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COHORT STUDIES

Comparison of efficacy between anti-IL-6 receptor antibody and other biological disease-modifying antirheumatic drugs in the patients with rheumatoid arthritis who have knee joint involvement: the ANSWER cohort, retrospective study

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Abstract

Objective We aimed to investigate the efficacy of anti-IL-6 receptor antibody (aIL-6) and other biologic disease-modifying antirheumatic drugs (bDMARDs), such as TNF inhibitor and CTLA4-Ig in the treatment of rheumatoid arthritis (RA) in patients with knee joint involvement.

Methods We retrospectively analyzed 1059 treatment courses of patients with RA who visited our hospitals and were treated with bDMARDs. We categorized them into two groups, with or without knee joint involvement. We investigated the clinical disease activity index (CDAI) at baseline and 12 weeks after the initiation of bDMARDs. We compared the improvement of the markers between aIL-6 and other bDMARDs.

Results Treatment with aIL-6 significantly increased ΔCDAI ($n=91$, 15.4 ± 1.1; mean ± SEM) in patients with knee joint involvement, compared to other bDMARDs ($n=232$, 11.0 ± 0.7) at 12 weeks ($P=0.006$). Following the multivariate analysis adjusted by the CDAI levels at baseline, age, gender, concomitant use of methotrexate, and the first use of bDMARDs, ΔCDAI levels were significantly higher in aIL-6, compared to other bDMARDs ($P=0.02$). However, there was no significant difference in ΔCDAI improvement between aIL-6 ($n=162$, 5.9 ± 0.6) and other bDMARDs ($n=573$, 6.2 ± 0.4) in patients without swollen knee joints. ΔCDAI levels were equally increased in patients with shoulder and elbow joint involvement.

Conclusion aIL-6 was more effective in the patients with RA and knee joint involvement, compared to other bDMARDs.

Keywords Rheumatoid arthritis · Antirheumatic agents · Interleukin-6

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Introduction

Rheumatoid arthritis (RA) is a progressive and chronic autoimmune disease affecting multiple joints [1]. Both genetic and environmental factors, such as gut microbiota and periodontal disease play important roles in the disease manifestation [2–5]. The treatment of RA has recently improved by the application of biologic disease-modifying antirheumatic drugs (bDMARDs) [6–8]. However, a previous study reported on persistent functional disability and the difficulty to achieve remission in patients with RA, accompanied by large joint involvement [9]. Among large joints, knee was supposed to be associated with severe disease of RA [10]. However, there have been no randomized controlled trials or cohort-based study which compare the efficacy of different bDMARDs in the RA patients with large joint involvement. This calls for the need of developing a better treatment strategy for RA with large joint involvement.

In this study, we aimed to investigate the efficacy of anti-IL-6 receptor antibody (aIL-6) and other bDMARDs in the treatment of patients with RA and knee joint involvement. We also analyzed the efficacy of those bDMARDs in the patients with RA who have elbow and shoulder joint involvement. This study sought to answer whether regular physical examination to detect swelling of large joints is useful in the decision making of bDMARDs treatment initiation in RA.

Methods

Patients

The Kansai Consortium for Well-being of Rheumatic Disease Patients (ANSWER) cohort is an observational multi-center registry of patients with RA in the Kansai district of Japan [13–16]. Our study included data of patients from seven institutes, namely the Kyoto University, Osaka University, Osaka Medical College, Kobe University, Nara Medical University, Kansai Medical University, and Osaka Red Cross Hospital. We retrospectively analyzed 4670 bDMARDs treatment courses with RA in our cohort who underwent treatment with one of the bDMARDs (tocilizumab; TCZ, sarilumab; SAR, abatacept; ABT, adalimumab; ADA, certolizumab pegol; CZP, etanercept; ETN, golimumab; GLM, infliximab; IFX, and infliximab-biosimilar; IFX-BS), including both intravenous and subcutaneous agents from 2011 to 2019. We excluded 120 treatment courses of Janus Kinase (JAK) inhibitors.

Patients with RA fulfilled the 1987 RA classification criteria of the American College of Rheumatology (ACR) [17] or 2010 ACR and the European League Against Rheumatism (EULAR) criteria [18]. We included 1059 bDMARDs treatment courses examined at both CDAI levels and 28 joints score at baseline and 12 weeks post-treatment.

