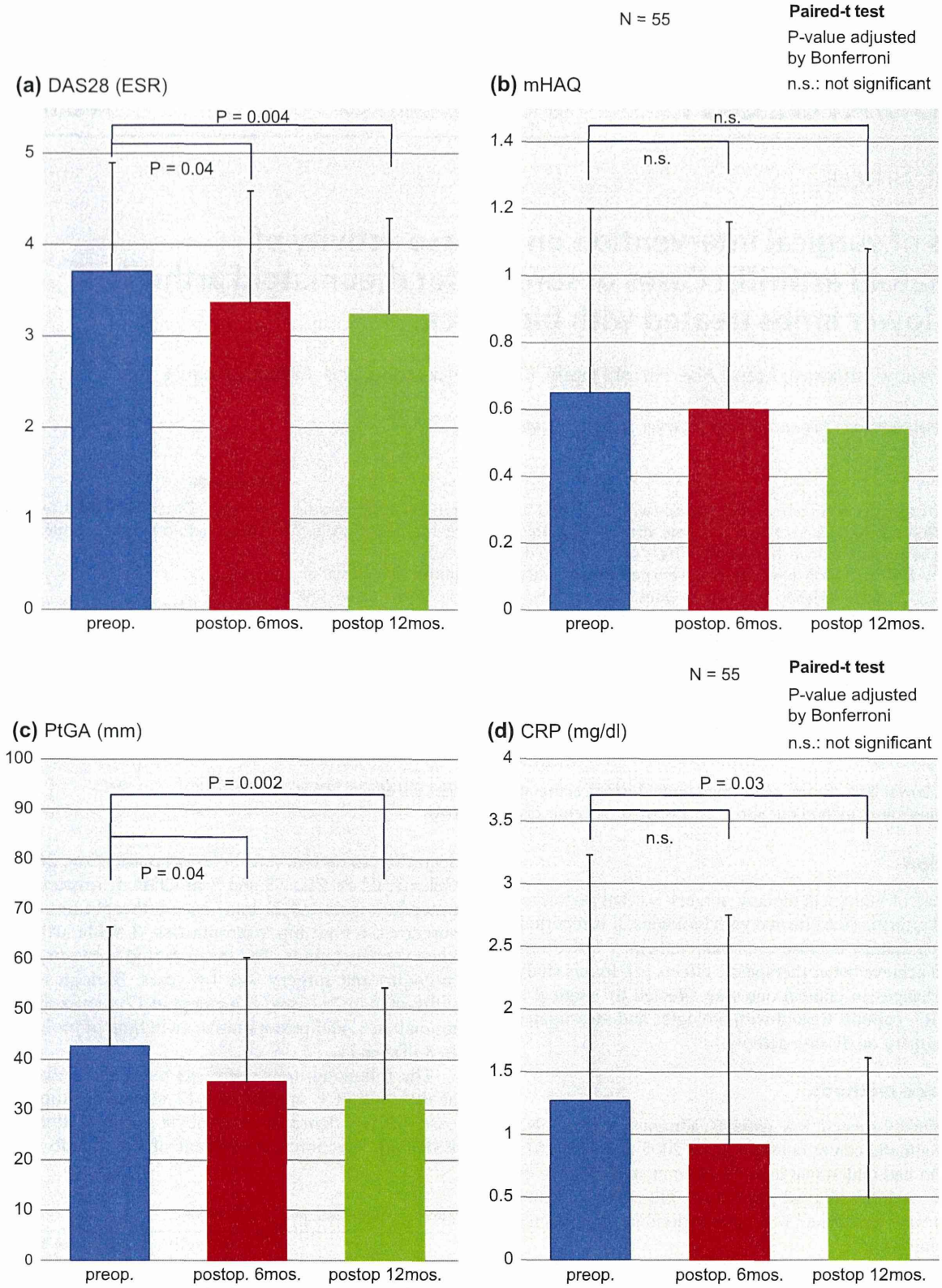

Figure 1. (a) Mean score of DAS28-ESR before surgery and at 6 and 12 months postoperatively. (b) Mean score of the mHAQ before surgery and at 6 and 12 months postoperatively. (c) Mean score of PGA on the time of before surgery and at 6 and 12 months postoperatively. (d) Mean score of CRP on the time of before surgery and at 6 and 12 months postoperatively.

the modified Health Assessment Questionnaire (mHAQ) [7], patient global assessment (PtGA) using visual analog scale and serum C-reactive protein (CRP) level. A kind and its dose of medication including disease-modifying antirheumatic drugs (DMARDs) and prednisolone (PSL) during the follow-up period and postoperative presence of infection or delayed wound healing were investigated.

All cases in this study group did not change medication from more than 3 months before surgery.

Also, comparisons were performed on the basis of the preoperative DAS28-ESR between the patients with high and moderate disease activity, namely the poorly controlled group: DAS28-ESR was 3.2 or more, and the patients with low disease activity and remission, namely the well-controlled group: DAS28-ESR was less than 3.2.

Statistical analysis

Mean values and standard deviations (SD) for each group were calculated. The outcome measures including DAS28-ESR, mHAQ, PtGA and CRP were compared at the point of just before the surgery, 6 months postoperatively and 12 months postoperatively. All of the outcomes were analyzed by Student t-test with Bonferroni method. It corrected to counteract the multiple comparisons among the groups of before surgery, 6 months postoperatively and 12 months postoperatively. P value of less than 0.05 was considered to indicate a significant difference. The P value in Figures 1 and 3 was adjusted it to double of the raw P-value.

