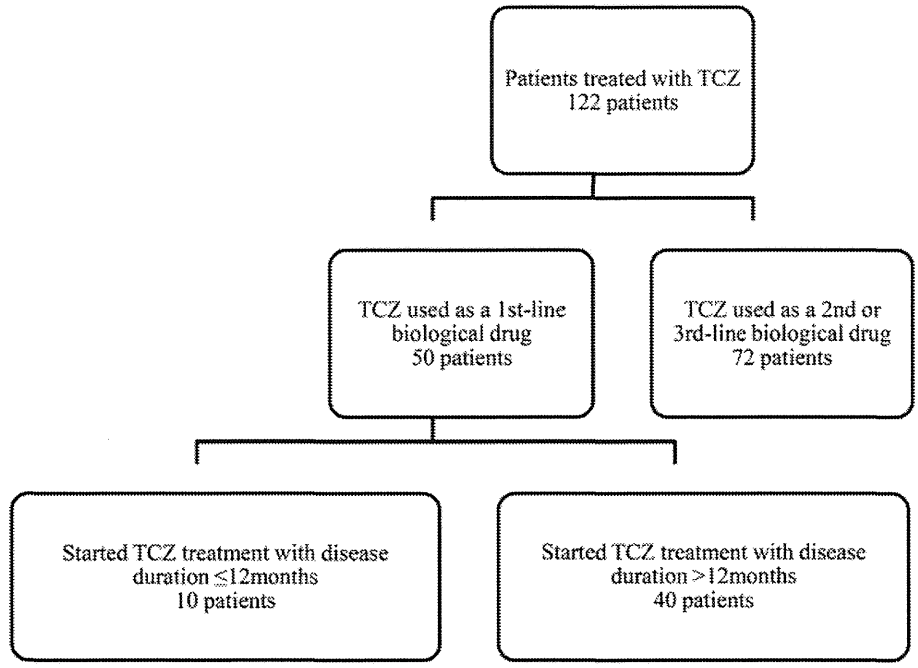

Fig. 1 Breakdown of the patients. *TCZ* tocilizumab

observed prior to treatment with TCZ. Significance was assessed based on a p value of 0.05. In order to identify the contributory factors when using the conventional remission criterion and the new remission criterion, a multivariate logistic regression model was employed to calculate the odds ratios adjusted for multiple variables and 95 % confidence limits. All statistical analyses were performed with the JMP version 9.0.2 statistical software package (SAS Institute Inc., Cary, NC, USA).

Results

The baseline characteristics of the 122 patients enrolled in this study are set out in Table 1. Their average age was 55.8 ± 13.5 years, mean disease duration was 124.1 ± 112.8 months, and 59.0 % (72/122) of them had been using an anti-TNF agent. Their average DAS28-ESR score prior to treatment with TCZ was 5.8 ± 1.3. In terms of previous anti-TNF agent use, 72 patients had and 50 patients had not previously received an anti-TNF agent, and corticosteroid usage was 80.6 % in the former set and 54.0 % in the latter ($p = 0.0017$). Baseline CRP prior to TCZ treatment was significantly higher in those who had previously used an anti-TNF agent, at 4.2 ± 3.1 mg/dL, than in those who had not, at 2.6 ± 2.2 mg/dL ($p = 0.0033$). Furthermore, on dividing the 50 patients who had received TCZ as a first-line biological drug into two groups (those with a disease duration at baseline of 12 months or less and those with a disease duration of longer than 12 months), the only apparent significant difference between the two groups was provided by their Steinbrocker stage scores [14] ($p = 0.0359$).

Therapeutic response to tocilizumab

The DAS28-ESR scores for the 122 patients were improved at 6 months ($p < 0.0001$), and the improvement was maintained at 12 months, going from 5.8 ± 1.3 at baseline to 3.2 ± 1.5 at 6 months and 3.0 ± 1.6 at 12 months (Fig. 2a). The remission rates according to the conventional criterion (DAS28-ESR <2.6) were 38.5 % at 6 months and 43.4 % at 12 months, and remission rates under the new criterion (Boolean definition: all ≤1) were 10.7 % at 6 months and 15.6 % at 12 months (Fig. 2b).

The evolution of DAS28-ESR over time did not change depending on whether anti-TNF agents had previously been used. The scores improved from 6.0 ± 1.4 at baseline to 3.3 ± 1.6 at 6 months and 3.0 ± 1.7 at 12 months in those who had previously used an anti-TNF agent, and from 5.6 ± 1.1 at baseline to 2.9 ± 1.5 at 6 months and 2.8 ± 1.5 at 12 months in those who had not (Fig. 2c). A trend for the remission rate of those who had previously used an anti-TNF agent to be higher than the remission rate of those who had not previously used an anti-TNF agent (48.0 % at 6 months and 50.0 % at 12 months versus 31.9 % at 6 months and 38.9 % at 12 months, respectively) under the conventional criterion was observed, but this difference in rate was not significant (Fig. 2d). Under the new criterion, there was a trend for remission to be higher in those who had not previously used anti-TNF agents

