

1 *Original Article*

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3 **Clinical and ultrasound features of difficult-to-treat rheumatoid arthritis: A multicenter**
4 **RA ultrasound cohort study**

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33 ultrasound

34

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37

38 **Authors' contributions:** SYK made substantial contributions to the study's concept. All authors
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54

55 **Running Head:** Ultrasound features of D2T RA

56

57

58 **Abstract**

59 **Objectives:** The optimal strategy for difficult-to-treat (D2T) rheumatoid arthritis (RA) have not
60 been identified, and the ultrasound characteristics of D2T RA have not been reported. We
61 investigated the clinical characteristics and factors contributing the outcome in D2T RA in a
62 multicenter RA ultrasound observational cohort.

63 **Methods:** We reviewed 307 Japanese patients diagnosed with RA who underwent treatment with
64 biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). We
65 compared the differences in patient characteristics between the D2T RA and non-D2T RA
66 groups. We examined the factors contributing to a good response (defined as b/tsDMARD
67 continuation and Clinical Disease Activity Index [CDAI] ≤ 10 at 12 months) in the D2T RA
68 patient group.

69 **Results:** Forty-three patients (14%) were categorized as D2T RA, and the remaining 264 (86%)
70 were classified as non-D2T RA at baseline. The gray scale (GS) score, disease duration, and
71 CDAI at the initiation of treatment were significantly higher in the D2T RA group compared to
72 the non-D2T RA group. In contrast, the power Doppler (PD) score was not significantly different
73 between the two groups. Among the 43 D2T RA patients, 20 patients achieved a good response.
74 The introduction of CTLA4-Ig was significantly associated with the achievement of a good
75 response by performing inverse probability weighting with propensity score. The GS and PD
76 scores at baseline were not significantly associated with therapeutic response at 12 months in
77 D2T RA patients.

78 **Conclusions:** Patients with D2T RA had high clinical and ultrasound activity and poor responses
79 to treatment with b/tsDMARDs. CTLA4-Ig was associated with a good response at 12 months in
80 D2T RA patients.

81

82 **Trial Registration:** The study is registered with the University Hospital Medical Information
83 Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/>; #UMIN000012524) and was
84 approved by the Institutional Review Board of Nagasaki University (approval no. 13102866).

85

86 **Introduction**

87 The principle of the induction of early remission following the use of the treat-to-target strategy
88 (1) has been established in clinical settings for the treatment of rheumatoid arthritis (RA). The
89 development of multiple targets for RA therapy has provided more choices for treating patients
90 with RA. Despite these promising drugs and strategies, some patients with RA continue to suffer
91 from their diseases because of difficulties in achieving remission. These patients' backgrounds
92 are heterogenous, and their practical management is a clinical challenge. **The European alliance**
93 **of associations for rheumatology** (EULAR) has published its definition of difficult-to-treat (D2T)
94 RA (2), and several studies have elucidated the clinical characteristics of D2T RA based on the
95 EULAR D2T RA definition, which consists of seropositivity, long disease duration, high Disease
96 Activity Score in 28 joints for Rheumatoid Arthritis-erythrocyte sedimentation rate (DAS28-
97 ESR) score, pulmonary diseases, and fibromyalgia comorbidity (3). However, the optimal
98 strategy and treatment options for D2T RA have not been identified.

99 The EULAR has recommended using joint imaging in the clinical management of RA (4),
100 and an evaluation by ultrasound has been part of the evaluation for patients with RA in clinical
101 practice. In addition, **the EULAR recommendation for the management of D2T RA (5)**
102 **states, "where there is doubt on the presence of inflammatory activity based on clinical**
103 **assessment and composite indices, ultrasonography may be considered for this evaluation."**
104 Systematic evaluations by ultrasound help rheumatologists identify subclinical inflammation
105 even in RA patients in clinical remission, and it has been suggested that subclinical inflammation
106 might predict radiographic damage progression in the future (6). An ultrasound evaluation also
107 distinguishes actual joint inflammation from joint pain that may be due to other mechanisms
108 such as fibromyalgia and orthopedic diseases (7, 8). Although these advantages of ultrasound