Then, we subdivided the patients into two groups, with or without knee joint involvement at baseline. This flowchart was shown in Fig. 1. In addition, we analyzed their baseline clinical characteristics, such as age, sex, disease activity [disease activity score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR), C-reactive protein (DAS28-CRP), and Simplified Disease Activity Index (SDAI)], matrix metalloproteinase-3 (MMP-3), disease duration of RA, concomitant doses of methotrexate (MTX) and prednisolone (PSL), rheumatoid factor, and anti-cyclic citrullinated peptide antibody positivity, and Health Assessment Questionnaire disability index [DI] score. The LAI28 score was calculated using the following formula: 24 × (swelling joint counts of knee) + 12 × (swelling joint counts of shoulder) + 12 × (swelling joint counts of elbow) + 8 × (swelling joint counts of wrist) + (swelling joint counts of metacarpophalangeal joint, proximal interphalangeal joint and interphalangeal joint) (Supplementary Figure 1). This observational study was conducted in accordance with the tenets of the Declaration of Helsinki. Our study was approved by ethics committees of the above-mentioned seven institutes. The details of the study are provided in the homepage of the Osaka University Graduate School of Medicine (approval number: 15300). All patients agreed with the use of their medical information for this research by providing their written informed consent or by opt-out method.

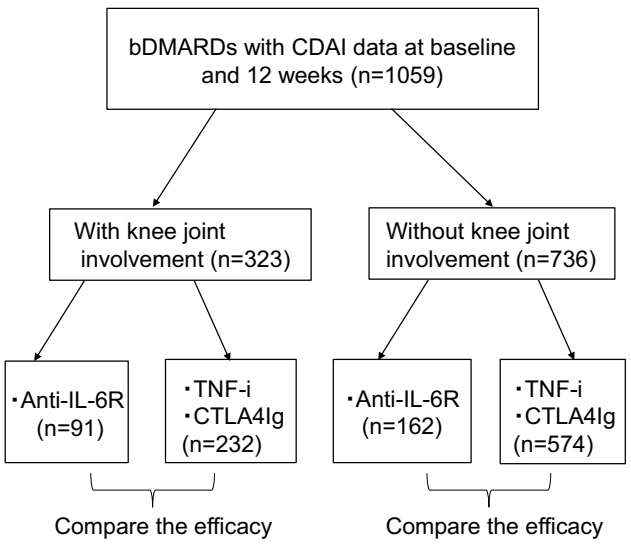

Fig. 1 Flow diagram of included participants. *RA* rheumatoid arthritis, *CDAI* clinical disease activity index, *Anti-IL-6R* anti-IL-6 receptor antibody, *TNF-i* TNF inhibitor, *bDMARDs* biologic disease-modifying antirheumatic drugs

Treatments

The patients were subjected to the following bDMARDs: TCZ, SAR, ABT, ADA, CZP, ETN, GLM, IFX, and IFX-BS. The aforementioned bDMARDs were categorized into two groups as follows: (1) anti-IL-6 receptor antibody (aIL-6; TCZ, SAR) and (2) others (ABT, ADA, CZP, ETN, GLM, IFX, and IFX-BS). We excluded the targeted synthetic DMARDs, such as JAK inhibitors.

Outcomes

We classified the patients into two groups, with or without knee joint involvement for further analyses. Knee joint involvement was defined as at least one swelling at the knee joints. Moreover, we analyzed the patients, with or without shoulder and elbow joint involvement. It was defined as the presence of at least one swelling at the shoulder or elbow joints. We compared the baseline clinical characteristics between the aIL-6 group and others. We evaluated the CDAI, SDAI, and DAS28-CRP of both groups, 12 weeks post-treatment. The primary outcome of interest was the difference of ΔCDAI at 12 weeks post-treatment between aIL-6 and other bDMARDs group. The secondary outcome was the difference of ΔSDAI, ΔDAS28CRP at 12 weeks post-treatment between aIL-6 and other bDMARDs group.

