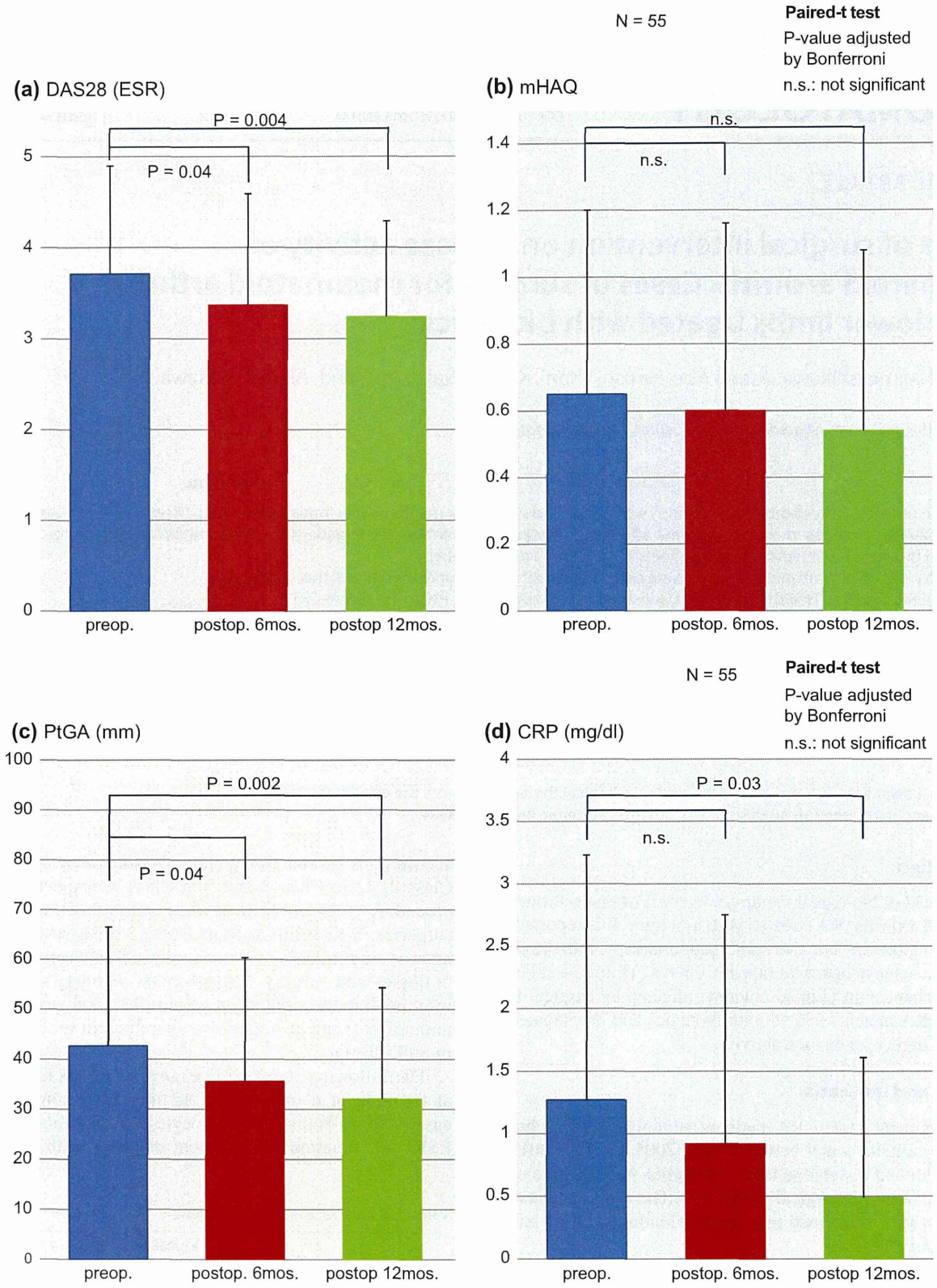

Figure 1. (a) Mean score of DAS28-ESR before surgery and at 6 and 12 months postoperatively. (b) Mean score of the mHAQ before surgery and at 6 and 12 months postoperatively. (c) Mean score of PGA on the time of before surgery and at 6 and 12 months postoperatively. (d) Mean score of CRP on the time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

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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.