Table 1 Baseline characteristics of the rheumatoid arthritis patients treated with tocilizumab (TCZ) who were enrolled in the present study

	All cases (n = 122)						Prior use of anti-TNF agent		No prior use of anti-TNF agent (TCZ as 1st-line biologic)	
							With anti-TNF agent (n = 72)	Without anti-TNF agent (n = 50)	Baseline disease duration ≤12 months (n = 10)	Baseline disease duration >12 months (n = 40)
	Mean ± SD	Median	25th percentile	75th percentile	Min	Max	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Gender, female (%)	77.1						75.0	80.0	70.0	82.5
Age (years)	55.8 ± 13.5	59.0	46.0	66.0	24.0	82.0	55.0 ± 13.9	57.0 ± 13.0	56.8 ± 14.2	57.1 ± 12.9
RA duration (months)	124.1 ± 112.8	96.5	39.5	170.3	0	607.0	126.4 ± 117.0	120.9 ± 107.5	6.4 ± 4.5	149.6 ± 101.5
Steinbrocker stage scores (I/II/III/IV)	19/29/24/50						9/14/19/30	10/15/5/20	4/5/0/1	6/10/5/19
Steinbrocker class scores (1/2/3/4)	17/60/45/0						6/36/30/0	11/24/15/0	4/5/1/0	7/19/14/0
Previous anti-TNF agent use (%)	59.0						100.0	0.0	–	–
MTX use (%)	38.5						44.4	30.0	0.0	37.5
Baseline MTX dose (mg/week)	7.5 ± 2.0	8.0	6.0	8.0	2.0	12.0	7.6 ± 2.1	7.3 ± 2.0	–	7.3 ± 2.0
Corticosteroid use (%)	69.7						80.6	54.0	60.0	52.5
Prednisolone dose (mg/day)	4.7 ± 2.0	5.0	3.0	5.0	1.0	10.0	4.9 ± 2.0	4.3 ± 1.9	5.4 ± 2.5	3.9 ± 1.6
TJC (/28)	8.9 ± 7.4	6.5	4.0	12.0	0	28.0	9.6 ± 8.0	7.8 ± 6.3	8.4 ± 5.3	7.6 ± 6.6
SJC (/28)	7.1 ± 5.8	5.5	3.0	10.0	0	26.0	7.8 ± 6.6	6.1 ± 4.4	6.6 ± 3.7	5.9 ± 4.6
PtGA (mm)	55.6 ± 25.7	50.5	33.0	75.8	9.0	100.0	58.2 ± 26.7	51.9 ± 23.8	51.7 ± 27.8	52.0 ± 23.1
ESR (mm/h)	67.0 ± 34.3	65.5	40.0	94.3	2.0	100.0	70.6 ± 35.1	61.8 ± 32.7	71.4 ± 37.0	59.4 ± 31.7
CRP (mg/dL)	3.5 ± 2.9	3.1	1.2	5.1	0.1	17.7	4.2 ± 3.1	2.6 ± 2.2	2.6 ± 3.0	2.6 ± 2.0
DAS28-ESR	5.8 ± 1.3	5.7	4.9	6.6	2.1	9.2	6.0 ± 1.4	5.6 ± 1.1	5.8 ± 1.3	5.5 ± 1.0

SD standard deviation, *RA* rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score

(16.0 % at 6 months and 20.0 % at 12 months) than in those who had (6.9 % at 6 months and 12.5 % at 12 months), as was observed under the conventional criterion, but again this was not significant (Fig. 2d).

Then, presuming the application of the most recent EULAR recommendations and T2T, we divided the 50 patients who had received TCZ as a first-line biological drug into two groups [those with a disease duration at baseline of 12 months or less (≤12 M) and those with a disease duration at baseline of longer than 12 months (>12 M)]. In this situation, the DAS28-ESR scores were improved in both groups, changing from 5.8 ± 1.3 at baseline to 2.8 ± 1.6 at 6 months and 2.6 ± 1.4 at 12 months in the ≤12 M group, and from 5.5 ± 1.0 at baseline to 2.9 ± 1.4 at 6 months and 2.8 ± 1.6 at 12 months in the >12 M group. Thus, there was no significant difference between the changes seen in the two groups (Fig. 2e). Under the conventional criterion, the remission rates were comparable between the two groups: 50.0 % at 6 months and 50.0 % at 12 months in the ≤12 M group, and 47.5 % at 6 months and 50.0 % at 12 months in the >12 M group. Upon applying the new criterion, however, a difference appeared at 6 months, with remission rates of 40.0 % in the ≤12 M group against 10.0 % in the >12 M group (p = 0.0407). This disparity was maintained at the 12-month point as well, with remission rates of 50.0 % in the ≤12 M group against 12.5 % at 12 months in the >12 M group (p = 0.0181) (Fig. 2f).

Among the individual components of the new criterion (TJC ≤1, SJC ≤1, PtGA ≤1 cm, and CRP ≤1 mg/dL), the rate of achievement of PtGA ≤1 cm was significantly higher after 6 months in patients with a disease duration at baseline of 12 months or less (p = 0.0181) (Fig. 3).