Statistical analyses

While the Mann–Whitney test was used to assess the significance of differences for the continuous variables, the Pearson's chi-square test was used for the categorical variables. We conducted multiple linear regression for adjusted analyses. Age, gender, concomitant use of MTX, baseline disease activity, and first use of bDMARDs were used for adjustment. Statistical analyses were performed using JMP (ver.15). A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

Our study included 275 RA cases (323 bDMARDs treatment courses) with knee joint involvement and 561 RA cases (735 bDMARDs treatment courses) without knee joint involvement. Table 1 summarizes the baseline clinical characteristics of both groups. The mean ages of the patients who have knee joint involvement were 60.9 ± 14.7 in aIL-6 group, whereas 64.9 ± 13.6 in other bDMARDs group. aIL-6 group consists of relatively younger patients. The proportion of females was similar between the two groups. In the case of patients who have no knee involvement, the mean ages were 58.9 ± 13.7 in aIL-6 group and those were 60.7 ± 14.7 in other bDMARDs group.

We first analyzed the responses of bDMARDs in the RA patients, with or without knee joint involvement. The patients with knee joint involvement, treated with aIL-6 showed higher levels of CDAI at baseline (25.2 ± 11.8 vs 22.2 ± 11.0; mean ± SD; aIL-6 vs others; Table 1). Furthermore, the levels of DAS28-ESR and SDAI were elevated in the aIL-6 group. While the aIL-6 group included 91 TCZ-treated cases, others included IFX- ($n = 28$), IFX-BS- ($n = 2$), ADA- ($n = 25$), GLM- ($n = 53$), ETN- ($n = 14$), CZP- ($n = 25$), and ABT- ($n = 85$) treated cases.

The baseline disease activities, such as CDAI were comparable between the two groups (14.1 ± 8.2 vs 14.6 ± 9.2; aIL-6 vs others) in cases without knee joint involvement. The aIL-6 group included TCZ- ($n = 154$) and SAR- ($n = 8$) treated cases. In contrast, others included IFX- ($n = 52$), IFX-BS- ($n = 3$), ADA- ($n = 76$), GLM- ($n = 129$), ETN- ($n = 77$), CZP- ($n = 47$), and ABT-($n = 190$) treated cases.

Table 2 summarizes the clinical characteristics of patients with shoulder and elbow joint involvement at baseline.

Treatment with anti-IL-6 receptor antibody significantly increased ΔCDAI and ΔSDAI levels in patients with RA and knee joint involvement

We first investigated the impact of treatment with aIL-6 on an improvement in the disease activity scores, such as CDAI and SDAI. CDAI levels decreased from 25.2 ± 1.2 (mean ± SEM) to 10.0 ± 0.7 at baseline and 12 weeks after the initiation of aIL-6, respectively (Fig. 2a). In contrast, the levels decreased from 22.2 ± 0.7 to 11.2 ± 0.6 at baseline and 12 weeks after the induction of other bDMARDs, respectively. aIL-6 significantly improved ΔCDAI levels, compared to other bDMARDs (15.4 ± 1.1 vs 11.0 ± 0.7; aIL-6 vs others) after 12 weeks, in patients with knee joint involvement by the univariate analysis. Following the adjustment of multivariate analysis by CDAI levels at baseline, age, gender, concomitant use of MTX, and first use of bDMARDs, ΔCDAI levels in the aIL-6 group were significantly higher than those in others ($P = 0.02$; Fig. 2a, Supplementary Table 1). Furthermore, ΔSDAI in the aIL-6 group was significantly higher, compared to others (18.8 ± 1.2 vs 12.3 ± 0.8; $P < 0.001$: Supplementary Figure 2a, Supplementary Table 2). ΔDAS28CRP levels in the aIL-6 group were also higher than those in others ($P < 0.001$; Supplementary Figure 3a and 3b). The proportion of patients without a swollen knee joint at 12 weeks after the treatment was higher in the aIL-6 group, compared to other bDMARDs (68.1% in aIL-6 group vs 58.4% in others; Fig. 1b), although this difference was statistically insignificant. The proportion of patients in remission and low disease activity (LDA)

Table 1 Clinical characteristics of patients at initiation of each biologic agent with or without knee joint involvement

