

Real-world comparative effectiveness of bDMARDs and JAK inhibitors in elderly patients with rheumatoid arthritis

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Abstract

Background: In this retrospective cohort study, we compared the retention rates and effectiveness of biologic disease modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs: Janus kinase inhibitors) in elderly patients with rheumatoid arthritis (RA).

Methods: One hundred thirty four elderly RA patients (>65 years) who were initiated with bDMARDs (n = 80) or Janus kinase inhibitors (JAKi) (n = 54) between 2016 and 2020 in our institute were enrolled in this analysis. Follow-up was conducted at 4-week intervals from the start of bDMARDs or JAKi. We compared the drug relation and clinical response at 24 week between elderly RA patients treated with bDMARDs and JAKi.

Results: In the demographic data, longer disease duration, higher previous bDMARDs use and lower glucocorticoid use were observed in JAKi group. Otherwise there was no significant difference in the other variables between the bDMARDs and JAKi groups. In the matched analysis, there was no significant difference in drug retention rates between bDMARDs and JAKi groups. There was no significant difference in the incidence of drug discontinuation due to lack of effectiveness between the two groups. Also, there was no significant difference in the proportion of patients achieving good/moderate EULAR response at 24 week between these two groups.

Conclusions: In elderly RA patients initiated with bDMARDs or JAKi, drug retention rates of these targeted therapies did not differ significantly between these two groups. These findings suggest that elderly RA patients can achieve similar clinical improvement after initiating bDMARDs or JAKi.

Introduction

Rheumatoid arthritis (RA) is characterized by inflammatory polyarthritis and progressive joint destruction [1]. The prevalence of elderly patients with RA has shown an increasing trend, and these patients often have multiple comorbidities [2]. Previous studies have demonstrated distinct clinical features between elderly-onset RA (EORA) and younger-onset RA (YORA) [3]. The presence of comorbidities and uncertainty on the safety of treatments can render the therapeutic difficulties for patients with EORA [4]. Therefore, disability is of particular concern among elderly patients with RA [5]. Furthermore, EORA patients are considered to have more abrupt onset and more severe disease activity compared to YORA patients [6]. Despite the severe RA phenotype, EORA patients are more likely to be treated with glucocorticoids and lower doses of conventional synthetic disease modifying antirheumatic drugs (csDMARDs), including methotrexate (MTX) [7]. Although biologic disease modifying antirheumatic drugs (bDMARDs) are a treatment option for elderly patients with moderate or high RA disease activity, EORA patients are less frequently treated with bDMARDs compared with YORA patients due to the safety concerns [8]. Furthermore, RA patients who are refractory to multiple bDMARDs are also encountered in our clinical practice [9]. Janus kinase inhibitors (JAKi) are the first targeted synthetic disease modifying antirheumatic drugs (tsDMARDs) approved for the treatment of RA, and their efficacy is comparable to

those of bDMARDs [10]. Unlike the single cytokine targeting approach of bDMARDs, JAKi are designed to inhibit multiple inflammatory cytokines cascade implicated in the pathogenesis of RA [11]. Therefore, it is interest to investigate the factors that affect the effectiveness and safety of JAKi in elderly RA patients who are intolerant to csDMARDs. Although the safety profile of JAKi has been comparable to that of bDMARD in clinical trials [12], there is a paucity of real-world data on the usage of JAKi in elderly RA patients. From this viewpoint, we compared the effectiveness and safety of bDMARDs and JAKi in elderly RA patients in this study.