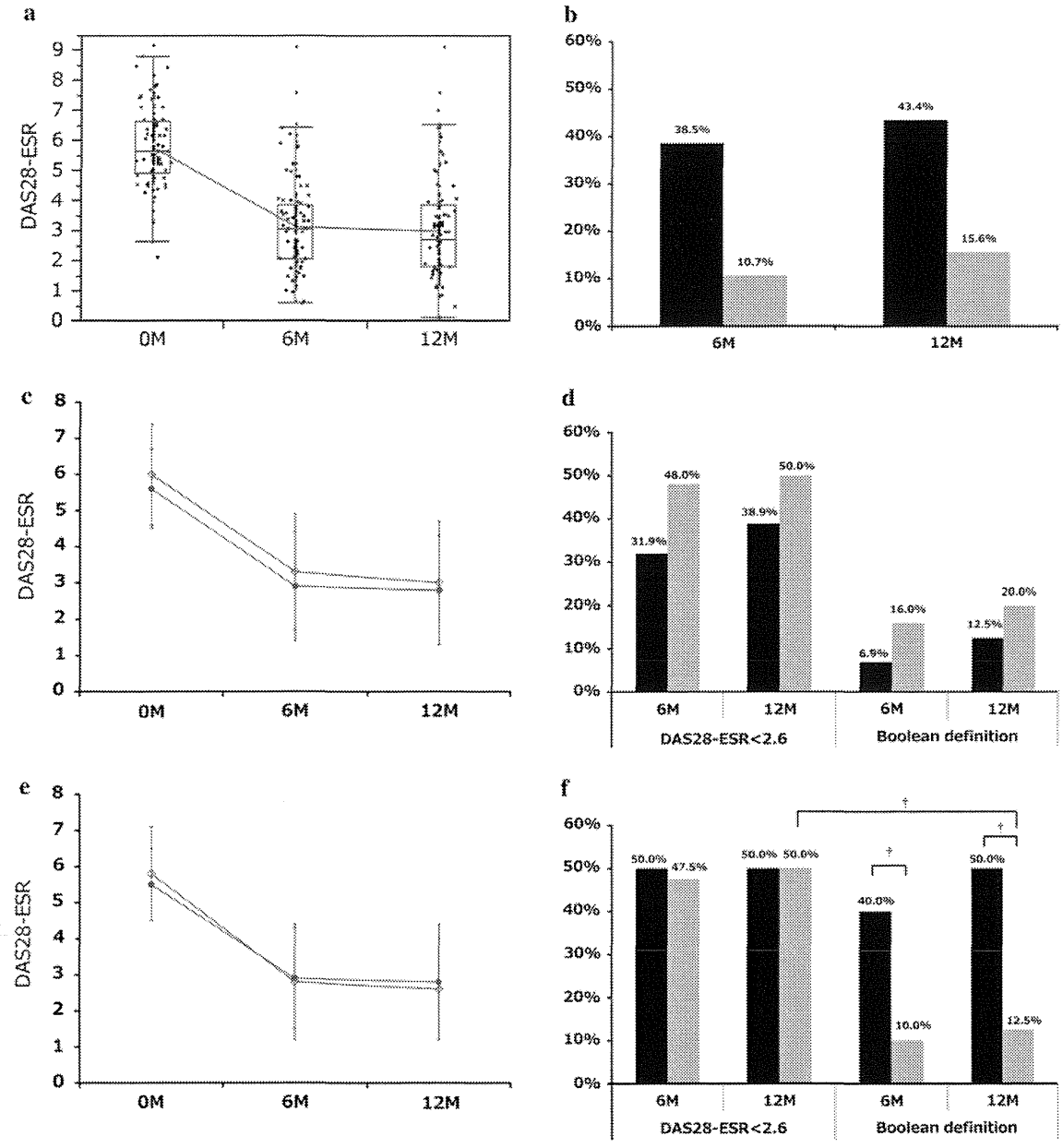

Fig. 2 Changes over time in DAS28-ESR, remission rates under the conventional criterion (DAS28-ESR <2.6), and remission rates under the new criterion (Boolean definition: all ≤1) in all patients ($n = 122$), in patients who had previously used anti-TNF agents, and by duration of disease at baseline (>12 vs. ≤12 months) for patients using TCZ as a first-line biologic. *DAS28* 28-joint count disease activity score, *ESR* erythrocyte sedimentation rate, *TNF* tumor necrosis factor, *6 M* 6 months, *12 M* 12 months. **a** Changes over time in DAS28-ESR in all patients ($n = 122$). The DAS28-ESR scores for the 122 patients were improved at 6 months ($p < 0.0001$). **b** Remission rates under conventional remission criteria (*black bars*) and new criteria (*gray bars*) in all patients ($n = 122$). **c** Changes over time in DAS28-ESR in patients who had previously used an anti-TNF agent (*empty squares*, $n = 72$) versus patients who had not previously used an anti-TNF agent (*filled circles*, $n = 50$). **d** Remission rates under the conventional and new criteria in patients who had (*black bars*) and had not (*gray bars*) previously used an anti-TNF agent. **e** Changes over time in DAS28-ESR by duration of disease at baseline in patients who used TCZ as a first-line biologic: disease duration ≤12 months (*empty squares*, $n = 10$) versus >12 months (*filled circles*, $n = 40$). **f** Remission rates under the conventional and new criteria by duration of disease at baseline in patients who used TCZ as a first-line biologic: disease duration ≤12 months (*black bars*) versus >12 months (*gray bars*). †Fisher's exact test, remission rate under the new criterion, >12 versus ≤12 months; 6 M ($p = 0.0407$), 12 M ($p = 0.0181$). Conventional criterion versus new criterion 12 M ($p < 0.0001$)