109 might contribute to the prognosis of D2T RA and suggest differences in pathophysiology
110 between D2T RA and non-D2T RA, no ultrasound evaluations of D2T RA have been reported.
111 We have conducted a multicenter prospective observational cohort study of patients with active
112 RA who received treatment with biologics or targeted synthetic disease-modifying antirheumatic
113 drugs (b/tsDMARDs) at 27 participating rheumatology centers in the Kyushu region of Japan,
114 since June 2013 (9–15). In that cohort study, ultrasound is used to evaluate the efficacy of
115 treatment in RA.

116 We conducted the present study to investigate the clinical characteristics of patients with
117 D2T RA and factors that may contribute to patients' outcomes, using a multicenter RA
118 ultrasound prospective observational cohort. [Kyushu Multicenter Rheumatoid Arthritis
119 Ultrasound Prospective Observational Cohort Study (KUDOS)]

120

121 **Materials and methods**

122 *Study design*

123 This study is part of an ongoing non-randomized, multicenter, prospective cohort study of
124 patients with active RA who had received treatment with b/tsDMARDs at 16 of 27 participating
125 rheumatology centers in the Kyushu region of Japan since June 2013. We evaluated the clinical
126 disease activity and ultrasound findings every 3 months for the 12 months from the initiation of
127 the patients' treatment with b/tsDMARDs.

128 The study is registered with the University Hospital Medical Information Network
129 Clinical Trials Registry (<http://www.umin.ac.jp/ctr/>; #UMIN000012524) and was approved by
130 the Institutional Review Board of Nagasaki University (approval no. 13102866). All patients
131 provided informed consent for participation.

132

133 *Patients*

134 We reviewed the cases of 307 Japanese patients diagnosed with RA who underwent treatment
135 with a b/tsDMARD from June 2013 to May 2020 at 16 centers of the aforementioned 27 centers.
136 All patients were required to meet the American College of Rheumatology (ACR) 1987 (16)
137 and/or the ACR/EULAR 2010 criteria for RA (17). The b/tsDMARDs were administered in
138 dosages recommended by the manufacturers and included tumor necrosis factor (TNF) inhibitors
139 (TNFis); infliximab (3–10 mg/kg via intravenous infusion every 8 weeks or 3–6 mg/kg via
140 intravenous infusion every 4 weeks), adalimumab (40 mg via subcutaneous injection every 2
141 weeks), etanercept (50 mg via subcutaneous injection weekly), certolizumab pegol (400 mg via
142 subcutaneous injection every 4 weeks), golimumab (50 or 100 mg via subcutaneous injection
143 every 4 weeks), cytotoxic T lymphocyte-associated antigen-4 (CTLA4)-Ig; abatacept (125 mg
144 via subcutaneous injection weekly or 500–750 mg via intravenous infusion every 4 weeks),
145 interleukin (IL)-6 receptor inhibitors (IL-6is); tocilizumab (162 mg via subcutaneous injection
146 every 2 weeks or 8 mg/kg via intravenous infusion every 4 weeks), sarilumab (200 mg via
147 subcutaneous injection every 2 weeks), janus kinase (JAK) inhibitors (JAKis): tofacitinib (10 mg
148 via oral daily), baricitinib (4 mg via oral daily), and peficitinib (150 mg via oral daily).

149

150 *Clinical disease activity assessment*

151 The clinical disease activity of RA in each patient was evaluated every 3 months by the Disease
152 Activity Score for 28 Joints (DAS28) based on the erythrocyte sedimentation rate (ESR) or C-
153 reactive protein (CRP), and the Clinical Disease Activity Index (CDAI). Clinical remission was
154 defined as a CDAI score <2.8, and low disease activity was defined as a CDAI score ≤10. D2T

155 RA was defined as patients who had failed ≥ 2 b/tsDMARDs with different mechanisms of action
156 (MOAs), and were either moderately disease activity or taking at least 7.5mg prednisolone at
157 baseline in this study.