Materials And Methods

Patients and study design

We conducted a retrospective cohort study at the Department of Rheumatology, Fukushima Medical University Hospital and Fukushima Red Cross hospital. Among 601 elderly patients (age ≥ 65 years; Female 413, Male 189) diagnosed with RA during the study period (between July 1, 2016 and December 2021), 134 consecutive elderly (age ≥ 65 years) patients who were initiated with bDMARDs or tsDMARDs were enrolled. All the patients met the 1987 American College of Rheumatology (ACR) classification criteria for RA [13] and could be longitudinally followed up until 52 weeks after initiation of bDMARDs or tsDMARDs. The following bDMARDs were used in our cohort: 18 tumor necrosis factor inhibitors (TNFi) (9 etanercept, 8 golimumab, and 1 certolizumab pegol), 30 interleukin-6 inhibitors (IL-6i) (29 tocilizumab or 1 sarilumab), and 32 abatacept. The tsDMARDs included 54 JAKi (14 tofacitinib, 36 baricitinib, and 4 upadacitinib). This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study (No.2020-110) was provided by the Ethics Committee of Fukushima Medical University.

Clinical evaluations

At the start of treatment, baseline data were collected from medical records, including demographics (age, gender), disease characteristics (disease duration, titers of anticyclic citrullinated protein [CCP] antibody and rheumatoid factor [RF]), measures of disease activity (swollen joint count [SJC], tender joint count [TJC], patient global assessment [PtGA], physician global assessment [PGA]), and C-reactive protein [CRP], and treatment details (current glucocorticoid and MTX doses, previous use of csDMARDs and b/tsDMARDs). Treatment selection was at the discretion of the treating physician, based on the clinical condition, presence of geographical barriers to transportation, and possibility of greater adherence. Disease activity score in 28 joints using CRP (DAS28-CRP) were also retrieved from the records.

Follow-up

Serial assessments of disease activity including laboratory parameters and treatment-related information regarding disease activity were collected at every 4 weeks after initiation of therapy. If treatment was discontinued, the date and reason of discontinuation were recorded. Clinical response after 24 weeks

after the start of treatment was assessed according to the European Alliance of Associations for Rheumatology (EULAR) response as follows [14]: Good responders: improvement > 1.2 , and a present DAS28 ≤ 3.2 . Moderate responders: improvement > 0.6 to ≤ 1.2 , and a present DAS28 ≤ 5.1 ; or improvement > 1.2 , and a present DAS28 > 3.2 . Nonresponders: improvement ≤ 0.6 , or improvement > 0.6 to ≤ 1.2 , and a present DAS28 > 5.1 . Type and number of adverse events that had caused bDMARDs or tsDMARDs discontinuation were examined. Decisions to discontinue these DMARDs due to adverse events were made by the treating physicians based on a comprehensive evaluation of physical findings, laboratory findings and radiological examinations.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation or median (interquartile range) and categorical variables were presented as frequency (percentage). The chi-squared test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables. Drug retention was analyzed using Kaplan–Meier plots and between-group differences assessed using the log-rank test. Cumulative incidences of discontinuation due to lack of effectiveness or adverse effects were compared using the Log-rank test for the Kaplan-Meier model. Data processing and statistical analyses were performed using SPSS Statistics (version 25.0 for Windows, Chicago, IL, USA). Two-tailed p values < 0.05 were considered indicative of statistical significance.

Results

Clinical characteristics of elderly RA patients who was initiated with bDMARDs or JAKi

Among the 600 elderly RA patients treated in our institute, 134 (22.3%) patients who were initiated with bDMARDs ($n = 80$) or JAKi ($n = 54$) were included in this study. Demographic and disease-related characteristics features of the whole RA patients initiated with these targeted therapies are shown in Table 1. The characteristics of patients in each group are shown in Table 2. The number of patients initiated with JAKi was relatively small. Two different patient groups (bDMARDs and JAKi) had divergent baseline disease characteristics, in which longer disease duration and higher previous bDMARDs use and the proportion of glucocorticoid-free patients were observed in JAKi group. There was no significant between-group difference with respect the other variables.