Results

Overall results

Preoperative DAS28-ESR decreased from 3.71 ± 1.19 (mean ± SD) to 3.37 ± 1.22 at 6 months and to 3.24 ± 1.05 at 12 months postoperatively. Also, preoperative mHAQ score and PtGA improved from 0.65 ± 0.55 and 42.68 ± 23.84 to 0.6 ± 0.56 and 35.6 ± 24.75 at 6 months, and to 0.54 ± 0.54 and 32.07 ± 22.26 at 12 months postoperatively (Figure 1a, b, c). Serum CRP level decreased from preoperative 1.27 ± 1.96 mg/dl to postoperative 0.92 ± 1.83 mg/dl at 6 months and to 0.49 ± 1.12 mg/dl at 12 months (Figure 1d). In all these items except mHAQ between preoperative and postoperative 6 months, between preoperative and postoperative 12 months and serum CRP level between preoperative and postoperative 6months, statistical significant difference was noted.

The mean dose of oral PSL decreased from 4.4 ± 3.8 mg/day to 4.1 ± 2.6 mg/day postoperatively. During the postoperative follow-up period, there was no change in medication: DMARDs and PSL were used in the same dose in 20 (36.4%) patients. Decrease in medication: one unchanged and the other decreased, or both decreased was performed in 23 (41.8%) patients. In contrast, increase in medication: one drug unchanged and the other increased, or both increased was performed in 4 (7.3%) patients, and switching to different drugs or adding on a new DMARD was performed in 8 (14.5%) patients (Figure 2).

To investigate the effects of surgery alone on disease activity, excluding the effect of drugs, the same outcome measures were evaluated in 43 (78.2%) patients in whom no change or decrease in medication was performed. As a result, DAS28-ESR decreased with statistical significance from 3.53 ± 1.17 preoperatively to 3.16 ± 1.16 at 6 months and to 3.16 ± 0.98 at 12 months postoperatively. However, there was not a significant change in mHAQ score with preoperative 0.68 ± 0.56 and postoperative 0.64 ± 0.58 at 6 months, and 0.62 ± 0.58 at 12 months. (Figure 3a, b).

PtGA and serum CRP decreased from 40.9 ± 24.8 and 1.29 ± 2.05 mg/dl to 32.1 ± 24.5 and 0.77 ± 1.73 mg/dl at 6 months postoperatively, 29.7 ± 22.3 and 0.38 ± 1.08 mg/dl at 12 months, and statistically significant differences were noted (Figure 3c, d).

In all these items except mHAQ between preoperative and postoperative 6 months, between preoperative and postoperative 12 months, DAS28-ESR between preoperative and postoperative 6 months serum CRP level between preoperative and postoperative 6 months, statistical significant difference was noted.

There was neither occurrences of postoperative infection nor delayed surgical wound healing in all cases.

Findings related to group

In the poorly controlled group, DAS28-ESR improved significantly from preoperative 4.53 ± 0.70 to the postoperative score 3.98 ± 0.99 at 6 months and 3.71 ± 0.1 at 12 months, whereas in the well-controlled group, low disease activity or remission was maintained during postoperative 12 months as indicated preoperative 2.50 ± 0.66 to the postoperative score 2.54 ± 1.04 at 6 months and postoperative 2.51 ± 0.81 at 12 months (Figure 4).

The rate of low disease activity at postoperative 12 months was 31.3% in the poorly controlled group, whereas it was 82.6% in the well-controlled group, indicating that low disease activity or remission persisted at a high rate in the well-controlled group.

There was not a significant change in the mHAQ score in the poorly controlled group indicating preoperative 1.26 ± 0.79, postoperative 1.0 ± 0.93 at 6 months and 1.09 ± 0.82 at 12 months. In the same way, mHAQ score in the well-controlled group was not significantly decreased from preoperative 1.06 ± 1.32 to postoperative 0.8 ± 1.32 at 6 months and 0.9 ± 1.4 at 12 months. PtGA in the poorly controlled group, a significant decrease was noted from preoperative 49.9 ± 22.1 to postoperative 45.7 ± 25.8 at 6 months and 36.66 ± 25.70 at 12 months. However, PtGA in the well-controlled group, there was not a significant change, indicating preoperative 30.96 ± 22.85 to postoperative 22.2 ± 16.8 at 6 months and 25.39 ± 16.58 at 12 months. Serum CRP levels in the poorly controlled group improved significantly from preoperative 1.61 ± 2.06 mg/dl to postoperative1.32 ± 2.18 at 6 months 0.63 ± 1.04 mg/dl at 12 months. However, in the well-controlled group, there was not a significant change, indicating preoperative 0.79 ± 1.75 to postoperative 0.36 ± 0.97 at 6 months and 0.49 ± 1.45 at 12 months.

To summarize, the poorly controlled group showed improvement in all the items except mHAQ score, and the well-controlled group showed improvement keeping low disease activity.

Improvement in terms of EULAR criteria [6] was shown in Table 2. Rates of responses were as follows: good response was 3.6%, moderate response was 38.2% and no response was 58.2% (Table 2).

Discussion

As treatment of RA with biologics has spread, surgical trends for RA have changed greatly [8]. Concurrently, effects of surgical intervention on disease activity have been reported, and a favorable effect of combination of biologics and surgery has been described [1]. We experienced several cases, in which postoperative dose of DMARDs or PSL was successfully decreased after surgery, and those in which postoperative disease activity were ameliorated over a long period of time. Thus, by recruiting the surgically-treated cases, we examined the details of changes in drug therapy that can affect postoperative disease activity.