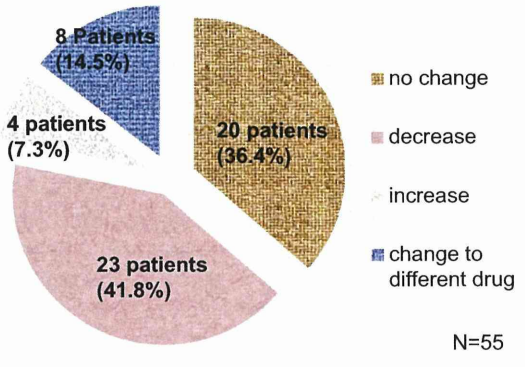

Figure 2. Postoperative medication.

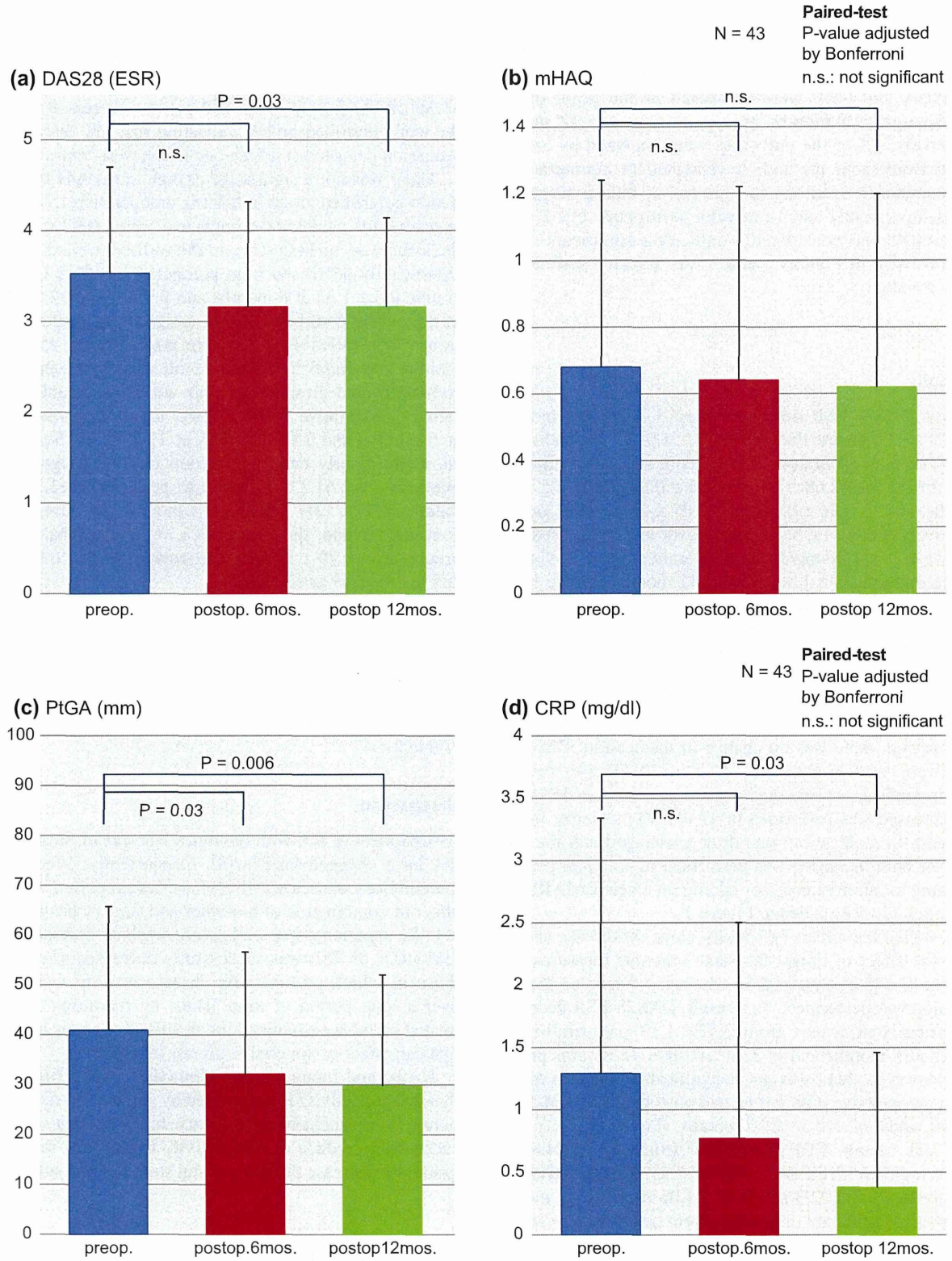

Figure 3. (a) Mean score of DAS28-ESR on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased medication. (b) Mean score of the modified HAQ on the time of before surgery and at 6 and 12 months postoperatively in the group of no change or decreased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

