50 (28.7)	30 (34.9)	18 (36.7)				
Dose, mg/day	4.8	4.9	4.8	4.4	0.88			
Total amount, mg	12666.0	17102.5	5236.0	11733.9	0.09			
Biologics, n (%)								
TNFi	166 (53.7)	108 (62.1)	42 (48.8)	16 (32.7)				
TCZ	92 (29.8)	58 (33.3)	25 (29.1)	9 (18.4)	**< 0.01**	**< 0.01**	**< 0.01**	**< 0.01**
ABA	51 (16.5)	8 (4.6)	19 (22.1)	24 (49.0)				
Complications, n (%)								
Pulmonary diseases	56 (18.1)	23 (13.2)	19 (22.1)	14 (28.6)	**< 0.05**	0.08	**0.02**	0.41
Cardiovascular diseases	22 (7.1)	5 (2.9)	12 (14.0)	5 (10.2)	**< 0.01**	**< 0.01**	**0.04**	0.60
Lifestyle diseases	75 (24.3)	26 (14.9)	29 (33.7)	20 (40.8)	**< 0.01**	**< 0.01**	**< 0.01**	0.46
Diabetes mellitus	16 (5.2)	6 (3.4)	6 (7.0)	4 (8.2)				
Hypertension	53 (17.2)	18 (10.3)	18 (20.9)	17 (34.7)				
Hyperlipidemia	23 (7.4)	7 (4.0)	10 (11.6)	6 (12.2)				
Renal function eGFR	80.8 ± 22.3	88.2 ± 19.9	73.5 ± 23.4	67.1 ± 17.9	**< 0.01**	**< 0.01**	**< 0.01**	0.0977

Significant data are in bold face. DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; Stage/Class: Steinbrocker classification; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; PSL: prednisolone; TNFi: tumor necrosis factor inhibitor; TCZ: tocilizumab; ABA: abatacept; eGFR: estimated glomerular filtration rate.

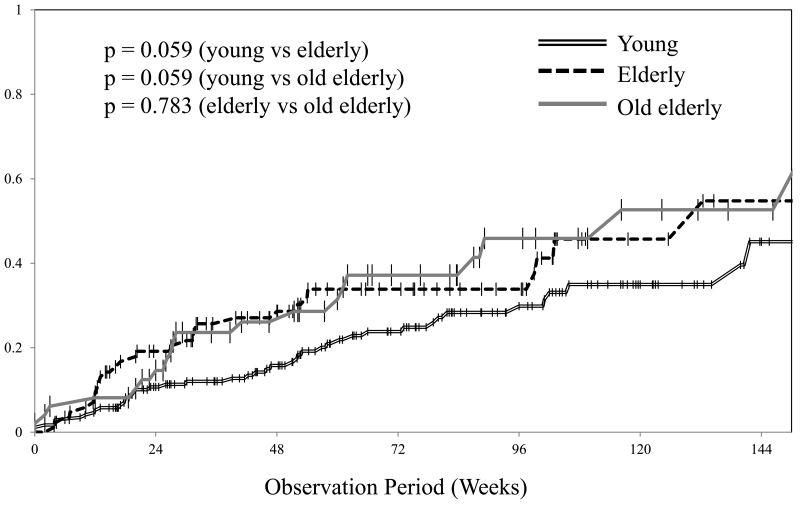

Figure 1. Discontinuation rate of biologic agents in the young group, the elderly, and the older elderly.

Table 2. Risk factors associated with adverse events leading to withdrawal of biologic agents.

Variables	OR	95% CI	p	Multiple Regression p, stepwise method
Age, yrs				
< 65 yrs vs ≥ 65 yrs	2.68	1.31–5.48	< 0.01	**0.015**
Disease duration, weeks	—	—	0.08	0.617
Sex	1.55	0.66–3.64	0.34	
DAS28-ESR	—	—	0.86	
HAQ-DI	—	—	0.12	0.090
Current smoking	1.31	0.61–2.80	0.54	
Brinkman index	—		0.39	
Concomitant use of MTX	0.49	0.22–1.13	0.14	0.151
mg/weeks	—	—	0.22	
Amount, mg	—	—	0.22	
Concomitant use of PSL	1.48	0.73–2.97	0.27	
mg/day	—	—	0.91	
Amount, mg	—	—	0.71	
Biologics				
TNFi	—	—		
TCZ	—	—	0.26	
ABA	—	—		
Pulmonary diseases	2.76	1.31–5.81	0.01	**< 0.01**
Cardiovascular diseases	2.26	0.78–6.54	0.17	0.086
Lifestyle diseases	1.32	0.62–2.80	0.54	
Renal function				
eGFR	—		0.103	0.151

Significant data are in bold face. DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; PSL: prednisolone; TNFi: tumor necrosis factor inhibitor; TCZ: tocilizumab; ABA: abatacept; eGFR: estimated glomerular filtration rate.