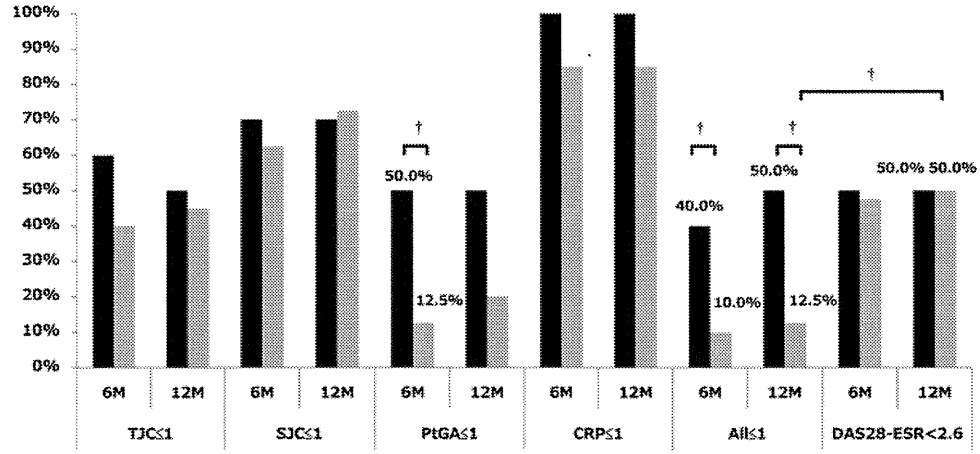

Fig. 3 Rates of achievement of TJC ≤1, SJC ≤1, PtGA ≤1 (cm), and CRP ≤1 (mg/dL) under the new remission criterion by duration of disease at baseline (>12 vs. ≤12 months) in patients using TCZ as a first-line biologic: *black bars* ≤12 months; *gray bars* >12 months. *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *6 M* 6 months, *12 M* 12 months. †Fisher's exact test, >12 versus ≤12 months. PtGA ≤1: 6 M ($p = 0.0181$). All ≤1: 6 M ($p = 0.0407$), 12 M ($p = 0.0181$)

Table 2 Patient baseline factors for achieving remission at 12 months after the initiation of TCZ treatment under the conventional criterion and under the new criterion, and patient baseline factors in group A (those who did not meet the new criterion but met the conventional criterion) and group B (those who met both the new and conventional criteria), as determined by univariate logistic analysis

Baseline clinical parameters	Conventional remission		New remission		Group A/group B	
	Chi-square	*p* value	Chi-square	*p* value	Chi-square	*p* value
Gender	4.27	0.0387	0.05	0.8305	1.61	0.2048
Age	0.19	0.6619	3.32	0.0686	4.59	0.0321
RA duration	1.62	0.2038	9.65	0.0019	6.56	0.0105
Steinbrocker stage scores	3.54	0.0601	11.33	0.0008	8.38	0.0038
Steinbrocker class scores	4.73	0.0296	6.84	0.0089	3.40	0.0652
Previous anti-TNF agent use	1.48	0.2245	1.24	0.2649	0.35	0.5522
MTX use	1.80	0.1802	0.12	0.7273	0.12	0.7284
Corticosteroid use	7.30	0.0069	7.37	0.0066	2.48	0.1153
TJC	11.10	0.0009	2.15	0.1429	0.26	0.6131
SJC	6.89	0.0087	3.16	0.0753	0.56	0.4555
PtGA	11.14	0.0008	3.12	0.0773	0.02	0.9004
ESR	4.64	0.0312	2.68	0.1018	0.54	0.4633
CRP	0.30	0.5846	0.36	0.5500	0.77	0.3812
DAS28-ESR	14.59	0.0001	3.90	0.0482	0.00	0.9979

RA rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *Group A/group B* the patients were divided into group A, who met the conventional but not the new criterion (34 patients), and group B, who met both the conventional and new criteria (19 patients)

Identification of the factors that contribute to remission under the conventional and new criteria

Baseline data on gender, age, RA duration, stage, class, previous use of an anti-TNF agent, MTX use, corticosteroid use, TJC, SJC, PtGA, ESR, CRP, and DAS28-ESR for the patients treated with TCZ were used in a univariate logistic analysis (Table 2). The factors that multivariate logistic analysis identified as contributing to the achievement of remission at 12 months after the initiation of TCZ treatment under the conventional criterion were RA duration [odds ratio (OR) 0.9956, 95 % confidence interval (CI)