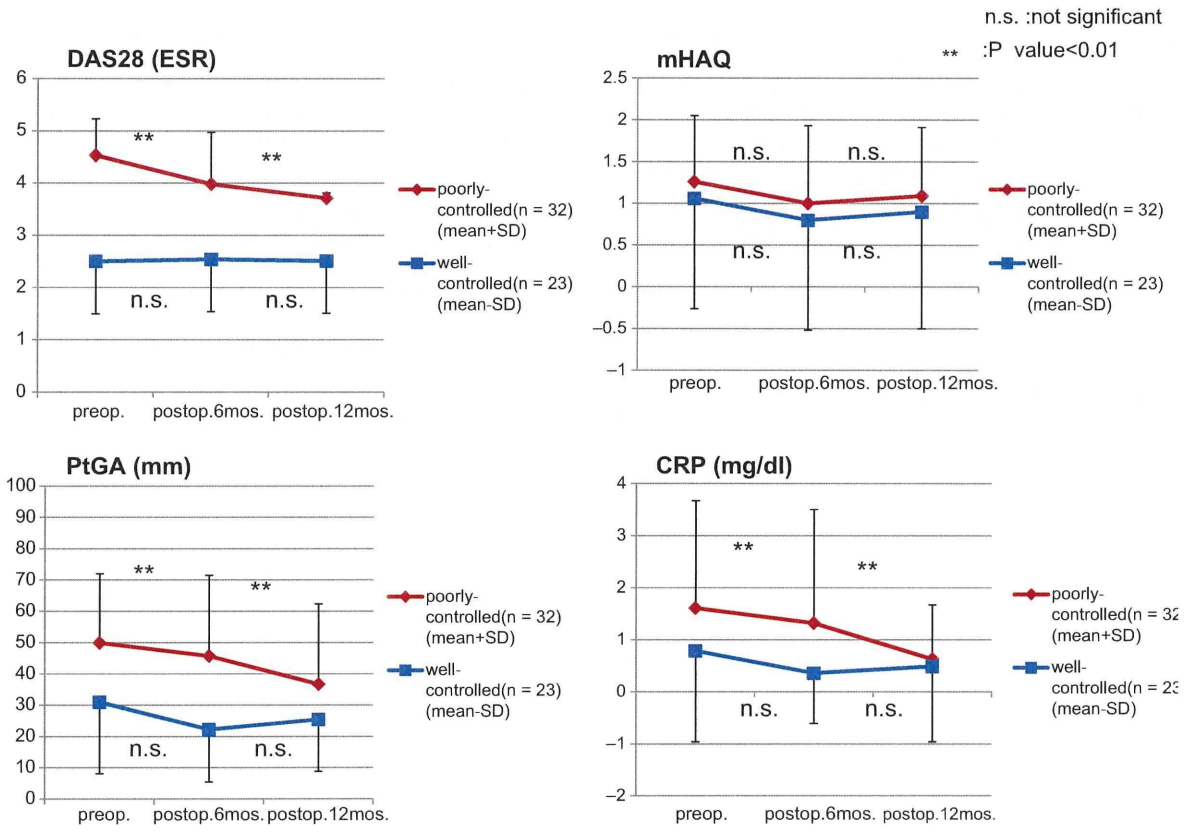

Figure 4. Comparison of the well-controlled group and poorly controlled group. Poorly controlled group: the patients with high and moderate disease activity (DAS28-ESR score of 3.2 or more), Well-controlled group: the patients with low disease activity and remission (DAS28-ESR score of less than 3.2).

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	2 cases	7 cases	14 cases
3.2–5.1 Moderate activity	6 cases	6 cases	14 cases
> 5.1 High activity	2 cases	2 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.

References

1. Hayashi M, Kojima T, Funahashi K, Kato D, Matsubara H, Shioura T, et al. Effect of total arthroplasty combined with anti-tumor necrosis factor agents in attenuating systemic disease activity in patients with rheumatoid arthritis. Mod Rheumatol. 2012;22(3): 363–9.
2. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.
3. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
4. Koike R, Takeuchi T, Eguchi K, Miyasaka N; Japan College of Rheumatology. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. Mod Rheumatol. 2007;17(6):451–8.
5. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc. 1949;140(8):659–62.
6. van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis.

Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996;39(1):34–40.
7. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137–45.
8. Momohara S, Tanaka S, Nakamura H, Mibe J, Iwamoto T, Ikari K, et al. Recent trends in orthopedic surgery performed in Japan for rheumatoid arthritis. Mod Rheumatol. 2011;21(4):337–42.
9. Kanbe K, Inoue K. Efficacy of arthroscopic synovectomy for the effect attenuation cases of infliximab in rheumatoid arthritis. Clin Rheumatol. 2006;25(6):877–81.