Joint involvement	Knee (+)			Knee (−)		
Variable	aIL-6 ($n=91$)	Others ($n=232$)	P value	aIL-6 ($n=162$)	Others ($n=574$)	P value
Age (years)	60.9 ± 14.7	64.9 ± 13.6	0.01	58.9 ± 13.7	60.7 ± 14.7	0.12
Female sex (%)	79.1	78.0	0.7	80.0	78.1	0.81
BMI (kg/m^2)	22.4 ± 3.5	22.3 ± 3.7	0.71	21.9 ± 3.8	21.8 ± 3.9	0.98
Disease duration (years)	9.0 ± 10.5	8.9 ± 10.1	0.81	11.3 ± 9.7	9.2 ± 10.2	0.001
RF positivity (%)	80.0	82.1	0.9	81.6	84.4	0.8
ACPA positivity (%)	83.3	90.9	0.59	76.5	85.5	0.29
DAS28-CRP	4.95 ± 1.17	4.48 ± 1.13	< 0.001	3.53 ± 1.16	3.53 ± 1.2	0.79
DAS28-ESR	5.36 ± 1.19	4.96 ± 1.25	0.02	4.05 ± 1.26	4.08 ± 1.32	0.93
CDAI	25.2 ± 11.8	22.2 ± 11.0	0.03	14.1 ± 8.2	14.6 ± 9.2	0.78
SDAI	29.0 ± 13.1	24.9 ± 12.4	0.01	15.7 ± 8.9	16.1 ± 10.1	0.93
LAI28	54.9 ± 21.9	53.2 ± 20.4	0.58	11.5 ± 11.5	12.2 ± 11.9	0.35
HAQ-DI	1.3 ± 0.9	1.3 ± 0.8	0.65	0.9 ± 0.7	0.9 ± 0.8	0.62
PSL usage (%)	45.0	41.8	0.9	46.3	38.2	0.0001
PSL dose (mg/day)	5.6 ± 3.5	5.2 ± 3.0	0.76	5.2 ± 3.9	4.3 ± 2.9	0.13
MTX usage (%)	48.3	56.9	0.17	61.1	64.5	0.46
MTX dose (mg/week)	8.7 ± 3.3	8.5 ± 3.2	0.69	7.8 ± 3.0	8.2 ± 2.9	0.18
1st bio (%)	46.2	67.0	< 0.001	32.1	59.1	< 0.001
2nd bio (%)	29.7	18.9	0.04	30.9	22.5	0.03
≥ 3rd bio (%)	24.2	14.2	0.05	37.0	18.5	< 0.001

Values represent mean ± standard error (SE), unless otherwise noted

The significance of differences was assessed using the Kruskal–Wallis nonparametric test for continuous variables and Pearson's chi-square test for categorical variables

aIL-6 anti-IL-6 receptor antibody, others include TNF inhibitor and CTLA4-Ig, *BMI* Body Mass Index, *RF* rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *DAS28-CRP* Disease Activity Score in 28 joints using C-reactive protein, *DAS28-ESR* Disease Activity Score in 28 joints using erythrocyte sedimentation rate, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *LAI28* Lansbury Articular Index of 28 joint counts, *HAQ-DI* Health Assessment Questionnaire Disability Index, *PSL* prednisolone, *MTX* methotrexate, *Bio* biologic agent

increased from 6.6 to 58.2% in aIL-6 group. In contrast, these rates increased from 9.5 to 53.0% in others (Supplementary Figure 4a). The proportion of patients in high disease activity (HDA) at 12 weeks using CDAI was 5.5% in aIL-6 group, whereas 9.5% in others (Supplementary Figure 4a). The ratio in HDA at 12 weeks using SDAI was 3.5% in aIL-6 group, whereas 7.5% in others. The proportion in HDA at 12 weeks using DAS28-CRP was 4.7% in aIL-6 group, whereas 20.4% in others (Supplementary Figure 4b).

Thus, TCZ, the anti-IL-6 receptor antibody ameliorated the disease activity in patients with RA and knee joint involvement.