0.9910–0.9997], corticosteroid use (OR 0.2536, CI 0.0863–0.6876), TJC (OR 0.8698, CI 0.7866–0.9457), ESR (OR 0.9577, CI 0.9356–0.9772), and CRP (OR 1.7700, CI 1.3530–2.4636). The contributory factors under the new remission criterion were RA duration (OR 0.9787, CI 0.9644–0.9899), corticosteroid use (OR 0.2422, CI 0.0661–0.8210), SJC (OR 0.8109, CI 0.6723–0.9488), ESR (OR 0.9749, CI 0.9483–0.9989), and CRP (OR 1.4336, CI 1.0608–1.9684). The baseline items that contributed to remission according to both the conventional and new criteria were thus RA duration, corticosteroid use, and CRP. After assigning patients who had achieved remission under the conventional criterion but failed to do so under the new criterion to group A ($n = 34$), and those who had achieved remission under both the conventional and new criteria to group B ($n = 19$), we carried out multivariate analysis (note that no patient failed under the conventional criterion and succeeded under the new criterion only, and 69 patients failed to achieve remission under either the new or conventional criterion).

The analysis identified RA duration only (OR 1.0190, CI 1.0077–1.0343) (Table 3).

Discussion

In evaluations of the clinical response to TCZ using the conventional remission criterion of DAS28-ESR <2.6, the weights of CRP and ESR are higher than those of the TJC and SJC data [12, 13], which has been reported to give rise to disparately higher remission rates [15–18] than those indicated by the SDAI with the new remission criteria [4, 19], the CDAI [4, 20], or the Boolean definition [4].

However, those papers review the results for TCZ used in patients with a disease duration of about 10 years, and are not related to findings from investigations based on treatment guidelines or goals and remission criteria that seek to improve patient outcomes, such as those that have been proposed internationally in recent years.

In this study, we reviewed the progress of patients in the TBC registry who were started on TCZ treatment in the "early phase" of the disease; that is, those with an RA duration of 12 months or less at the initiation of TCZ treatment. Co-author Dr. Kojima previously reported that RA patients with a disease duration of <4.8 years that were treated with TCZ for 52 weeks showed a significantly higher remission rate than patients with a longer disease duration, based on DATA from TBCR [10]. However, in that work, we did not analyze early-phase RA patients who were treated with TCZ based on the recommendations of EULRA. In the present work, we found that if TCZ was given early and, moreover, as the first-line biological drug (in accordance with the EULAR recommendations), remission rates as high as 50.0 % at 12 months could be achieved using the new stricter remission criteria of the Boolean definition. We were also able to confirm that these findings were comparable with remission rates obtained based on the conventional criterion DAS28-ESR <2.6.

On the other hand, in patients with an RA duration exceeding 12 months, there was considerable disparity between the remission rates of 50 % obtained under the conventional criterion and 12.5 % under the new criterion

Table 3 Multivariate logistic analysis-based extraction of patient baseline factors for achieving remission under the conventional and new criteria, and extraction of patient baseline factors in group A (those who did not meet the new criterion but did meet the conventional criterion) and group B (those who met both the new and conventional criteria)

Baseline clinical parameters	Conventional remission		New remission		Group A/group B	
	Odds ratio (95 % confidence interval)	*p* value	Odds ratio (95 % confidence interval)	*p* value	Odds ratio (95 % confidence interval)	*p* value
Gender	–	–	4.4029 (0.9264–27.9475)	0.0836	0.2680 (0.0462–1.2500)	0.1113
Age	1.0348 (0.9963–1.0772)	0.0828	–	–	–	–
RA duration	0.9956 (0.9910–0.9997)	0.0413	0.9787 (0.9644–0.9899)	0.0012	1.0190 (1.0077–1.0343)	0.0040
Corticosteroid use	0.2536 (0.0863–0.6876)	0.0089	0.2422 (0.0661–0.8210)	0.0252	–	–
TJC	0.8698 (0.7866–0.9457)	0.0026	–	–	–	–
SJC	–	–	0.8109 (0.6723–0.9488)	0.0159	1.1935 (0.9316–1.6209)	0.1959
PtGA	0.9804 (0.9598–1.0001)	0.0567	–	–	–	–
ESR	0.9577 (0.9356–0.9772)	<0.0001	0.9749 (0.9483–0.9989)	0.0510	1.0249 (0.9945–1.0609)	0.1249
CRP	1.7700 (1.3530–2.4636)	0.0002	1.4336 (1.0608–1.9684)	0.0191	0.4951 (0.1380–1.4795)	0.2348

Multivariate logistic regression models (stepwise selection)

RA rheumatoid arthritis, *TNF* tumor necrosis factor, *MTX* methotrexate, *TJC* tender joint count (28-joint count), *SJC* swollen joint count (28-joint count), *PtGA* patient global assessment, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* 28-joint count disease activity score, *Group A/group B* the patients were divided into group A, who met the conventional but not the new criterion (34 patients), and group B, who met both the conventional and new criteria (19 patients)

(Fig. 2f). If we consider the baseline characteristics (Table 1), this disparity appears to have been caused by differences in disease stage, which indicates the degree of disease progression.