Table 1

Baseline characteristics of elderly RA patients at initiation of bDMARD or JAKi	
Characteristic	n = 134
Age (years), median (IQR)	74 (69–80)
Female, n (%)	99(73.9%)
Disease duration(years), median (IQR)	8.8 (2.4–17.1)
RF-positive, n (%)	102 (76.1%)
ACPA-positive, n (%)	88 (65.7%)
CRP (mg/dL), median (IQR)	1.45 (0.49–3.28)
DAS28-CRP, median (IQR)	4.2 (3.4-5.0)
eGFR (mL/min), median (IQR)	77 (60.1–104)
Interstitial lung disease, n (%)	22 (16.4%)
MTX use, n (%)	61 (45.5%)
MTX dose (mg/week), median (IQR)	6 (4–8)
GC use, n (%)	48 (35.8%)
GC dose (mg/day), median (IQR)	5 (3–7)
Other csDMARDs use, n (%)	41 (30.6%)
Prior bDMARDs use, n (%)	49 (36.6%)

RA: rheumatoid arthritis; bDMARDs: biological disease-modifying anti-rheumatic drugs; JAKi: Janus kinase inhibitors; IQR: interquartile range; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; CRP: c-reactive protein; DAS28-CRP: disease activity score28-c-reactive protein; eGFR: estimated glomerular filtration rate; MTX: methotrexate; GC: glucocorticoid; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

Table 2

Comparison of characteristics between bDMARDs group and JAKi group in elderly RA patients			
	bDMARDs (<i>n</i> = 80)	JAKi (<i>n</i> = 54)	p-Value
Age (years), median (IQR)	73 (68–79)	75 (70-81.3)	0.08
Female, n (%)	60 (75%)	39 (72.2%)	0.72
Disease duration (years), median (IQR)	7 (1.4–14.8)	11 (3.4–22.3)	0.049*
RF-positive, n (%)	64 (81%)	38 (76%)	0.495
ACPA-positive, n (%)	54 (73.9%)	34 (79%)	0.536
CRP (mg/dL), median (IQR)	1.37 (0.31–3.8)	1.47 (0.58–3.04)	0.896
DAS28-CRP, median (IQR)	4.01 (3.3–4.81)	4.44 (3.67–5.03)	0.092
eGFR (mL/min), median (IQR)	71 (53.3–83)	72.3 (59.2–84.3)	0.476
Interstitial lung disease, n (%)	13 (16.3%)	9 (16.7%)	0.949
MTX use, n (%)	37 (46.3%)	24 (44.4%)	0.837
MTX dose (mg/week), median (IQR)	6 (6–8)	6 (4–8)	0.688
GC use, n (%)	39 (48.8%)	9 (16.7%)	< 0.001*
GC dose (mg/day), median (IQR)	5 (3-7.5)	3.5 (1-5.5)	0.201
Other csDMARDs use, n (%)	35 (43.8%)	6 (11.1%)	< 0.001*
Prior bDMARDs use, n (%)	22 (27.5%)	27 (50%)	0.008*
Follow up periods (month), median (IQR)	20 (13-29.8)	24.5 (12-35.5)	0.26

bDMARDs: biological disease-modifying anti-rheumatic drugs; JAKi: Janus kinase inhibitors; RA: rheumatoid arthritis; IQR: interquartile range; CRP: c-reactive protein; DAS28-CRP: disease activity score28-c-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; eGFR: estimated glomerular filtration rate; MTX: methotrexate; GC: glucocorticoid; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs. * *p* < 0.05.

Drug retention rates and reasons for discontinuation

Among 80 patients initiated with bDMARDs, treatment was discontinued in fifteen patient (18.8%) due to insufficient effectiveness, fourteen patients (17.5%) due to adverse events, including impairment of infection (3; 21.4%), neoplasms (3; 21.4%), cardiovascular complications (2; 14.3%), allergic reaction (2; 14.3%), liver function (1; 7.1%), renal dysfunction (1; 7.1%), hematological complications (1; 7.1%), hypothyroidism (1; 7.1%) and two patients due to remission, one patient due to patient preference. Among 54 patients initiated with JAKi, treatment was discontinued in six patients (11.1%) due to insufficient effectiveness, eight patients (14.8%) due to adverse events, including neoplasms (2; 25%), gastrointestinal complications (2; 25%), cardiovascular complications (1; 12.5%), infection (1; 12.5%),

impairment of liver function (1; 12.5%), hematological complications (1; 12.5%). None of the patients in either group experienced any severe or life-threatening AEs. There were no significant differences in the incidence of drug discontinuation due to adverse effects between bDMARDs and JAKi groups (Fig. 1).