158

159 *Ultrasound assessment*

160 Sonographers registered by the Japan College of Rheumatology (JCR) performed the ultrasound
161 assessments of articular synovia of 22 joints in each patient every 3 months after the introduction
162 of b/tsDMARDs. The ultrasound-evaluated joints included bilateral wrists and the first to fifth
163 metacarpophalangeal and proximal interphalangeal joints. Systematic multiplanar gray scale
164 (GS) and power Doppler (PD) joint examinations were performed using a multifrequency linear
165 transducer (12–24 MHz) and one of the following scanners: Toshiba AplioXG, Aplio300 or
166 Aplioi800, GE Logic series 7 or 8 or Hitachi Hi Vision Avius, and Noblus or HI Vision Preirus.
167 All scanners were the latest machines with the joint mode that were available at the time of the
168 study. The 22 joints were scanned on the dorsal aspect, with the joint in a neutral position.
169 Standardized joint and probe positions were used according to JCR guidelines. Each joint was
170 given a GS score and a PD score from 0 to 3 semi-quantitatively. The sum of the GS and PD
171 scores was used as an indicator of disease activity. **Ultrasound-based RA remission was defined**
172 **as a total PD score of 0.** Interobserver reliability was confirmed in a previous investigation (**the**
173 **intraclass correlation coefficients for GS and PD scores were 0.7 and 0.9, respectively**) (9).

174

175 *Statistical analyses*

176 Categorical variables are presented as frequencies, and quantitative variables are presented as
177 medians and interquartile ranges. The association between variables was assessed using Fisher's

178 exact test for categorical variables and Wilcoxon's rank sum test for quantitative variables. To
179 address missing data obtained after the rescue or treatment switch, we applied the last
180 observation carried forward (LOCF) method, which used all available observed data, including
181 after rescue or switch, with patients analyzed according to their original treatment assignment.

182 We first examined the differences in patient background and treatment course between the
183 D2T RA and non-D2T RA groups. We used LUNDEX index to compare response to treatment
184 between D2T RA and non-D2T RA groups (Kristensen et al. Arthritis Rheum 2006; 54: 600-6.).
185 We then examined factors contributing to a good response to treatment in the D2T RA patient
186 group. We defined 'good response' as both the continuation of b/tsDMARD treatment and a
187 CDAI score ≤ 10 at 12 months in accordance with the treat-to-target strategy [Ann Rheum Dis.
188 2010 Apr;69(4):631-7.], and we categorized other cases as 'poor response'.

189 We found that among MOAs, CTLA4 had a higher percentage of good responses in the
190 D2TRA group in a data-driven manner. Subsequently, we inferred the effect of the CTLA4-Ig
191 use on the good-response rate as an odds ratio (OR) by using a logistic regression. The
192 coefficients were estimated via the svyglm function incorporating the sampling weights in order
193 to address the differences in the background between the treatment groups (18). The overlap
194 weight with the propensity score determined the sampling weight (19). The logistic regression
195 model to obtain the propensity scores included the following covariates: anti-cyclic citrullinated
196 protein antibody (ACPA) positivity, concomitant use of methotrexate (MTX), CDAI score, GS
197 score at baseline, and more than three MOAs used in the past.

198 All statistical analyses were performed with JMP pro 15.0 software (SAS Institute, Cary,
199 NC, USA), GraphPad Prism ver. 9.0 (GraphPad Software, San Diego, CA) or R ver. 4.2.0 (R
200 Foundation for Statistical Computing, Vienna, Austria). Unless stated otherwise, two-tailed p-

201 values <0.05 were considered significant. In the search for factors contributing to good response,
202 p<0.20 was considered significant because this was an exploratory study.