The Health Assessment Questionnaire (HAQ) devised by Smolen and colleagues is constructed from an activity-related HAQ (ACT-HAQ) component and a damage-related HAQ (DAM-HAQ) component. It has been pointed out that the DAM-HAQ is correlated with the total Sharp score (TSS), and that if DAM-HAQ continues to worsen, no improvement in HAQ score can occur [21]. The salient points here are the effects arising from the irreversible progression of the disease and the poor correlation between clinical remission, such as that indicated by DAS representing inflammatory symptoms, and structural or functional remission.

Our study likewise indicated that, although an improved TJC or SJC (reflecting an improvement in inflammatory symptoms) may be seen, regardless of the disease duration (Fig. 3), only a small proportion of those with an RA duration exceeding 12 months at the initiation of TCZ treatment achieved PtGA $\leq$1 cm, and this had a major impact on the remission rate. Moreover, disease duration up to the initiation of TCZ treatment was also demonstrated to be a significant factor in achieving remission, not only under the conventional criterion but also under the new criterion (Table 3). In short, it appeared that patients with longer RA durations suffered irreversible progression of the disease, and that the PtGA could not be improved.

In summary, tocilizumab used as a first-line biological drug in patients with early-stage rheumatoid arthritis in accordance with the EULAR recommendations appears to provide high rates of remission, even under the new stricter criterion, and it can help to achieve the current goals of treatment.

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Conflict of interest N. Ishiguro received lecture fees (less than $10,000) from Mitsubishi Tanabe Pharma Corporation, Takeda Pharma Corporation, Eisai Pharma Corporation, Chugai Pharma Corporation, Bristol-Myers Squibb, and Abbott Laboratories. T. Kojima and A. Kaneko also received lecture fees (less than $5,000) from these companies. The other authors declare no conflict of interest.

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ORTHOPAEDIC SURGERY

Predictive factors of cervical spondylotic myelopathy in patients with lumbar spinal stenosis

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Abstract
Objective To analyze cervical spondylotic myelopathy (CSM) predictive factors in patients with lumbar spinal stenosis (LSS).
Methods Two hundred thirty-seven patients who visited for low back pain, lower limb pain and/or lower limb numbness and who were diagnosed with LSS were enrolled in this study. The ratio of males to females was 117–120, and the mean age was 68.8 years (range 45–87 years). LSS and CSM were diagnosed by characteristic symptoms, physical findings and MRI. We examined gender, age, Torg-Pavlov ratio (TPR), spondylolisthesis or spondylosis, LSS symptom types and number of stenosis segments with LSS to clarify predictive factors for CSM.
Results There were 21 (8.86%) patients with coexistent CSM among 237 LSS patients. CSM morbidity was significantly more common among males compared with females. TPR was 0.71 ± 0.09 in the CSM patients and 0.81 ± 0.10 in the non-CSM patients. TPR of the CSM patients was significantly smaller than that of the non-CSM patients. We analyzed to determine the predictive factors of CSM and TPR was identified. The predictive value of TPR for CSM was 0.78.
Conclusion Torg-Pavlov ratio was the most important predictive factor of CSM in patients with LSS.

Keywords Cervical spondylotic myelopathy · Lumbar spinal stenosis · Torg-Pavlov ratio · Predictive factor

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Introduction

The number of cases of coexistent cervical spondylotic myelopathy (CSM) and lumbar spinal stenosis (LSS) is increasing among the aging population worldwide [1–5]. First, such cases were reported by Teng as 'combined cervical and lumbar spondylosis' [6].

A retrospective analysis of 200 patients requiring cervical disc surgery was performed to determine the frequency of coexistent lumbar disc and spine abnormalities and it was observed that 30.5% of the patients had already undergone lumbar disc surgery [7]. In addition, Lee et al. [8] analyzed the incidence of asymptomatic cervical cord compression in 93 LSS patients and found 23.7% of the patients to have moderate or severe cervical cord compression by whole spine MRIs. These two reports suggest that it is possible for patients to develop CSM after LSS. However, there have been few reports investigating CSM morbidity and risk factors in patients with LSS.

If patients develop CSM with mainly lower limb symptoms following surgery for LSS and we delay operative treatment without evaluating the possibility of cervical lesions, their myelopathy could progress irreversibly and their activity of daily living decreases. Furthermore, it is important that we explain the possibility of upper and lower limb CSM symptoms following lumbar surgery to LSS patients. Because CT and MRI screenings can be burdensome for patients, it would be better to clarify predictive factors of CSM from the patient background, LSS types and plain lateral cervical radiographs.

Cervical canal stenosis has usually been evaluated by the anteroposterior diameter of the cervical spinal canal on plain lateral radiographs. However, this measurement includes a magnification error resulting from the focus-to-film distance and the object-to-film distance. The ratio of

the sagittal diameter of the cervical spinal canal to that of the vertebral body was developed by Torg and Pavlov as an indicator of the degree of developmental spinal canal narrowing [9]. This canal/body ratio (Torg–Pavlov ratio: TPR) excludes variable enlargement factors. In this study, we used TPR to evaluate cervical spinal stenosis.