Comparable effectiveness of the anti-IL-6 receptor antibody and other bDMARDs in patients with RA, without knee joint involvement

Next, we investigated the extent of improvement in CDAI and SDAI levels in patients without knee joint involvement. CDAI levels decreased from 14.2 ± 0.65 (mean ± SEM) to 8.3 ± 0.55 at baseline and 12 weeks after the initiation of aIL-6, respectively (Fig. 2c). The levels decreased from 14.6 ± 0.38 to 8.4 ± 0.56 at baseline and 12 weeks after the induction of other bDMARDs, respectively. Following the adjustment of multivariate analysis, ΔCDAI levels (5.9 ± 0.6 in aIL-6 group vs 6.2 ± 0.4 in others) were comparable between the two groups ($P=0.61$; Fig. 2c and Supplementary Table 3), 12 weeks post-treatment. In addition, ΔSDAI levels (5.8 ± 0.7 in aIL-6 group vs 6.0 ± 0.4 in others) were comparable following the adjustment ($P=0.46$; Supplementary Figure 2b and Supplementary Table 4). ΔDAS28CRP levels were slightly increased in aIL-6 group (Supplementary Figure 3c and 3d). The proportion of patients in remission and LDA increased from 32.7 to 72.8% and 34.1 to 69.3% in the in aIL-6 group and others, respectively (Supplementary Figure 4c and 4d). Therefore, aIL-6 and other bDMARDs were equally effective in patients without knee joint involvement.

Table 2 Clinical characteristics of patients at initiation of each biologic agent with shoulder or elbow joint involvement

Joint involvement	Shoulder (+)			Elbow (+)		
Variable	aIL-6 ($n=22$)	Others ($n=60$)	P value	aIL-6 ($n=48$)	Others ($n=128$)	P value
Age (years)	63.6 ± 13.2	67.1 ± 13.6	0.23	61.5 ± 12.0	62.5 ± 15.5	0.43
Female sex (%)	72.7	81.7	0.38	77.1	81.3	0.53
BMI (kg/m^2)	21.4 ± 3.6	22.2 ± 2.9	0.29	21.8 ± 3.0	21.7 ± 3.2	0.82
Disease duration (years)	12.2 ± 10.7	9.7 ± 11.2	0.19	14.4 ± 11.4	13.9 ± 11.9	0.62
RF positivity (%)	100	100	1.0	81.8	85.2	1.0
ACPA positivity (%)	100	88.9	1.0	100	96	1.0
DAS28-CRP	4.92 ± 1.24	4.95 ± 1.28	0.89	4.49 ± 1.12	4.41 ± 1.17	0.86
DAS28-ESR	5.45 ± 1.17	5.38 ± 1.36	0.88	5.15 ± 1.11	4.92 ± 1.31	0.43
CDAI	27.1 ± 12.8	27.4 ± 13.6	0.72	21.9 ± 11.9	22.4 ± 11.7	0.66
SDAI	31.7 ± 14.0	30.5 ± 14.5	0.85	24.4 ± 12.6	24.9 ± 12.5	0.63
LAI28	64.3 ± 29.7	52.2 ± 29.0	0.06	43.7 ± 29.3	48.9 ± 27.2	0.17
HAQ-DI	1.43 ± 0.88	1.45 ± 0.83	0.93	1.4 ± 0.8	1.3 ± 0.8	0.61
PSL usage (%)	40.9	43.3	1.0	43.8	45.3	0.87
PSL dose (mg/day)	6.5 ± 4.0	4.9 ± 2.6	0.32	5.7 ± 5.1	5.0 ± 2.3	0.43
MTX usage (%)	54.5	61.7	0.62	58.3	57.8	0.95
MTX dose (mg/week)	5.9 ± 3.4	7.1 ± 4.1	0.58	7.1 ± 3.1	8.1 ± 3.2	0.16
1st bio (%)	40.9	63.3	0.08	29.2	57.8	0.001
2nd bio (%)	27.3	25	1.0	33.3	24.2	0.25
≥ 3rd bio (%)	31.8	11.7	0.046	37.5	18.0	0.01