Kanbe and Inoue [9] and Momohara et al. [10] demonstrated that disease activity is suppressed by surgical resection of the synovium or replacement arthroplasty. In the present study, we could successfully reduce disease activity by surgical intervention and gradually decrease the dose of oral steroid in the study population.

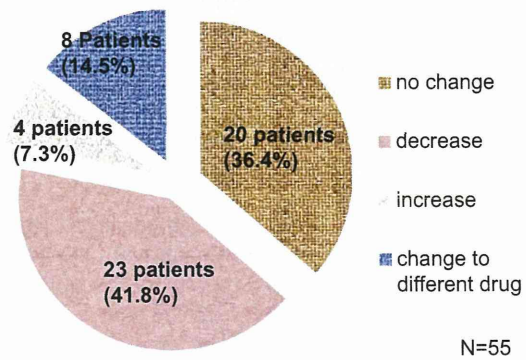

Figure 2. Postoperative medication.

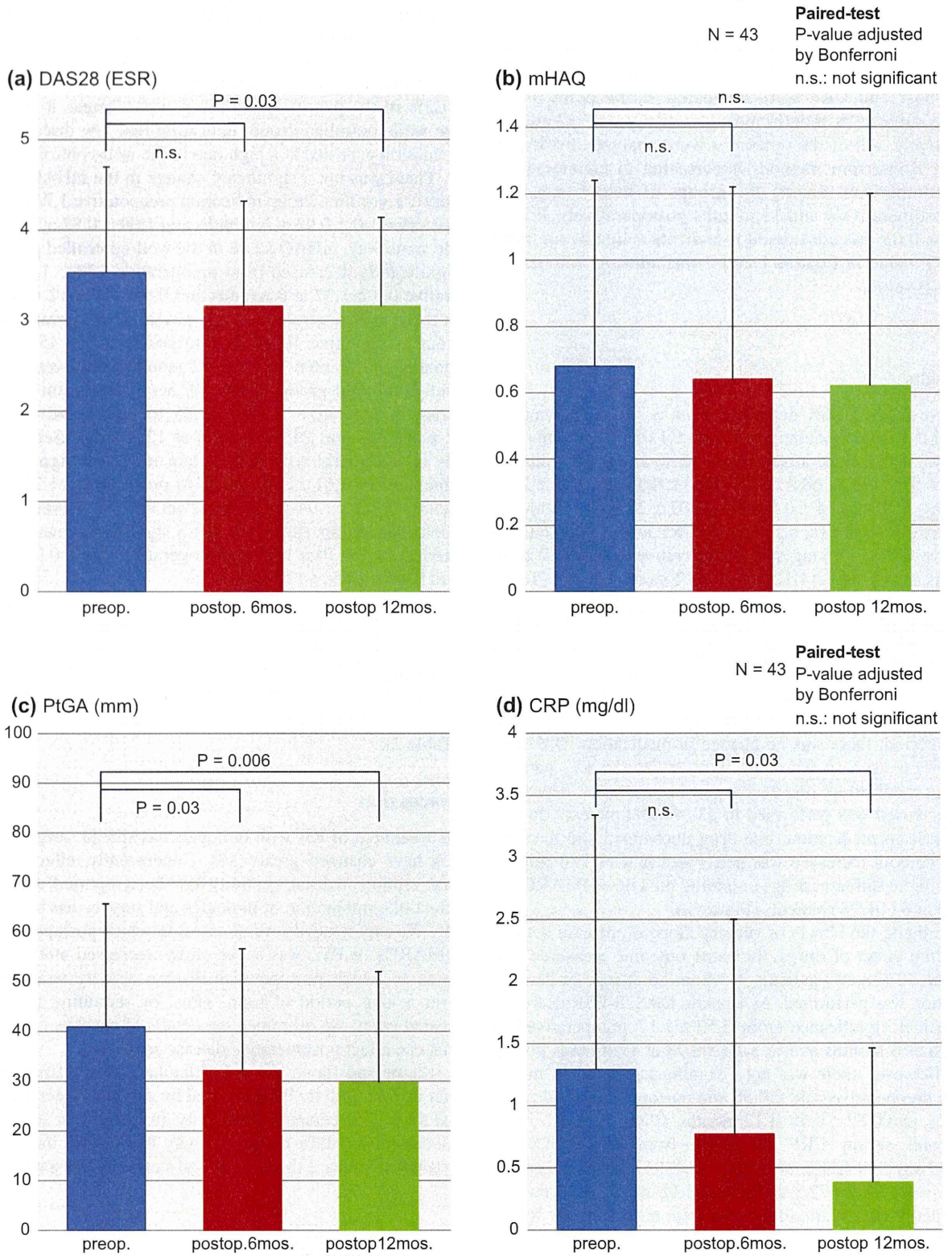

Figure 3. (a) Mean score of DAS28-ESR on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased medication. (b) Mean score of the modified HAQ on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased medication. (c) Mean score of PGA on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased medication. (d) Mean score of C-reactive protein (CRP) on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased medication.

When the patients were divided into the well-controlled and poorly controlled groups, remarkable improvement was observed in the poorly controlled group. Yano also reported a systemic effect of TKA on disease activity in patients with moderate or high disease activity [11]. Differences were found in each outcome measure of the DAS28-ESR, mHAQ, PtGA and CRP between the well-controlled group and poorly controlled group.