The purpose of the present study was to examine gender, age, TPR, spondylolisthesis or spondylosis, LSS symptom types and number of stenosis segments with LSS to clarify predictive factors for CSM in patients with LSS.

Materials and methods

Study design

From September 2007 to August 2009, 237 patients who visited Saitama Medical University Hospital for low back pain, lower limb pain and/or lower limb numbness and who were diagnosed with LSS were enrolled in this study. We used retrospective analysis to determine CSM predictive factors in patients with LSS. The IRB (Institution Review Board) of Saitama medical university approved this study.

Subjects

Lumbar spinal stenosis was diagnosed by characteristic symptoms, physical findings and MRI. The ratio of males to females was 117–120, and the mean age was 68.8 years (range 45–87 years). We excluded patients with trauma, lumbar compression fracture, lumbar disc herniation, ossification of ligaments, rheumatoid arthritis and destructive spondyloarthropathy.

Cervical spondylotic myelopathy was diagnosed on the basis of clinical and MRI findings. Patients who had either upper limb numbness, loss of manual dexterity or difficulty in walking as well as showed evidence of cervical cord compression on MRI corresponding to the segmental sign level were diagnosed with CSM. We excluded patients with ossification of the posterior longitudinal ligament and cervical disc herniation.

Spinal radiography

Plain lateral cervical radiographs were obtained with the patient standing and the neck held in a neutral position. The film-to-tube distance was fixed at 1.50 m, and the measurements were performed at C3 through C6 on a lateral digital radiograph of the cervical spine. The anteroposterior diameter of the spinal canal (from the midpoint of the posterior surface of the vertebral body to the nearest point of the corresponding lamina and spinous process) and the anteroposterior diameter of the vertebral body (between the midpoints of the anterior and posterior surfaces of the vertebral body) were measured. TPR (ratio between the sagittal diameter of the spinal canal and the vertebral body of the same level) was calculated for each level. A digital measurement tool was available on the picture archiving and communication systems software (HOPE/DrABLE-EX V03, FUJITSU LIMITED; Tokyo, Japan) and was used to analyze the images with accuracy limited to 0.10 mm. Each measurement was repeated 3 times by 3 observers, and the average value of 3 observers from C4 to C6 was used as the final measurement value. The resulting mean intra-observational coefficient of variation (CV) and mean inter-observational CVs for radiographic analysis were 0.10 and 0.89%, respectively.

If patients with LSS had spondylolisthesis of the lumbar spine on the plain lateral lumbar radiographs, the films were assessed to determine the percent of slip using the Taillard method [10]. We classified a slip of 10% or more as spondylolisthesis and a slip of <10% as spondylosis.

LSS symptom type

Lumbar spinal stenosis symptom types were diagnosed as unilateral lower leg symptoms or bilateral lower leg symptoms. We classified unilateral lower leg symptoms as the radicular type and bilateral lower leg symptoms as the non-radicular type.

Number of stenosis segments with LSS

The number of stenosis segments with LSS was diagnosed using axial MRI images based on the method described by Schizas [11]. Grades B, C and D were recognized as indicative of stenosis; we also classified segments based on whether stenosis was present in a single stenosis segment, double stenosis segments or multiple stenosis segments (3 or more segments).

Statistical analysis

A Chi-square test of independence was used to determine whether there were any significant differences between groups of males or females, radicular type or non-radicular type and spondylolisthesis or spondylosis. The Mann–Whitney's *U* test was used to determine the influence of age, TPR and the number of stenosis segments with LSS. Furthermore, we used multiple logistic regression analysis after univariate logistic regression analysis to determine which factors were predictive of CSM. Analyses were performed using statistical software (StatFlex Ver.6, Artech Co., Ltd; Osaka, Japan).

Results

CSM morbidity, gender and age in 237 LSS patients

There were 21 patients with coexistent CSM (CSM group) in 237 LSS patients; 216 LSS patients did not have coexistent CSM (non-CSM group). The CSM group included 17 males and 4 females and the non-CSM group 100 males and 116 females. CSM morbidity was significantly more common among males than females ($P = 0.00528$) (Table 1).

The mean age of the CSM group was 69.9 ± 7.0 years (mean ± SD), and that of the non-CSM group was 68.6 ± 8.6 years; no significant difference was observed between the CSM and non-CSM groups ($P = 0.52921$) (Table 2).

Spinal radiography

Torg-Pavlov ratio of the CSM group was 0.71 ± 0.09 and that of the non-CSM group was 0.81 ± 0.10; TPR of the CSM group was significantly smaller than that of the non-CSM group ($P = 0.00001$) (Table 2).

Torg-Pavlov ratio of male patients with LSS was 0.76 ± 0.08 and that of female patients with LSS was 0.85 ± 0.10; thus, TPR of males was significant smaller than that of females ($P = 0.00001$, Mann–Whitney's U test).