203

204 **Results**

205 *Patient characteristics*

206 **Forty-three patients (14%) were categorized as D2T RA, and the remaining 264 (86%) were**
207 **classified as non-D2T RA at baseline.** Table 1 summarizes the characteristics of the D2T RA and
208 non-D2T RA groups. The disease duration was significantly longer in the D2T RA group
209 compared to the non-D2T RA group. Clinical disease activity indicators such as the swollen joint
210 count (SJC), tender joint count (TJC), DAS28-ESR, Simplified Disease Activity Index (SDAI),
211 and CDAI measurements at baseline were significantly higher in the D2T RA group compared to
212 the non-D2T RA group. **The frequency of concurrent fibromyalgia was significantly higher in the**
213 **D2T RA group** than in the non-D2T RA group. Although the baseline GS score was significantly
214 higher in the D2T RA patients versus the non-D2T RA patients, we identified no significant
215 between-group differences in baseline PD scores. There were no significant differences in the
216 gender distribution, smoking history, ACPA positivity, concomitant MTX use, concomitant
217 prednisolone (PSL) use, patient pain visual analog scale (VAS), patient global VAS, physician
218 global VAS, or serum CRP levels between the two groups.

219 We performed a multiple stepwise logistic regression analysis to evaluate the patients'
220 baseline factors including disease duration, comorbid interstitial lung disease (ILD), rheumatoid
221 factor (RF) positivity, CDAI, and GS score. The analysis revealed that the baseline factors with
222 statistical significance that were associated with D2T RA included disease duration (OR 1.0032,

223 95% confidence interval [CI]: 1.00056–1.0058; p=0.018) and CDAI (OR 1.0374, 95%CI:
224 1.0053–1.0709; p=0.022).

225 In the D2T RA group, five patients (11.6%) were treated with CTLA4-Ig, five patients
226 (11.6%) with an IL-6i, 21 patients (48.8%) with a JAKi, and 12 patients (27.9%) with a TNFi. In
227 the non-D2T RA group, 82 patients (31.1%) were treated with CTLA4-Ig, 63 patients with an IL-
228 6i (23.9%), 26 patients with a JAKi (9.9%), and 93 patients with a TNFi (35.2%). The most
229 frequently used drug in the D2T RA group was JAK inhibitors.

230

231 *Retention of b/tsDMARD treatment in the D2T RA group vs. the non-D2T RA group*

232 There was no significant difference in retention rates at 12 months: D2T RA group, 69.8%; non-
233 D2T RA group, 75.3% (p=0.45). In the D2T RA group, the 12-month retention rates were 100%
234 (n=5/5) in the CTLA4-Ig group, 100% (n=5/5) in the IL-6i group, 62% (n=13/21) in the JAKi
235 group, and 58% (n=7/12) in the TNFi group. In the non-D2T RA group, the 12-month retention
236 rates were 79% (n=65/82) in the CTLA4-Ig group, 81% (n=51/63) in the IL-6i group, 85%
237 (n=22/26) in the JAKi group, and 68% (n=63/93) in the TNFi group.

238

239 *Efficacy of b/tsDMARD treatment in the D2T RA group vs. the non-D2T RA group*

240 Figure 1 depicts the results of our comparison of the remission rate a low disease activity rate at
241 12 months between the D2T RA group and non-D2T RA group. The rate of CDAI remission was
242 11.6% in the D2T RA group and significantly higher at 44.3% in the non-D2T RA group
243 (p<0.0001). The rate of PD remission was 20.9% in the D2T RA group and significantly lower
244 than that in the non-D2T RA group (48.9%) (p<0.0008). The good-response rate in the D2T RA
245 group (9.3%) was significantly lower than that in the non-D2T RA group (29.9%, p=0.0048).

246 The treatment response based on the clinical and ultrasound outcomes was thus better in the non-
247 D2T RA group than in the D2T RA group. LUNDEX adjusted rates of patients who achieved
248 CDAI ≤ 10 at 3, 6 and 12 months were 35.5%, 37.9% and 35.7% in D2T RA group, and 63.7%,
249 69.0% and 63.3% in non-D2T RA group.