Ranganath et al. investigated relationship among the use of oral DMARDs, disease activity and mHAQ in 889 RA patients [12]. They reported that the factors that improved mHAQ were maintenance of low disease activity as well as short disease duration and frequent changes or adding on DMARDs. They further stated that control of disease activity with drugs is important for functional improvement. In addition, Graell et al. noted that in 105 early RA

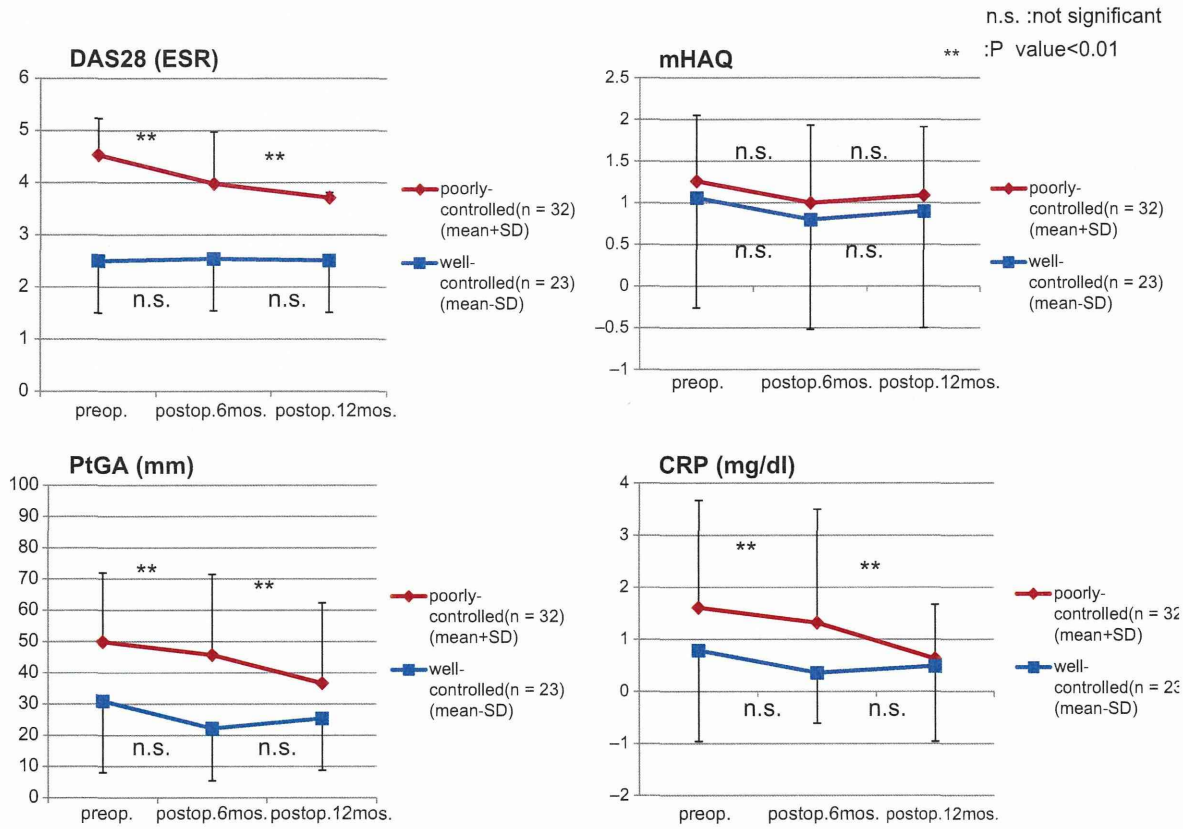

Figure 4. Comparison of the well-controlled group and poorly controlled group. Poorly controlled group: the patients with high and moderate disease activity (DAS28-ESR score of 3.2 or more), Well-controlled group: the patients with low disease activity and remission (DAS28-ESR score of less than 3.2).

patients with less than 2-year disease duration, treatment with DMARDs alone prevented functional impairment in only 26.6% of patients and that high age, mHAQ > 0.5, DAS28 > 5.1, high global assessment, positive rheumatoid factor and elevated ESR level were associated with functional impairment [13]. Among the subjects in the present study, the poorly controlled group had more impact on not only DAS28-ESR score but also PtGA score and CRP levels than the well-controlled group. But they still had frequent relapse or persisting inflammation at the nonsurgically-treated joints, resulting in only 31.3% of patients achieving low disease activity at 12 months postoperatively. Whereas, 82.6% of patients in the well-controlled group maintained low disease activity at 12 months postoperatively. In the poorly controlled group, impact of surgery on mHAQ was less than that in the well-controlled group. This might be a result by there being more number of disabled joints in the poorly controlled group than in the well-controlled group.

Regarding improvement of EULAR criteria, 41.8% of patients had a good or moderate response, and it was shown that combination therapy of biologics and surgery had produced a favorable effect on maintenance and improvement of postoperative low disease activity.

In recent years, along with dramatic advances in drug therapy, the therapeutic goal of T2T (treat to target) has been defined [14], and it has become important to evaluate RA disease activity more accurately and in a timely manner. The present study revealed that lower limb surgery performed under biological therapy enhances the effects of not only improving joint function but also of ameliorating systemic disease activity.

Table 2. Improvement in terms of EULAR criteria.