10. Momohara S, Inoue E, Ikari K, Yano K, Tokita A, Suzuki T, et al. Effect of total joint arthroplasty in patients with established rheumatoid arthritis: improved longitudinal effects on disease activity but not on health-related quality of life. Mod Rheumatol. 2011;21(5):476–81.
11. Yano K, Ikari K, Inoue E, Tokita A, Sakuma Y, Hiroshima R, et al. Effect of total knee arthroplasty on disease activity in patients with established rheumatoid arthritis: 3-year follow-up results of combined medical therapy and surgical intervention. Mod Rheumatol. 2010;20(5):452–7.
12. Ranganath VK, Paulus HE, Onofrei A, Khanna D, Reed G, Elashoff DA, et al. Functional improvement after patients with rheumatoid arthritis start a new disease modifying antirheumatic drug (DMARD) associated with frequent changes in DMARD: the CORRONA database. J Rheumatol. 2008;35(10):1966–71.
13. Graell E, Vazquez I, Larrosa M, Rodríguez-Cros JR, Hernández MV, Gratacós J, et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: prognostic factors after two years of follow-up. Clin Exp Rheumatol. 2009;27(2):284–91.
14. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69(4):631–7.

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BMC Research Notes

CASE REPORT Open Access

Tocilizumab treatment safety in rheumatoid arthritis in a patient with multiple sclerosis: a case report

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Abstract

Background: Multiple sclerosis is a relatively rare disease, and complications of multiple sclerosis and rheumatoid arthritis are much rarer. Since anti-tumor necrosis factor therapy increases exacerbations of multiple sclerosis, complications of demyelinating diseases contraindicate anti-tumor necrosis factor therapy. There have been few reports of anti-interleukin-6 receptor therapy for patients with rheumatoid arthritis complicated with multiple sclerosis.