The overall drug retention rates of bDMARDs and JAKi are shown in Fig. 2. There was no significant between-group difference with respect to the drug retention rates. Cumulative incidence of drug discontinuation due to lack of effectiveness were also compared between these two groups. However, there were no significant differences in the incidence of drug discontinuation due to lack of effectiveness between bDMARDs and JAKi groups (Fig. 3).

Drug effectiveness at 24 weeks

Clinical response according to EULAR response after 24 weeks were compared bDMARDs and JAKi groups (Fig. 4). At week 24, the proportion of patients achieving good/moderate EULAR response seems to be higher in JAKi group, however there was no significant difference between elderly patients initiating bDMARDs and JAKi groups (bDMARDs; 88.6% versus JAKi; 91.8%, $p = 0.158$).

Discussion

Elderly patients with RA frequently have comorbidities and functional disability [15]. Additionally, these patients are more likely to show intolerant to csDMARDs including MTX [16]. In general, bDMARDs tend to show similar treatment response between EORA and YORA [17]. The efficacy of JAKi appears to be similar in elderly RA patients in clinical trial [18]. In the RA-BUILD and RA-BEAM studies, baricitinib showed similar efficacy (ACR 20/50/70, CDAI/SDAI disease low disease activity and remission) between young (< 50 years) and old (> 65 years) patients [18]. However, elderly patients are more likely to experience AEs with the use of JAKi, tofacitinib [19], and the safety of JAKi in elderly patients remains completely determined. Clinical trial data demonstrated that JAKi represent the comparable response profiles in RA patients with MTX-inadequate response (MTX-IR) and impressive efficacy in head-to-head trials against TNFi, the most established bDMARD [20]. However, the effectiveness or safety of JAKi in elderly RA patients is yet to be determined in real-world setting. In this observational study subjected elderly (aged > 65 years) RA patients, we compared the effectiveness and retention rates of bDMARDs and JAKi. We found no significant difference in the overall drug retention rates between bDMARDs and JAKi. To the best to our knowledge, this is the first study to compare the drug retention rates and safety of bDMARD and JAKi in elderly RA patients with moderate to high disease activity. In particular, we report on the real-world experience of elderly RA patients treated with JAKi. The rates of elderly RA patients achieving good/moderate EULAR response at 24 weeks were comparable in the bDMARDs and JAKi groups. Furthermore, the drug retention rates of bDMARD and JAKi were comparable, although the follow-up period was relatively short. Our results suggest that the effectiveness and safety of JAKi are comparable to those of bDMARDs even in elderly RA patients.

RA is associated with overproduction of a variety of cytokines using the JAK/STAT pathways in their receptor signaling [21]. Therefore JAKi may exert their effectiveness by inhibiting multiple cytokines cascades [11, 22]. Although, the difference in the efficacy and safety of these JAKi according to their JAK-isoform-selectivity has not been clarified [23], the efficacy appears to be comparable to that of bDMARDs [24]. Given that the drug retention is commonly influenced by both effectiveness and safety, the comparison of drug retention rate may reflect the efficacy and safety of bDMARDs or JAKi in elderly patients with RA. A systematic review revealed comparable outcomes of JAKi and bDMARDs therapy [25]. Consistent with these reports, in our cohort, the effectiveness of JAKi was comparable to that of bDMARDs. The incidence of drug discontinuation due to lack of effectiveness was comparable in the two groups. Therefore our data suggest that JAKi is a potential therapeutic option for elderly patients who are refractory to csDMARDs. However, it does not mean that JAKi should be recommended to most elderly RA patient with high disease activity. Since elderly RA patients are frequently accompanied with a variety of comorbidities that limit the treatment choice of JAKi [26]. After careful consideration of comorbidities, and the balance of risk and benefit, an appropriate choice of JAKi should be determined in elderly RA patients. Further prospective studies with a larger sample size can provide more detailed evidence to inform treatment decision-making (bDMARD or JAKi) in elderly RA patients.