250

251 *Factors associated with good response in the D2T RA group*

252 We examined factors at baseline contributing to good responses in the patients with D2T RA.
253 The following were identified as factors associated with good response to RA treatment (Table
254 2): ACPA positivity, concomitant MTX use, concomitant PSL use, number of swollen joints,
255 patient pain VAS, patient global VAS, physician global VAS, CRP levels, ESR, DAS28-ESR,
256 CDAI, >3 MOAs, and the introduction of CTLA4-Ig. In the analysis of propensity scores, the
257 introduction of CTLA4-Ig was significantly associated with good response (OR 1.762, 95%CI:
258 1.298–2.393; $p < 0.0006$).

259

260 **Discussion**

261 In this study of a cohort of RA patients treated with b/ts DMARDs, we observed that the disease
262 duration was significantly longer in the D2T RA group. The clinical disease activity and the total
263 GS score at baseline were also higher in the D2T RA patients compared to the non-D2T RA
264 patients. The treatment response based on clinical and ultrasound outcomes was better in the
265 non-D2T RA patients than in the D2T RA patients. In the D2T RA group, CTLA4-Ig was
266 significantly associated with a good response to RA treatment, defined as b/tsDMARD
267 continuation plus a CDAI value ≤ 10 at 12 months, even after the adjustments for the patients'
268 clinical background and disease activity at baseline by inverse probability weighting.

269 Our results demonstrated the long duration of the disease and high baseline disease
270 activity in patients with D2T RA. A longer disease duration was observed in D2T RA patients
271 compared to non-D2T RA patients in a 2021 study (20), but other investigations did not obtain a
272 similar finding (3,(21). This discrepancy in the disease duration among studies could be due to
273 the inclusion criteria of each cohort, since our present cohort consisted of patients treated with
274 b/tsDMARDs. Regarding disease activity, our results are consistent with several reports (3–5).

275 The higher GS score and comparative PD score in the present D2T RA group compared to
276 the non-D2T RA group compels us to consider the possible pathophysiological differences
277 between D2T RA and non-D2T RA. An ultrasound study demonstrated that the PD score is
278 associated with disease activity such as that shown by the DAS28, whereas the GS score is
279 related to structural damage (22). Based on our present results, we speculate that structural
280 damage rather than inflammation might contribute to the disease activity in D2T RA.

281 We observed that the patients with D2T RA had high clinical and ultrasound disease
282 activity and poor responses to treatment with b/tsDMARDs. On clinical evaluation, this result is
283 similar to that of an earlier investigation (21). Our analyses demonstrated that the D2T RA group
284 had a poor response to treatment not only on clinical evaluation but also on ultrasound
285 evaluation.

286 Our results elucidated that the set of patients with a good response to treatment (defined as
287 b/tsDMARD continuation and CDAI \leq 10 at 12 months) included more patients treated with
288 CTLA4-Ig compared to the set of patients with a poor response. The patients treated with
289 CTLA4-Ig had a 100% retention rate at 12 months. In addition, after adjusting the background
290 by using the inverse probability of treatment weights, we found that CTLA4-Ig was still a
291 significant factor associated with good response. To the best of our knowledge, this is the first

292 study to show CTLA4-Ig as a treatment related to D2T RA outcomes. Although another study
293 demonstrated that JAKi as a preferred treatment choice for D2T RA (23), our present findings
294 did not show a preferable outcome by JAKi treatment. The absence of a clinical response to the
295 first bDMARDs predicts multi-refractoriness to consecutive biologics (24), and inconsistency in
296 the effectiveness of b/tsDMARDs for D2T RA among studies might thus have occurred because
297 of the number and the order of the b/tsDMARDs already in use.