Values represent mean ± standard error (SE), unless otherwise noted

The significance of differences was assessed using the Kruskal–Wallis nonparametric test for continuous variables and Pearson's chi-square test for categorical variables

aIL-6 anti-IL-6 receptor antibody, others include TNF inhibitor and CTLA4-Ig, *BMI* Body Mass Index, *RF* rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *DAS28-CRP* Disease Activity Score in 28 joints using C-reactive protein, *DAS28-ESR* Disease Activity Score in 28 joints using erythrocyte sedimentation rate, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *LAI28* Lansbury Articular Index of 28 joint counts, *HAQ-DI* Health Assessment Questionnaire Disability Index, *PSL* prednisolone, *MTX* methotrexate, *Bio* biologic agent

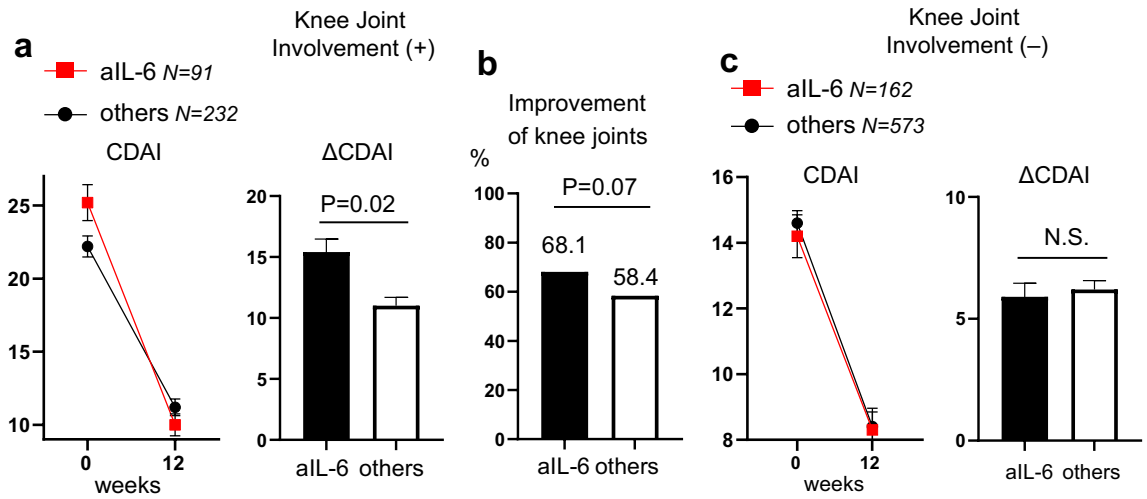

Fig. 2 Comparison of the clinical effectiveness between anti-IL-6 receptor antibody and other biologics at 12 weeks, with or without knee joint involvement. Patients with knee joint involvement **a** CDAI levels at 0 and 12 weeks, ΔCDAI levels at 12 weeks **b** SDAI levels at 0 and 12 weeks, ΔSDAI levels at 12 weeks **c** ratio of patients without swelling of knee joints, 12 weeks post-treatment. Patients without knee joint involvement **d** CDAI levels at 0 and 12 weeks, ΔCDAI levels at 12 weeks **e** SDAI levels at 0 and 12 weeks, ΔSDAI levels at 12 weeks, **a**–**b**, **d**–**e** mean ± SEM are plotted, *aIL-6* anti-IL-6 receptor antibody, *others* other biologics, *CDAI* clinical disease activity index, *SDAI* simplified disease activity index, *N.S.* insignificant

Comparable effectiveness of the anti-IL-6 receptor antibody and other bDMARDs in patients with RA and shoulder and elbow joint involvement

We next investigated the impact of aIL-6 on disease activity scores in patients with shoulder joint involvement. Both aIL-6 and other bDMARDs increased ΔCDAI, ΔSDAI andΔDAS28CRP at comparable levels (Fig. 3a, Supplementary Figure 5a, 5b, 6a, 6b and Supplementary Table 5, 6). ΔCDAI was 13.8 ± 2.3 and 13.7 ± 1.4 in the aIL-6 group and others, respectively. None of the patients had swollen shoulder joints, 12 weeks post-treatment (Fig. 3b). aIL-6 and other bDMARDs improved ΔCDAI, ΔSDAI, and ΔDAS28CRP at comparable levels in patients with elbow joint involvement (Fig. 3c, 3d, Supplementary Figure 5c, 5d, 6c, 6d and Supplementary Table 7, 8). The proportion of patients without swollen elbow joints was comparable at 12 weeks (Fig. 3d). In the patients without swelling of shoulder or elbow joint involvement, ΔCDAI in both groups were not statistically different (Supplementary Figure 7a, 7b).