The limitations of our study were as follows. First, this was a retrospective observational study with all its inherent biases that may affect the evaluation of treatment effectiveness. Second, the sample size was relatively small. Third, the standard tool to evaluate RA disease activity is limited in DAS28-CRP. Finally, TNF inhibitors, IL-6 receptor antibodies and abatacept were analyzed collectively as bDMARDs and the characteristics of each bDMARDs may not have been reflected. Similarly, tofacitinib, baricitinib and upadacitinib were analyzed collectively as JAKi and the characteristics of each JAKi may not have been reflected.

Conclusion

We compared the drug retention rates and effectiveness of bDMARDs and JAKi in elderly RA patients. There was no significant difference in the overall drug retention rates between bDMARDs and JAKi. Additionally, elderly RA patients initiated on bDMARDs or JAKi showed similar treatment effectiveness. Further investigation is warranted in larger datasets to draw more conclusive estimates on the effectiveness and safety of JAKi in elderly RA patients.

Abbreviations

ACR=American College of Rheumatology

bDMARDs=biologic DMARDs

csDMARDs = conventional synthetic DMARDs

DAS28CRP=disease activity score 28-joint count (DAS28) values calculated using C reactive protein (CRP)

DMARDs=disease-modifying antirheumatic drugs

EORA=elderly-onset RA

RA=Rheumatoid arthritis

tsDMARDs=targeted synthetic DMARDs

YORA=younger-onset RA

JAKi=JAK inhibitors

Declarations

Ethical Approval

Ethical approval for this study (No. 29281) was provided by the Ethics Committee of Fukushima Medical University.

Consent for publication

Not applicable

Availability of supporting data

Not applicable

Competing interests

KM has received research grants from Chugai, Pfizer, and AbbVie. Rest of the authors declares that they have no competing interests

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Authors' contributions

JT, YS, HM, YF, TA, NM, MF, TA, SS, ES, HW were involved in acquisition of laboratory data. JT and KM drafted manuscript.

JT, KM, MM participated in the sequence alignment and drafted the manuscript.

JT, KM, MM participated in the design of the study, TJ SY performed the statistical analysis. All authors read and approved the final manuscript.