	The EULAR response criteria		N = 55
< 3.2 Low activity 3.2–5.1 Moderate activity > 5.1 High activity	2 cases 6 cases 2 cases	7 cases 6 cases 2 cases	14 cases 14 cases 2 cases

Good response	3.6% (2/55)
Moderate response	38.2% (21/55)
No response	58.2% (32/55)

Conflict of interest

None.

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ORIGINAL ARTICLE

Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies

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Abstract The aim of this study was to compare the efficacy and retention rates of three biologics (abatacept, tocilizumab, and etanercept) after switching from first-course anti-TNF monoclonal antibody therapy. We performed a retrospective multicenter study of 89 patients who underwent second-course biologic therapy for 52 weeks after switching from first-course anti-TNF monoclonal antibody therapy. Patients at baseline had a mean age of 58.7 years, mean disease duration of 9.8 years, and mean clinical disease activity index (CDAI) of 22.4. There was no significant difference between the three drugs, except in rheumatoid factor positivity. Retention rates for abatacept, tocilizumab, and etanercept treatment at 52 weeks were 72.0, 89.5 and 84.6 %, respectively. The evaluation of CDAI indicated no significant difference at 52 weeks among the three drugs. Discontinuation due to all unfavorable causes did not significantly differ among the three drugs in hazard ratio-based evaluations. Our results show that patients treated with abatacept, tocilizumab, and etanercept achieved a high response rate with no significant differences in drug retention rates and clinical efficacy. These drugs

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represent good therapeutic options for patients with RA who are refractory to anti-TNF monoclonal antibody therapy.

Keywords Abatacept · Etanercept · Rheumatoid arthritis · Switching medications · Tocilizumab

Introduction

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune inflammatory disease that clinically manifests as joint pain and swelling [1]. In the past decade, treatment of RA has improved significantly with the introduction of tumor necrosis factor inhibitors (TNFi), which reportedly demonstrate high efficacy [2–4]. However, these drugs have little or no effect in about 30 % of treated patients, with two thirds demonstrating moderate to high disease activity at 1 year post-treatment [5]. In clinical practice, switching biologics remains a difficult issue. According to the European League Against Rheumatism recommendations, patients who do not respond to initial TNFi therapy should switch to a different TNFi or use a different class of biologics (abatacept, rituximab, or tocilizumab) [6]. While some studies reported on the outcomes of switching from TNFi to other biologics [7, 5, 8], no consensus has been reached on the strategy of switching.

Loss of therapeutic efficacy is readily observed with anti-TNF monoclonal antibodies (adalimumab and infliximab) in patients receiving concomitant low-dose methotrexate (MTX) due to immunogenicity-related issues [9–11]. This is one factor leading to withdrawal from anti-TNF monoclonal antibody therapy. The dose of concomitant MTX in Japan is lower compared to other countries [12], and switching from anti-TNF monoclonal antibodies is often required. To this end, we compared three drugs (abatacept, tocilizumab, and etanercept) that are considered to exhibit low immunogenicity [13, 14, 2].

In this study, etanercept, a drug with proven efficacy, was compared with abatacept and tocilizumab. In view of the different characteristics of available TNFi, switching from an anti-TNF monoclonal antibody to a TNF receptor fusion protein (etanercept) may be helpful if initial treatment fails. On the other hand, several new biologics with different mechanisms of action are now available (e.g., abatacept, rituximab, and tocilizumab). Some reports have compared switching to tocilizumab and abatacept [15, 16, 7]. Hyrich et al. reported that when the first TNFi treatment fails, the best alternative is to start on a different class of biologics [16]. However, there are no reports to date comparing new biologics with etanercept. Accordingly, this study aimed to compare patients who switched to etanercept, abatacept, and tocilizumab from first-course anti-TNF monoclonal antibody therapy.

Abatacept and tocilizumab are recently approved non-TNFi biologics that are marketed for the treatment of RA. Abatacept is the first member of a new class of biologics which inhibit T-cell activation by binding to CD80/86 and modulating its interaction with CD28. Based on this mechanism, abatacept is expected to achieve clinical efficacy in patients who respond inadequately or are naïve to other classes of biologics. Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was approved in 2008 for use in clinical practice in Japan. The efficacy of tocilizumab for RA has been demonstrated in several clinical trials [14, 17] as well as in actual practice [18, 19]. Both drugs show low immunogenicity, with anti-drug antibody production rate of 2.3 % for abatacept and 2.5 % for tocilizumab [13, 14]. The efficacy and safety of these drugs in patients who are naïve or refractory to TNFi therapy have been demonstrated in several randomized controlled clinical trials (RCTs) [20–23]. However, controversy exists as to whether a different TNFi (e.g., etanercept) should be selected or other elements of the inflammatory process should be modified when switching from anti-TNF monoclonal antibodies.

Patients may exhibit differential responses to the three agents (abatacept, tocilizumab, and etanercept) upon switching, although there is no direct evidence to support this. The present study compared retention rates and clinical efficacy of abatacept, tocilizumab, and etanercept switched from first-course anti-TNF monoclonal antibody therapy based on retrospectively registered observational data.