Case presentation: A 53-year-old Japanese woman with multiple sclerosis and rheumatoid arthritis was admitted to our hospital because her rheumatoid arthritis was uncontrolled with oral methotrexate, tacrolimus, and prednisolone. She had developed multiple sclerosis when she was 25 years old and was treated with glucocorticoid therapy. Her multiple sclerosis was in remission for more than 9 years. Because anti-tumour necrosis factor therapy can exacerbate demyelinating disease, the anti-interleukin-6 receptor antibody tocilizumab was started at 8 mg/kg every 4 weeks. At the second administration of tocilizumab, complete remission was achieved. She has remained in remission with tocilizumab without recurrence of multiple sclerosis for more than 5 years.

Conclusion: Anti-interleukin-6 therapy was safely used in this patient with rheumatoid arthritis without exacerbations of multiple sclerosis.

Keywords: Rheumatoid arthritis, Multiple sclerosis, Tocilizumab, Interleukin-6, Tumour necrosis factor

Background

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system characterised by repeated relapses and remissions. The prevalence rate of MS in Japan is reportedly 8 to 9 per 100,000 persons. High-dose glucocorticoid therapy is used for initial and relapsed progression of MS with or without immunosuppressive agents. Although MS is an autoimmune inflammatory disease, as is rheumatoid arthritis (RA), and although the level of tumour necrosis factor (TNF) in cerebrospinal fluid is correlated with the severity and progression of the disease [1], anti-TNF therapy fails and actually increases exacerbations [2,3]. Therefore, complications of demyelinating diseases contraindicate anti-TNF therapy. There have been few reports of anti-interleukin (IL)-6 receptor therapy for patients with RA complicated with MS.

We herein describe a patient with RA and MS treated with anti-IL-6 receptor therapy.

Case presentation

A 53-year-old Japanese woman was admitted to Niigata Rheumatic Centre, Shibata city, Japan. She had been diagnosed with MS associated with right optic neuritis and thoracic myelitis when she was 25 years old and treated with high-dose prednisolone (PSL). The myelitis had relapsed three times when she was 36, 37 and 40 years old and treated with high-dose PSL. Oligoclonal

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IgG band was found in cerebral spinal fluid (CSF) and IgG and myelin basic protein in CSF were elevated (4.9 mg/dL and 1.2 mg/dL, respectively). Brain T2 weighted magnetic resonance imaging (MRI) showed high intensity area beside left lateral ventricle indicating asymptomatic plaque lesion due to MS. High intensity area was also shown in T2 weighted MRI of cervical spinal cord. Anti-aquaporin 4 antibody was negative. Slight right hemiparesis remained, and she needed a cane to walk outside. The MS achieved remission and PSL was stopped for 9 years. When she was 50 years old, polyarthritis developed, and rheumatoid factor and C-reactive protein (CRP) levels were high. She was diagnosed with RA. The PSL was restarted at 7.5 mg daily and methotrexate (MTX) was begun. Because the MTX could not be increased over 8 mg/week because of mild elevation of transaminases, tacrolimus (3 mg daily; TAC) was added to MTX and leukocyte apheresis was performed. However, the RA activity remained high: the CRP was 2.3 mg/dL and the disease activity score (DAS28ESR) was 4.94 (moderate disease activity). Furthermore, joint space narrowing of both knees and ankles had progressed obviously over 1 year. Because anti-TNF therapy can exacerbate demyelinating disease, the anti-IL-6 receptor antibody tocilizumab (TCZ) was started at 8 mg/kg every 4 weeks. At the second administration of TCZ, the CRP was <0.1 mg/dL and the DAS28ESR was 2.0 (complete remission). The MTX and TAC were tapered and stopped in 6 months, and the PSL was tapered to 0.5 mg daily in 1 year. The health assessment questionnaire disability index (HAQ DI) in 1 year was 1.88 and functional disability was remained. At the 5-year follow-up, she remained in remission with TCZ.