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Figures

Discontinuation due to adverse events

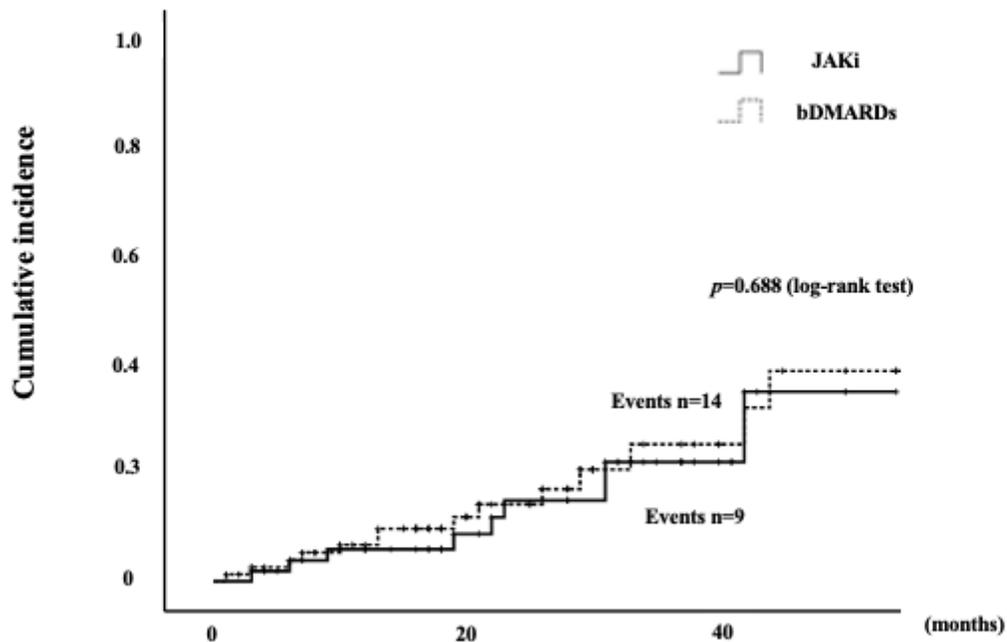


Figure 1

Cumulative incidences of discontinuation of bDMARDs and JAKi due to adverse events. There were no significant differences in the incidence of drug discontinuation due to adverse effects between bDMARDs and JAKi groups

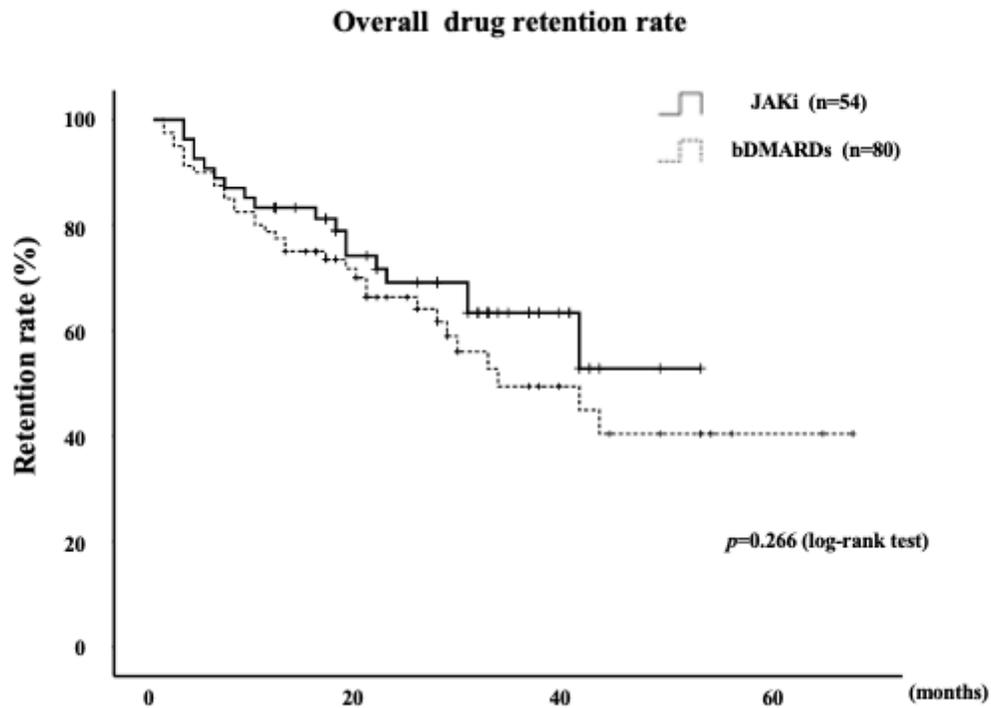


Figure 2

Kaplan–Meier curve related to the overall cumulative drug retention rate of bDMARDs and JAKi in elderly patients initiating these molecular targeting treatment. There was no significant between-group difference with respect to the drug retention rates.