Materials and methods

Tsurumai Biologics Communication Registry

The Tsurumai Biologics Communication Registry (TBCR) was developed in 2008 to explore the long-term prognosis of biologics in clinical practice and consisted of patients who were starting biologic treatments. Data were collected prospectively from 2008 and retrospectively for patients treated up to 2008 [24]. The present study included all patients (n=89) who switched to abatacept, tocilizumab, or etanercept as a second biologic agent from first-course anti-TNF monoclonal antibody due to inadequate efficacy from September 2010 to September 2011 at Nagoya University Hospital or one of 12 other institutions affiliated with the TBCR and were prospectively enrolled in the TBCR. During the study period, we were able to choose freely among the five biological DMARDs (infliximab, etanercept, adalimumab, tocilizumab, abatacept) at our discretion as a second-line as well as a first-line biologic. All patients met the 1987 American College of Rheumatology classification criteria for RA and received abatacept, tocilizumab, or etanercept infusions according to the drug label and Japan College of Rheumatology guidelines for treatment. Patient anonymity was maintained during data collection, and the security

of personal information was strictly controlled. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine.

Data collection

Data were retrospectively collected from clinical records. The following demographic data were recorded at the initiation of treatment (baseline, week 0): disease duration, concomitant treatment (methotrexate [MTX] or prednisolone), joint damage (Steinbrocker stage), and daily dysfunction (Steinbrocker class). The following disease parameters were recorded at baseline and at 24 and 52 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, general health on a visual analog scale (GH-VAS), and serum C-reactive protein (CRP) levels. Disease activity was evaluated at each time point using the 28-joint disease activity score with CRP (DAS28-CRP) and the clinical disease activity index (CDAI) which included data from the cited disease parameters.

Statistical analysis

Demographic and disease characteristics were reported using descriptive statistics. All results are expressed as mean±SD or percentage. Student's *t*-test was used for two-group comparisons and the chi-square test for categorical variables. The last observation carried forward (LOCF) method was used in each analysis. All statistical tests were two-sided, and significance was defined as $p<0.05$. Drug continuation rates were estimated by plotting Kaplan–Meier curves and were compared using log-rank test. Hazard ratios (HRs) for cause-specific drug discontinuation were calculated using the Cox proportional hazards model, adjusted for variables such as disease duration, age, sex, and concomitant use of MTX and CDAI. All analyses were performed with SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients

We examined 89 patients who switched to abatacept, tocilizumab, and etanercept as a second biologic agent from first-course anti-TNF monoclonal antibody therapy due to inadequate efficacy. Of these, 25 (28.1 %) had switched to abatacept, 38 (42.7 %) had switched to tocilizumab, and 26 (29.2 %) had switched to etanercept.

Baseline characteristics of all patients are shown in Table 1, categorized by the second biologic agent. Mean age was 58.7 ±12.1 years, mean disease duration was 9.8±8.3 years, and mean DAS28-CRP and CDAI were 4.6±1.2 and 22.4±11.0, respectively. A significant difference was found in rheumatoid factor positivity among the three drugs. No significant differences were found in factors reported to affect the effects of biologics, including MTX use, MTX dose, and disease duration. In the present study, the rate of concomitant MTX use was 78.7 %, with a mean dose of 7.4 mg/week.

Drug continuation rates

Drug continuation rates were analyzed with Kaplan–Meier curves (Fig. 1). At 52 weeks, continuation rates for abatacept, tocilizumab, and etanercept were 72.0, 89.5, and 84.6 %, respectively (log-rank test, $p=0.121$), for discontinuation due to all unfavorable causes (Fig. 1a). When classified according to reasons for discontinuation, continuation rates at 52 weeks for abatacept, tocilizumab, and etanercept were 88.0, 97.1, and 90.5 % (log-rank test, $p=0.374$), respectively, for discontinuation due to adverse events (Fig. 1b), and 82.6, 91.9, and 95.7 % (log-rank test, $p=0.182$), respectively, for discontinuation due to inadequate efficacy (Fig. 1c). It should be noted that discontinuation of tocilizumab due to adverse events and discontinuation of etanercept due to inadequate efficacy were low, although there was no significant difference. All drugs exhibited good retention rates.

Clinical efficacy

Figure 2 shows changes in tender joint counts, swollen joint counts, GH-VAS, CRP, DAS28-CRP, and CDAI at 0, 24, and 52 weeks. The decline over time in TJC, SJC, GH-VAS, CRP, DAS28-CRP, and CDAI significantly improved at all time points. TJC and SJC showed similar improvements without significant differences among the three drugs. GH-VAS was clearly higher in abatacept-treated patients (44.2±27.3) compared to others (tocilizumab, 23.9±23.0, $p=0.004$; etanercept, 24.8±20.8, $p=0.007$) at 24 weeks, but there was no significant difference at 52 weeks. GH-VAS decreased more gradually in abatacept-treated patients. CRP levels were clearly lower with tocilizumab compared to abatacept at 24 weeks (tocilizumab, 0.16±0.85; abatacept, 0.87±1.16; $p=0.002$) and 52 weeks (tocilizumab, 0.21±0.87; abatacept, 0.91±0.98; $p=0.001$). DAS28-CRP showed no difference among the three drugs at 24 weeks but was lower with tocilizumab compared to abatacept at 52 weeks (tocilizumab, 2.51±1.12; abatacept, 3.22±1.11; $p=0.016$). As shown in Fig. 3, all three drugs demonstrated good efficacy at 52 weeks in the evaluation based on CDAI. Remission rates and percentages of subsequent low disease activity for abatacept, tocilizumab, and etanercept were 20.7, 28.6, and 20.6 %, respectively, and 49.8, 68.2, and 70.6 %, respectively.