In summary, aIL-6 and other bDMARDs were equally effective in the patients with shoulder or elbow joint involvement.

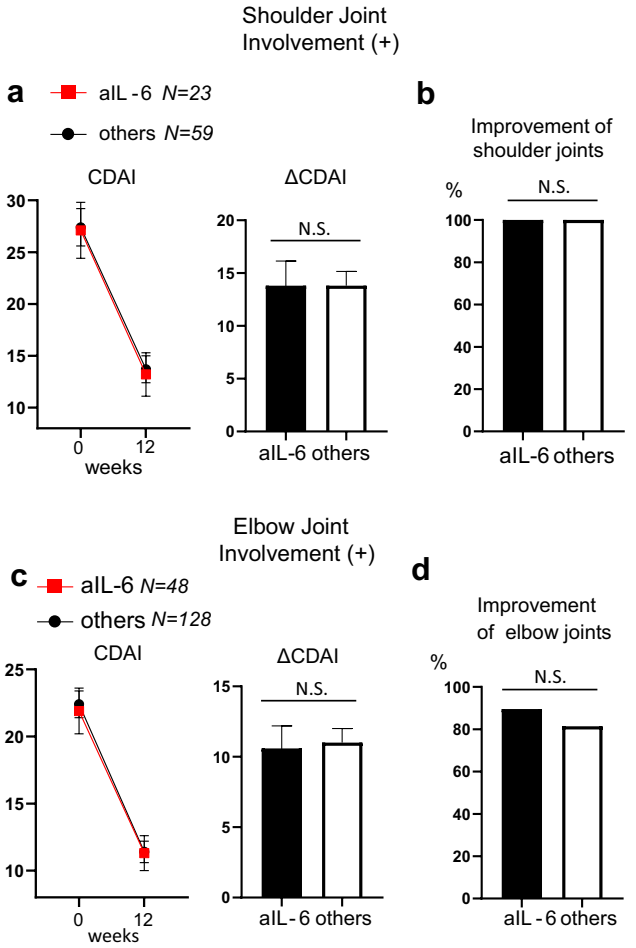

Fig. 3 Comparison of the clinical effectiveness between anti-IL-6 receptor antibody and other biologics at 12 weeks, with shoulder or elbow joint involvement. Patients with shoulder joint involvement **a** CDAI levels at 0 and 12 weeks, ΔCDAI levels at 12 weeks **b** SDAI levels at 0 and 12 weeks, ΔSDAI levels at 12 weeks (c) ratio of patients without swelling of shoulder joints, 12 weeks post-treatment. Patients with elbow joint involvement (**d**) CDAI levels at 0 and 12 weeks, ΔCDAI levels at 12 weeks (**e**) SDAI levels at 0 and 12 weeks, ΔSDAI levels at 12 weeks (**f**) ratio of patients without swelling of shoulder joints at 12 weeks after the treatment **a**, **b**, **d**, **e** mean ± SEM are plotted, *aIL-6* anti-IL-6 receptor antibody, *others* other biologics, *CDAI* clinical disease activity index, *SDAI* Simplified Disease activity index, *N.S.* insignificant

Lansbury articular index 28 is a useful marker to predict the response of the anti-IL-6 receptor antibody

We explored the disease activity index that predicts the future response of aIL-6 at baseline. We categorized the patients, such as LAI28 (≤ 30 or > 30), CDAI levels (≤ 22 or > 22), SDAI levels (≤ 26 or > 26), DAS28-CRP (≤ 4.1 or > 4.1), and CRP (≤ 3 or > 3) at the initiation of bDMARDs. aIL-6 significantly increased ΔCDAI in patients with baseline LAI28 score > 30 after the multivariate adjustment with baseline CDAI, age, gender, concomitant use of MTX and the first use of bDMARDs ($P = 0.02$, Supplementary Figure 8a). In contrast, aIL-6 and other bDMARDs increased ΔCDAI at comparable levels in other higher disease activity groups (Supplementary Figure 8a). Furthermore, they equally increased ΔCDAI in the lower disease activity group (Supplementary Figure 8b). aIL-6 improved ΔCDAI in the lower CDAI (≤ 22) and lower SDAI (≤ 26) group. Nonetheless, the difference was small. In summary, aIL-6 significantly increased ΔCDAI in patients with higher LAI28 score at baseline.