Discontinuation due to lack of effectiveness

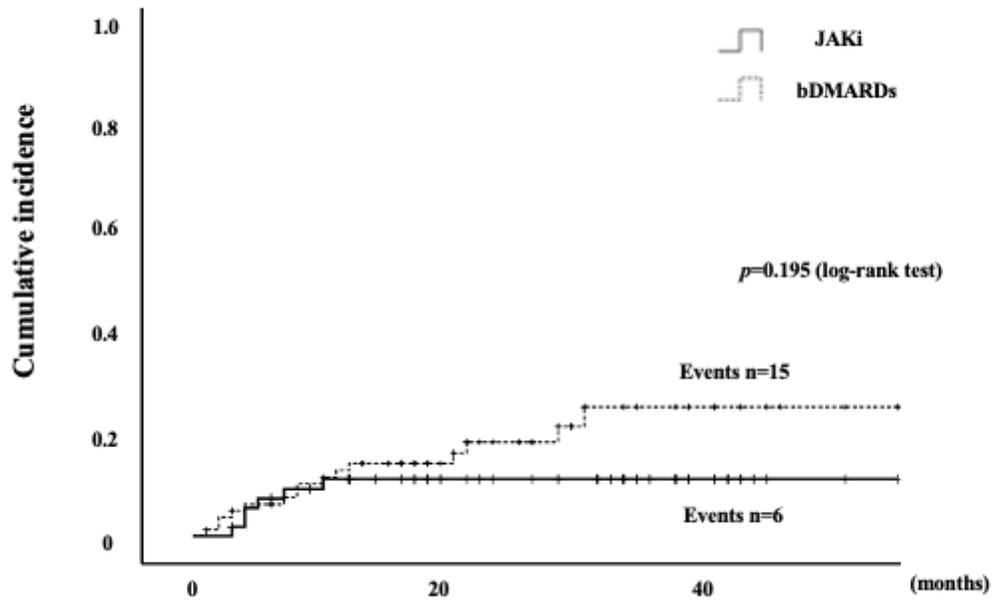


Figure 3

Cumulative incidences of discontinuation of bDMARDs and JAKi due to lack of effectiveness. There were no significant differences in the incidence of drug discontinuation due to lack of effectiveness between bDMARDs and JAKi groups.

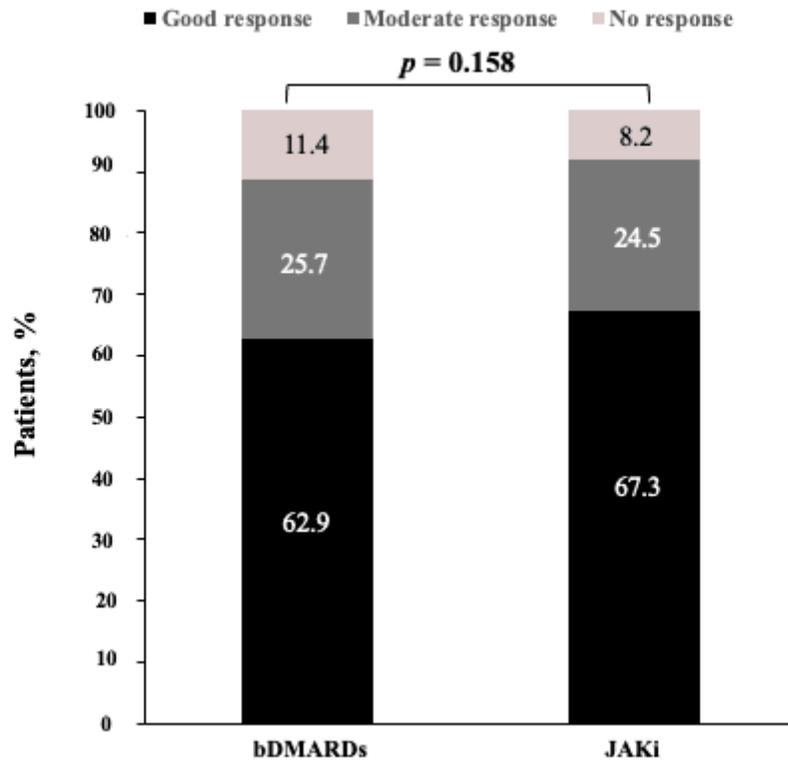


Figure 4

Proportion of patients achieving EULAR response between elderly patients initiating with bDMARDs and JAKi at 24 week. There was no significant difference between elderly patients initiating bDMARDs and JAKi groups (bDMARDs; 88.6% versus JAKi; 91.8%, $p=0.158$).