Serum interferon (IFN) -γ was negative (≤0.1 IU/mL) and serum high sensitivity TNF-α was within normal range (1.6 pg/mL) before starting TCZ therapy. Both of them kept the same levels for a year. Serum IL-6 level was elevated, 51.2 pg/mL (normal range; ≤4.0 pg/mL) before starting TCZ therapy and it was 57.1 pg/mL a year later.

Discussion

Complications of MS and RA are rare, and only a few cases have been reported [4,5]. In two case reports, the duration between the onset of each disease was long (8–20 years), and RA or MS was preceded by the other and the two diseases did not flare at the same time [4,5]. Our patient with MS also developed RA 25 years after the onset of MS, which was well controlled without medication for 9 years. Thus, the onset mechanisms of MS and RA are expected to fundamentally differ despite the fact that both are autoimmune inflammatory diseases.

On the other hand, there are several reports of patients with RA who developed demyelinating diseases during anti-TNF therapy [6-8] and patients with MS who developed inflammatory arthritis during IFN-β therapy [9,10]. The mechanisms of demyelinating disease induced by anti-TNF therapy are not clear, but inhibition of TNF leads to IFN-γ production, which is associated with MS [11]. Moreover, TNF polymorphism may be associated with anti-TNF therapy-induced demyelinating diseases [12]. IFN-β therapy for preventing recurrence of relapsing-remitting MS and secondary progressive MS is now widely used. Arthritis reportedly develops during IFN-β therapy in patients with MS, and the HLA phenotype may be involved in its pathogenesis [9]. Elevated levels of IL-6 in the serum in response to IFN-β therapy may also be associated with arthralgia [10].

In comparison, few studies have reported anti-IL-6 therapy in demyelinating disorders. A case report of a 72-year-old woman with leukoencephalopathy that developed in a Phase 3 clinical trial of TCZ for treating RA has been published [13]. However, the relationship between TCZ and leukoencephalopathy was not clear because the possibility of infection had not been completely excluded and the symptoms did not improve after discontinuing TCZ.

Studies involving mouse models of MS (experimental autoimmune encephalomyelitis, EAE) and RA (collagen-induced arthritis, CIA) have revealed that Th-17 plays an important role in the development of both diseases [14,15]. Furthermore, IL-6 mainly affects the differentiation of Th-17 in the mouse, and anti-IL-6 therapy inhibits the onset of EAE and CIA. Meanwhile, TNF affects local inflammation [14,15]. Thus, anti-IL-6 therapy may control EAE and CIA earlier and more radically than anti-TNF therapy. In humans, IL-6 mainly affects the differentiation of Th-17, as in the mouse, and anti-IL-6 therapy should theoretically inhibit both RA and MS. However, the cytokine pathways differ in humans and mice, and further studies are needed to determine whether anti-IL-6 therapy can be used safely in patients with MS.

Conclusion

Here, we reported a patient with RA complicated by MS who was treated with anti-IL-6 therapy for more than 5 years without an exacerbation of the MS. Because anti-TNF therapy can induce and worsen demyelinating diseases, anti-IL-6 therapy is a potential treatment for patients with RA complicated by MS.

Consent

Written informed consent was obtained from the patient for publication of this Case Report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
RA: Rheumatoid arthritis; MS: Multiple sclerosis; TNF: Tumour necrosis factor; IL: Interleukin; PSL: Prednisolone; CSF: Cerebral spinal fluid; MRI: Magnetic resonance imaging; CRP: C-reactive protein; MTX: Methotrexate; TAC: Tacrolimus; TCZ: Tocilizumab; IFN: Interferon; EAE: Experimental autoimmune encephalomyelitis; CIA: Collagen-induced arthritis.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HS, DK, AA, SI, HI, KN and AM made substantial contributions to conception and acquisition of data and analysis and interpretation of data. TK, MN and IN helped to draft the manuscript. All authors read and approved the final manuscript.