Discussion

In the present study, aIL-6 effectively ameliorated the disease activity of RA with knee joint involvement, 12 weeks post-treatment. In contrast, both aIL-6 and other bDMARDs ameliorated the disease activity at comparable levels in patients with shoulder or elbow joint involvement. Therefore, aIL-6 is specifically effective in patients with RA and knee joint involvement.

The patients with knee joint involvement were treated with aIL-6 and showed a relatively low rate of the concomitant use of MTX (48.3%), lower proportion of the first use of bDMARDs (46.2%), and higher disease activity scores at baseline. In such situations, it is of interest to note that aIL-6 significantly ameliorated the disease activity scores, such as CDAI, SDAI, and DAS28-CRP, compared to

other bDMARDs. Moreover, we recorded a higher ratio of improvement of the knee swelling joints in the aIL-6 groups, 12 weeks post-treatment.

The knee is the biggest joint that is affected in patients with RA [19]. A knee has 26 times the joint surface of a metacarpophalangeal joint [20]. Patients with RA, with knee joint involvement have high serum CRP levels [10]. Furthermore, patients with knee arthritis report a higher level of radiological destruction of their hands and feet. Knee involvement was associated with higher disease activity and CRP levels in this study. Holt et al. reported on the correlation between the concentration of synovial IL-6 levels and plasma IL-6 and CRP levels [21]. Increased serum IL-6 levels were positively correlated with serum CRP levels and DAS28 [22]. It would be an interesting future issues to analyze how synovial IL-6 levels contributes to IL-6 levels in peripheral blood.

Previous reports showed that serum MMP-3 levels were correlated with the LAI score [23, 24]. Gorai et al. reported on the association between the ultrasound score weighted with LAI28 and serum MMP-3 level [25]. Moreover, researchers observed decreased serum levels of MMP-3, following total knee arthroplasty or total arthroscopic knee synovectomy [26, 27]. Thus, MMP-3 levels and LAI28 are useful markers for recognizing knee joint involvement before treatment of RA.

Moreover, high LAI28 reflected the involvement of knee joint and possibly predicted the improvement of RA disease activity by aIL-6. Previous reports showed that the baseline serum levels of IL-6 and CRP did not predict the efficacy of anti-IL-6 receptor antibody [11, 28]. Large joints, such as the knee, shoulder and elbow equally contributed to the total score, in terms of the disease activity index, such as DAS28, SDAI, and CDAI. In contrast, LAI28 highly depends on the joint size. Involvement of the knee substantially contributes to the total LAI28 score (Supplementary Figure 1). Thus, investigating LAI28 before the initiation of bDMARDs might prove useful for selecting the bDMARDs for RA treatment.

Our study had some limitations. First, this was a retrospective study and the clinical characteristics of the patients varied among the groups. This calls for the need of a prospective control-matched analysis. Second, the assessment of joint swelling and analyzing the disease activity scores were inadequate to predict the longer outcomes of joint damage. Future studies are needed to investigate whether aIL-6 prevents the destruction of the knee joint. Third, considering the evaluation of knee joint involvement by palpation, we could not rule out the possibility of the swollen knee being a consequence of osteoarthritis [29, 30]. Further studies are needed to be analyzed after the removal of patients with knee osteoarthritis. Fourth, we did not describe the safety data for both the groups. Lastly, although age, gender, concomitant use of MTX, baseline disease activity, and first use of bDMARDs were used for adjustment, disease duration was also needed to be considered for the adjustment.

In conclusion, aIL-6 was effective in patients with RA and knee joint involvement in this cohort. Moreover, the LAI28 score is a valuable biomarker for predicting the efficacy of aIL-6. Our findings will prove useful for future decision making on the use of bDMARDs in patients with RA and large joint involvement.

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Declaration

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