Factors related to AE leading to discontinuation. Multiple regression analysis identified ages > 65 and pulmonary complications as factors associated with AE leading to discontinuation of the drug (Table 2). Of note, age > 75 was no greater a risk than the ages 65–75.

The pulmonary complications were 27 interstitial lung disease (ILD), 4 with chronic obstructive pulmonary disease (COPD), 5 old tuberculosis, 1 a history of *Pneumocystis jirovecii*, 9 nontuberculosis mycobacterium, 4 chronic bronchiolitis, 3 bronchiectasis, and 7 with asthma. In the 31 patients with ILD and/or COPD, 8 (27.6%) developed AE including 2 infections (nail

candidiasis, bronchitis). No exacerbation of nontuberculosis mycobacterium was found.

Regarding PSL, the prevalences of AE were 11.8% with PSL and 6.3% without PSL in the young group (p = 0.45), 21.7% and 22.5% in the elderly group (p = 1.00), and 38.5% and 20.8% in the older elderly group (p = 0.27), respectively.

Comparison of the elderly/old elderly RA with biologic agents with those without. We compared AE between elderly/older elderly patients with biologics and those without (Supplementary Table 3, available online at jrheum.org). At baseline, patients receiving biologics had worse disease activity, worse HAQ-DI score, and more complications. AE leading to discontinuation were more frequent in those with biologic than those without, although it was not statistically different.

DISCUSSION

In our study, we revealed that whereas age > 65 y/o was an independent risk factor for AE leading to discontinuation of biologic agents, no significant difference was found between the ages 65–74 and ≥ 75 years, suggesting that biologic agent use in older patients needs caution, but it is possible to administer biologic agents safely in very elderly patients.

Our finding that older age is associated with AE of biologic agents is consistent with findings reported in other studies. Although most studies focused on serious infection, Strangfeld, *et al* reported a fully adjusted incidence rate ratio of developing a serious infection of 1.6 in patients > 60 y/o[2], and Zink, *et al* developed an individual risk score for the likelihood of a serious infection determined to add to the risk score if age was > 60 y/o[9]. Similarly, our present results found the OR of an AE leading to discontinuation of a biologic agent to be 2.8 in patients aged ≥ 65 compared with patients aged < 65. The worse disease control at baseline in the elderly and older elderly patients, which was because of less intensive treatment and longer disease duration, and insufficient disease control during biologic agent treatment, could be an additional risk factor for AE.

The frequency of AE leading to discontinuation of biologic agents in older elderly patients was comparable with that in elderly patients. Looking at the difference in background characteristics[10,11], eGFR and comorbidities of pulmonary disease, CV disease, or DM were equivalent between the 2 groups. In addition, smoking habit and Brinkman index were lower in the older elderly group. Those results suggest that a generally good condition of few comorbidities and lack of smoking history could enable the safe use of biologic agents in old patients[12,13,14]. Comparing between elderly/older elderly patients with biologics and those without, we should note that biologics could be a risk for AE, including infections, although the patients treated with biologic agents had more risk factors in our study[9,15,16].

Our study had some limitations. First, our study was a retrospective single-center study. Although the number of patients aged > 75 years using biologic agents was rather large for a single-center registry, there might be some biases. Second, nobody was treated with rituximab because it has not been approved in Japan for RA.

Although older age > 65 years is an independent risk factor for AE of biologic agents as well as pulmonary complications, the risk in patients > 75 y/o was comparable with that in patients 65–74 y/o. Further research is needed to optimize individualized treatment for elderly patients.

ACKNOWLEDGMENT

The authors thank Harumi Kondo and Mayumi Ota for helping with the acquisition of clinical information.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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