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References

1. Sharief MK, Hentges R: **Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis.** *N Engl J Med* 1991, **325**:467–472.
2. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group: **TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study.** *Neurology* 1999, **53**:457–465.
3. van Oosten BW, Barkhof F, Truyen L, Boringa JB, Bertelsmann FW, von Blomberg BM, Woody JN, Hartung HP, Polman CH: **Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2.** *Neurology* 1996, **47**:1531–1534.
4. Attout H, Toussirot E, Auge B, Chavot D, Wendling D: **Rheumatoid arthritis and multiple sclerosis in the same patient. Two case-reports.** *Rev Rhum Engl Ed* 1999, **66**:169–172.
5. Mpofu S, Moots RJ: **A case of multiple sclerosis associated with rheumatoid arthritis and positive anticardiolipin antibodies.** *Ann Rheum Dis* 2003, **62**:376.
6. Fromont A, De Seze J, Fleury MC, Maillefert JF, Moreau T: **Inflammatory demyelinating events following treatment with anti-tumor necrosis factor.** *Cytokine* 2009, **45**:55–57.
7. Lozeron P, Denier C, Lacroix C, Adams D: **Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy.** *Arch Neurol* 2009, **66**:490–497.
8. Tristano AG: **Neurological adverse events associated with anti-tumor necrosis factor alpha treatment.** *J Neurol* 2010, **257**:1421–1431.
9. Levesque MC, Ward FE, Jeffery DR, Weinberg JB: **Interferon-beta1A-induced polyarthritis in a patient with the HLA-DRB1*0404 allele.** *Arthritis Rheum* 1999, **42**:569–573.
10. Nakatsuji Y, Nakano M, Moriya M, Kishigami H, Tatsumi C, Tada S, Sadahiro S, Naka T, Mitani K, Funauchi M, Azuma T, Watanabe S, Kinoshita M, Kajiyama K, Yuasa Y, Kaido M, Takahashi MP, Naba I, Hazama T, Sakoda S, Osaka Neurological Research Consortium: **Beneficial effect of interferon-beta treatment in patients with multiple sclerosis is associated with transient increase in serum IL-6 level in response to interferon-beta injection.** *Cytokine* 2006, **36**:69–74.
11. Mitoma H, Horiuchi T, Hatta N, Tsukamoto H, Harashima S, Kikuchi Y, Otsuka J, Okamura S, Fujita S, Harada M: **Infliximab induces potent anti-inflammatory responses by outside-to-inside signals through transmembrane TNF-alpha.** *Gastroenterology* 2005, **128**:376–392.
12. Kirk CW, Droogan AG, Hawkins SA, McMillan SA, Nevin NC, Graham CA: **Tumour necrosis factor microsatellites show association with multiple sclerosis.** *J Neurol Sci* 1997, **147**:21–25.
13. Kobayashi K, Okamoto Y, Inoue H, Usui T, Ihara M, Kawamata J, Miki Y, Mimori T, Tomimoto H, Takahashi R: **Leukoencephalopathy with cognitive impairment following tocilizumab for the treatment of rheumatoid arthritis (RA).** *Intern Med* 2009, **48**:1307–1309.
14. Fujimoto M, Serada S, Mihara M, Uchiyama Y, Yoshida H, Koike N, Ohsugi Y, Nishikawa T, Ripley B, Kimura A, Kishimoto T, Naka T: **Interleukin-6 blockade suppresses autoimmune arthritis in mice by the inhibition of inflammatory Th17 responses.** *Arthritis Rheum* 2008, **58**:3710–3719.
15. Serada S, Fujimoto M, Mihara M, Koike N, Ohsugi Y, Nomura S, Yoshida H, Nishikawa T, Terabe F, Ohkawara T, Takahashi T, Ripley B, Kimura A, Kishimoto T, Naka T: **IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis.** *Proc Natl Acad Sci U S A* 2008, **105**:9041–9046.

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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