298 Our study has several limitations. First, the cohort was from a region of Japan, not from all
299 over the country. Second, the sample size is insignificant for analyses. For example, the
300 significant association between CTLA4-Ig and good response in D2T RA was based on only five
301 patients treated with CTLA4-Ig. Third, because all of the patients in our cohort were able to
302 afford to start and continue b/tsDMARD treatment and undergo additional ultrasound
303 examinations at their expense, socioeconomic biases might have affected the results. Fourth, we
304 did not evaluate radiographic changes using the modified total Sharp score, which is the gold
305 standard for evaluating structural joint damages. Fifth, we did not evaluate the patients'
306 comorbidities after they started b/tsDMARDs treatment. Sixth, the use of non-steroidal anti-
307 inflammatory drugs and csDMARDs other than MTX has not been taken into account. We have
308 not been able to confirm the status of medication adherence. Despite these limitations, this study
309 adds new information regarding the value of ultrasound assessment and the use of CTLA4-Ig for
310 D2T RA.

311 In conclusion, the patients with D2T RA had high clinical and ultrasound disease activity
312 and poor response to treatment with biologics and targeted synthetic disease-modifying
313 antirheumatic drugs. Notably, the use of CTLA4-Ig was found to be associated with a good
314 response to treatment at 12 months in the D2T RA patients.

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Table 1. Comparison of baseline characteristics **and treatment** between the D2T RA and non-D2T RA groups

	D2T RA n=43	Non-D2T RA n=264	p-value
Age	65.0 (55.0–72.0)	67.0 (57.0–75.0)	0.78
Female, n (%)	36 (83.7)	205 (77.7)	0.43
Disease duration, months	120 (77–200)	48 (12–120)	<0.01
Smoking history, n (%)	11/40 (27.5)	61/249 (24.5)	0.70
RF-positive, n (%)	37/42 (88.1)	193/262 (73.6)	0.052
ACPA-positive, n (%)	37/42 (88.1)	226/262 (86.3)	1.00
b/tsDMARD history, n (%)	43 (100)	82 (31.1)	<0.01
ILD, n (%)	12/42 (28.6)	48/255 (18.8)	0.15
Fibromyalgia, n (%)	4/33 (12.1)	1/175 (0.57)	<0.01
MTX use, n (%)	21 (48.8)	144/261 (55.2)	0.51
MTX dose, mg/week	0 (0–10)	6 (0–10)	0.82
PSL use, n (%)	23 (53.5)	137 (51.9)	0.87
No. of tender joints	7 (3–15)	5 (2–9)	<0.01
No. of swollen joints	6 (3–11)	4 (2–8)	0.02
Patient pain VAS, mm	48.0 (28.5–70.0)	38.0 (20.0–60.0)	0.050
Patient global VAS, mm	48.0 (30.0–67.0)	40.0 (20.0–62.8)	0.058
Physician global VAS, mm	43.0 (38.0–60.0)	40.0 (25.0–52.8)	0.10
CRP, mg/dL	0.61 (0.2–3.7)	0.8 (0.2–2.3)	0.27
ESR, mm/h	47 (22–70)	36 (20–62)	0.19
DAS28 (ESR)	5.3 (4.4–6.4)	4.9 (3.9–5.7)	<0.01
SDAI	27.0 (18.8–36.5)	20.0 (13.1–29.1)	<0.01
CDAI	24.5 (15.0–36.5)	18.1 (12.0–27.0)	<0.01
Total GS score	15.0 (8.0–23.0)	10.0 (6.0–18.0)	0.02
Total PD score	8.0 (3.0–14.0)	5.0 (2.3–11.0)	0.23
Total Combined score	16.0 (8.0–25.0)	11.0 (6.0–18.8)	0.03

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CDAI \leq 10 at 3 months (%)	35.5	63.7
CDAI \leq 10 at 6 months (%)	37.9	69.0
CDAI \leq 10 at 12 months (%)	35.7	63.3

The data are median (interquartile range) or number (%). Variables were compared using the Fisher's exact test or the Wilcoxon rank-sum test. ACPA: anti-citrullinated protein antibody, b/tsDMARD: biological/target-specific disease-modifying antirheumatic drug, CDAI: Clinical Disease Activity Index, CRP: C-reactive protein, DAS28: Disease Activity Score in 28 joints, ESR: erythrocyte sedimentation rate, GS: gray scale, ILD: interstitial lung disease, MTX: methotrexate, PD: power Doppler, PSL: prednisolone, RF: rheumatoid factor, SDAI: Simplified Disease Activity Index, VAS: visual analog scale.