Table 1 Baseline characteristics of patients with rheumatoid arthritis who switched from anti-TNF monoclonal antibodies

	Overall (n=89)	Abatacept (n=25)	Tocilizumab (n=38)	Etanercept (n=26)	p value
Age (year)	58.7±12.1	62.8±9.3	56.7±12.4	57.5±13.3	0.315
Sex (% female)	82	80	78.9	88.5	0.593
Disease duration (year)	9.8±8.3	11.4±9.5	7.9±6.1	11.0±9.6	0.207
Stage (I/II/III/IV, %)	19.1/21.3/24.7/32.6	20.0/20.0/24.0/36.0	19.4/22.2/33.3/25.0	19.2/23.1/15.4/42.3	0.627
Class (I/II/III/IV, %)	13.5/50.6/29.2/4.5	12.0/52.0/36.0/0	16.8/52.8/27.8/2.8	11.5/50.0/26.9/11.5	0.453
RF positive (%)	82.9	70.6	78.6	96	**0.002**
Previous biological DMARDs (%)					
Adalimumab	37.1	60	26.3	30.8	
Infliximab	62.9	40	73.7	69.2	
MTX use (%)	78.7	80	73.7	84.6	0.567
MTX dose (mg/week)[a]	7.4	7.5	7.3	7.8	0.716
Oral steroid use (%)	58.4	64	59.5	53.8	0.760
Oral steroid dose (mg/day)[a]	4.2	3.8	4	4.8	0.433
MMP-3 (ng/mL)	257.0±235.2	217.1±190.0	317.4±271.6	183.9±129.0	0.371
SJC, 0–28	5.4±4.8	5.9±5.6	5.7±4.9	4.7±3.7	0.546
TJC, 0–28	6.4±5.6	5.3±4.1	6.0±5.7	7.9±6.6	0.439
ESR (mm/h)	53.1±27.1	57.4±32.1	51.1±24.9	53.0±26.4	0.475
CRP (mg/dL)	2.6±2.6	1.7±1.9	2.9±2.8	3.0±2.9	0.374
GH-VAS 0–100 mm	54.1±22.9	53.7±25.2	53.9±22.4	54.6±22.3	0.514
DAS28-ESR	5.3±1.2	5.2±1.2	5.3±1.2	5.4±1.3	0.267
DAS28-CRP	4.6±1.2	4.4±1.1	4.7±1.2	4.8±1.1	0.266
CDAI	22.4±11.0	21.2±11.0	22.4±11.1	23.5±11.2	0.266
SDAI	24.8±11.6	23.1±11.3	24.7±11.5	26.4±12.3	0.335

Data are presented as mean±SD, unless otherwise indicated

Stage Steinbrocker stage, *Class* Steinbrocker class, *RF* rheumatoid factor, *MTX* methotrexate, *MMP-3* matrix metalloproteinase-3, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *GH-VAS* general health visual analog scale, *DAS28* disease activity score in 28 joints, *CDAI* clinical disease activity index, *SDAI* simplified disease activity index

[a] Mean among patients receiving the drug

Multivariate analysis

We calculated HRs for cause-specific drug discontinuation using multivariate Cox proportional HR analysis (Table 2) adjusted by disease duration, age, sex, concomitant MTX use, and CDAI. Discontinuation due to all unfavorable causes did not significantly differ among abatacept, tocilizumab, and etanercept, although discontinuation of tocilizumab due to adverse events and discontinuation of etanercept due to inadequate efficacy tended to be less common. There was no significant difference in inadequate efficacy and adverse events across the three drugs.

Discussion

The recent introduction of two new biologics, abatacept and tocilizumab, into the market represents interesting new therapeutic opportunities for patients with RA who are resistant to TNFi. In the present study, no apparent difference in terms of efficacy was observed among abatacept, tocilizumab, and etanercept after switching from anti-TNF monoclonal antibodies.

In general, when patients respond poorly to the first TNFi after 3 to 4 months, switching to a different biologic agent is considered [6]. If the secondary loss of efficacy is due to anti-drug antibodies, switching to a second TNFi might prove effective [16]. In many cases, the first treatment is discontinued due to immunogenicity-related problems associated with the concomitant use of low-dose MTX. In such cases, the biologics with low immunogenicity are useful. Etanercept does not require concomitant MTX necessarily and could thus demonstrate the expected efficacy [2]. In contrast, if the secondary loss of efficacy is due to TNF no longer being the primary cytokine, switching to other classes of biologics will be required. Whenever possible, the switching of biologics should be decided based on the cause of secondary loss of efficacy; however, there is currently no method to determine this. Moreover, there is no consensus regarding the strategy of switching biologics.