Table 2. Comparison of baseline characteristics and treatment between patients with and without good response

	Good n=20	Poor n=23	p-value
Age	65.0 (56.0–71.0)	68.0 (55.0–76.0)	0.40
Female, n (%)	17 (85.0)	19 (82.6)	1.00
Disease duration, months	117 (67–187)	120 (77–217)	0.72
RF-positive, n (%)	17 (85.0)	20 (90.9)	0.66
ACPA-positive, n (%)	16 (80.0)	21 (95.5)	0.17
ILD, n (%)	5 (25.0)	7 (31.8)	0.74
Fibromyalgia, n (%)	1/11 (9.1)	3/22 (13.6)	1.00
MTX use, n (%)	13 (65.0)	8 (34.8)	0.07
PSL use, n (%)	8 (40.0)	15 (65.2)	0.13
>3 MOAs, n (%)	4 (20.0)	12 (52.2)	0.056
No. of tender joints	6.0 (2.3–13.0)	10.0 (4.0–15.0)	0.24
No. of swollen joints	5.0 (2.0–6.8)	8.0 (4.0–12.0)	0.055
Patient pain VAS, mm	40 (20–57)	60 (40–78.5)	0.04
Patient global VAS, mm	40 (21–55)	60 (40–70)	0.04
Physician global VAS, mm	39 (31–49)	60 (40–70)	<0.01
CRP, mg/dL	0.5 (0.05–2.1)	1.4 (0.24–5.76)	0.01
ESR, mm/h	36.5 (18.5–57.3)	60.0 (28.0–87.0)	0.03
DAS28 (ESR)	4.8 (4.2–5.8)	5.9 (5.2–7.1)	0.01
CDAI	20.0 (11.9–26.7)	28.5 (22.0–41.0)	0.02
Total GS score	15.0 (3.3–21.0)	14.0 (10.0–32.0)	0.21
Total PD score	6.5 (3.0–12.0)	9.0 (4.0–18.0)	0.29
Total Combined score	17.0 (4.0–21.0)	15.0 (11.0–32.0)	0.26
MOAs used:			0.02*
CTLA4-Ig, n	5	0	
MOAs other than CTLA4-Ig, n	15	23	

TNF inhibitors	5	7
IL-6 inhibitors	3	2
JAK inhibitors	7	14

Data are median (interquartile range) or number (%). Variables were compared using the Fisher's exact test or the Wilcoxon rank-sum test. *: CTLA4-Ig or others. ACPA: anti-citrullinated protein antibody, CDAI: Clinical Disease Activity Index, CRP: C-reactive protein, DAS28: Disease Activity Score in 28 joints, ESR: erythrocyte sedimentation rate, GS: gray scale, ILD: interstitial lung disease, MOAs: mechanisms of action, MTX: methotrexate, PD: power Doppler, PSL: prednisolone, RF: rheumatoid factor, VAS: visual analog scale.

Figure Legends:

Fig. 1 .

Comparison of the remission or low disease activity rates at 12 months between the difficult-to-treat (D2T) rheumatoid arthritis (RA) group and non-D2T RA group.

(A) The achievement rates of Clinical Disease Activity Index (CDAI) value ≤ 10 after 12 months were as follows: D2T RA, 46.5%; non-D2T RA, 70.8%. **(B)** The achievement rates of a CDAI value ≤ 2.8 were D2T RA, 11.6%; non-D2T RA, 44.3%. **(C)** The achievement rates of a power Doppler (PD) score 0 were D2T RA, 20.9%; non-D2T RA, 48.9%.