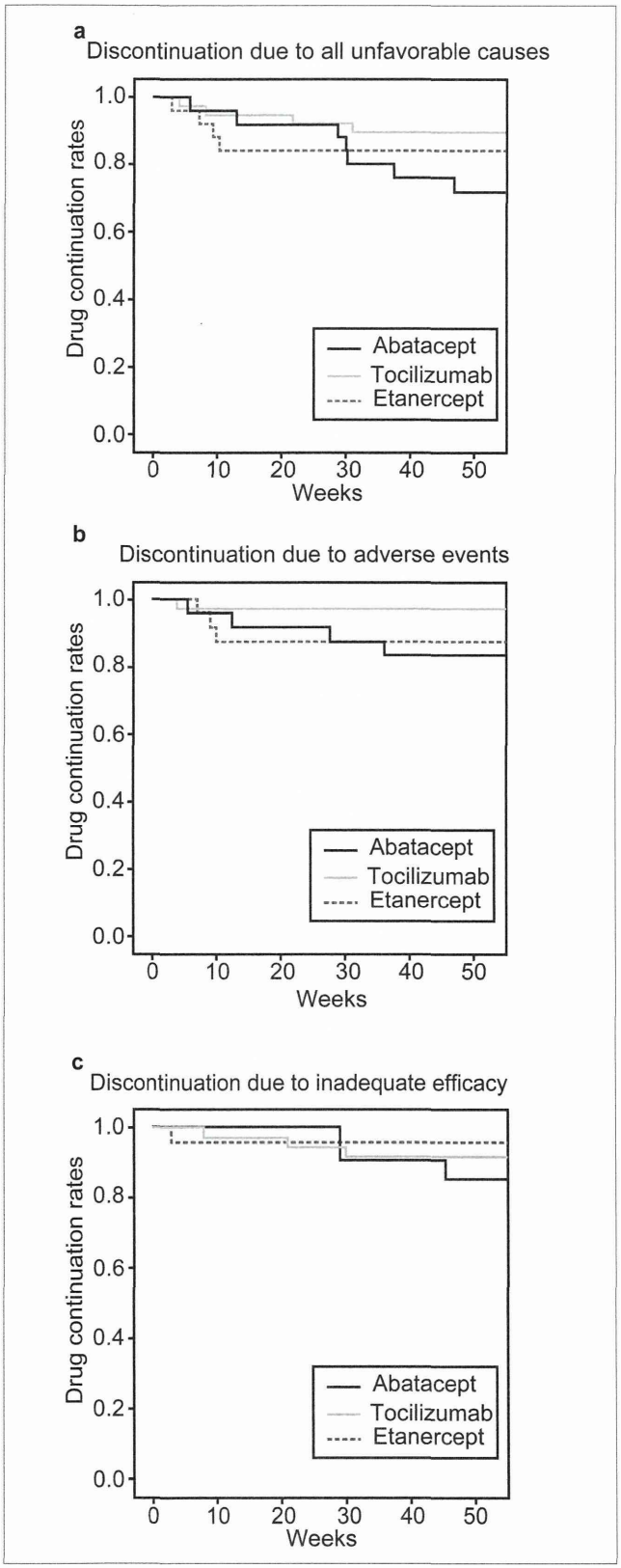

Fig. 1 Patient retention in abatacept, tocilizumab, and etanercept treatment. Kaplan–Meier curves of treatment continuation rates among patients with rheumatoid arthritis over 52 weeks of treatment. **a** Discontinuation due to all unfavorable causes. **b** Discontinuation due to adverse events. **c** Discontinuation due to inadequate efficacy

The present observational study was based on data from a multicenter registry regarding the clinical efficacy of abatacept, tocilizumab, and etanercept in patients with RA in whom anti-TNF monoclonal antibody therapy previously failed. Therefore, the present results reflect treatment outcomes of the "real world."

Several studies have reported on switching from TNFi to other biologics. One meta-analysis revealed no difference in ACR50 response to rituximab, tocilizumab, abatacept, and golimumab when switched from TNFi [15]. According to the Danish DANBIO study, 48-week retention rates of abatacept and tocilizumab after switching from TNFi were 54 and 64 %, respectively [7]. The retention rates in our study were better (68.0 % for abatacept and 89.5 % for tocilizumab). In the DANBIO study, the mean DAS28-CRP at 48 weeks was 3.3 for abatacept and 2.5 for tocilizumab, which were comparable to our results at 52 weeks (abatacept, 3.22±1.11; tocilizumab, 2.51±1.12). In addition, 48-week remission rate in the DANBIO study was 26 % for abatacept and 58 % for tocilizumab, which are better or almost the same as our results (17.4 and 55.6 %, respectively). The ATTAIN study, which examined patients who switched from TNFi to abatacept, reported the percentages of low disease activity and remission to be 24.2 and 13.9 %, respectively [25]. Compared to these, the percentages of low disease activity and remission in the present study were better (34.8 and 17.4 %, respectively). In the RADIATE study, DAS28 remission rate at 24 weeks (DAS28-CRP 2.6) was 30.1 % in patients who switched from TNFi to tocilizumab [20], compared to 50.0 % in the present study. This difference might be attributed to low DAS28CRP values at baseline and the short disease duration of 7.9± 6.1 years in our study. As for patients who switched to etanercept from TNFi, the RADIUS study [26] reported a 52-week retention rate of 74 % in comparison to 84.6 % in our study. Taken together, our results are in good agreement with previous reports.

It should be emphasized that, in the present study, response rates and survival could not be compared among abatacept, tocilizumab, and etanercept due to the non-randomized, retrospective design. However, slight differences in clinical responses and disease activity (as judged by DAS28 CRP) among the three drugs appeared to be primarily due to the large decrease of CRP and ESR in tocilizumab-treated patients. Given that tocilizumab is an IL-6 antagonist and since IL-6 enhances the formation of CRP and ESR, our findings raise the question as to whether DAS28 is a valid tool for assessing disease activity for drugs that affect CRP and ESR. When evaluating tocilizumab, we believe that CDAI would serve as a useful tool since it does not involve CRP and ESR. In the present study, significant differences were found in CRP and DAS28-CRP when abatacept and tocilizumab were compared; however, as shown in Fig. 2f, there was no significant difference among the three drugs in terms of CDAI. The