There were 9 patients with spondylolisthesis and 12 patients with spondylosis in the CSM group and 117 patients with spondylolisthesis and 99 patients with spondylosis in the non-CSM group. CSM morbidity was not significantly different between patients with spondylolisthesis or spondylosis ($P = 0.43176$) (Table 1).

LSS symptom type

One patient had radicular type and 20 patients had non-radicular type in the CSM group. Forty patients had radicular type and 176 patients had non-radicular type in the non-CSM group. CSM morbidity was not significantly different between patients with radicular type or non-radicular type ($P = 0.13820$) (Table 1).

Number of stenosis segments with LSS

Six patients in the CSM group had a single stenosis segment, 9 patients had double stenosis segments and 6 patients had multiple stenosis segments. In the non-CSM group, 94 patients had a single stenosis segment, 81 patients had double stenosis segments and 41 patients had multiple stenosis segments. CSM morbidity was not significantly different among patients with number of stenosis segments with LSS ($P = 0.15354$) (Table 3).

CSM predictive factors in patients with LSS

We used univariate logistic regression analysis to select predictive factors of CSM (Table 4). The factors with a

Table 1 Gender, spondylolisthesis or spondylosis and LSS symptom types of 237 LSS patients of CSM group and non-CSM group

	CSM group ($n = 21$)	Non-CSM group ($n = 216$)	Total	p value
Gender				
Male	17	100	117	0.00528
Female	4	116	120	
Spondylolisthesis or spondylosis				
Spondylolisthesis	9	117	126	0.43176
Spondylosis	12	99	111	
LSS symptom type				
Radicular type	1	40	41	0.13820
Non-radicular type	20	176	196	

Chi-square for independence test. CSM morbidity was significantly high among males than females. There was no significant difference in spondylolisthesis or spondylosis and LSS symptom types in Chi-square for independence test

LSS lumbar spinal stenosis, *CSM* cervical spondylotic myelopathy

Table 2 Age and TPR of 237 LSS patients of CSM group and non-CSM group

	CSM group ($n = 21$) (mean ± SD)	Non-CSM group ($n = 216$) (mean ± SD)	p value
Age	69.9 ± 7.0	68.8 ± 8.6	0.52921
TPR	0.71 ± 0.09	0.81 ± 0.10	0.00001

Mann–Whitney's U test. TPR of males was significant smaller than that of females

TPR Torg-Pavlov ratio, *LSS* lumbar spinal stenosis, *CSM* cervical spondylotic myelopathy, *SD* standard deviation

Table 3 Number of stenosis segments with LSS of 237 LSS patients of CSM group and non-CSM group

	CSM group ($n = 21$)	Non-CSM group ($n = 216$)	Total	p value
Single stenosis segment	6	94	100	
Double stenosis segments	9	81	90	0.15354
Multiple stenosis segments	6	41	47	

Mann–Whitney's U test. There was no significant difference in number of stenosis segments with LSS

LSS lumber spinal stenosis, *CSM* cervical spondylotic myelopathy

Table 4 CSM predictive factors in patients with LSS

Predictive factor	Odds ratio	95% confidence interval	*p* value
Gender	4.83911	1.57653–14.85	0.00586
Age	1.01827	0.96269–1.077	0.52729
TPR	0.00000	0.00000–0.000	0.00005
LSS symptom type	4.54545	0.59252–34.86	0.14525
Spondylolisthesis	0.63462	0.25679–1.568	0.32458
Single stenosis segment	0.51915	0.19402–1.389	0.19173
Double stenosis segments	1.25000	0.50462–3.096	0.62970
Multiple stenosis segments	1.70732	0.62435–4.668	0.29732

Univariate logistic regression analysis

CSM cervical spondylotic myelopathy, *LSS* lumbar spinal stenosis, *TPR* Torg-Pavlov ratio

Table 5 Results of multiple logistic regression analysis

Predictive factor	Odds ratio	95% confidence interval	*p* value
TPR	0.00001	0.00000–0.009	0.00113

Multiple logistic regression analysis

CSM cervical spondylotic myelopathy, *LSS* lumbar spinal stenosis, *TPR* Torg-Pavlov ratio

probability >15% were excluded and Gender, TPR and LSS symptom type were included as the explanatory factors. Furthermore, TPR was identified as a predictive factor of CSM in multiple logistic regression analysis ($P = 0.00113$) (Table 5).

ROC curve for TPR associated with CSM morbidity in patients with LSS

We determined the receiver operating characteristic (ROC) curve for TPR associated with CSM morbidity in patients with LSS (Fig. 1). The area under ROC curve for TPR was 0.796. When the cut-off value of TPR was assumed to be 0.78, sensitivity of CSM in patients with LSS was 0.86, specificity was 0.63 and accuracy was 0.65.

Discussion

There were 21 patients with coexistent CSM in the 237 LSS patients. CSM morbidity was significantly more common among males compared with females and TPR of the CSM group was significantly smaller than that of the non-CSM group. However, CSM morbidity did not differ significantly with age, spondylolisthesis or spondylosis, LSS symptom types or number of stenosis segments with LSS. Only TPR was identified as a predictive factor of CSM in patients with LSS, the predictive value of TPR for CSM in patients with LSS was 0.78.

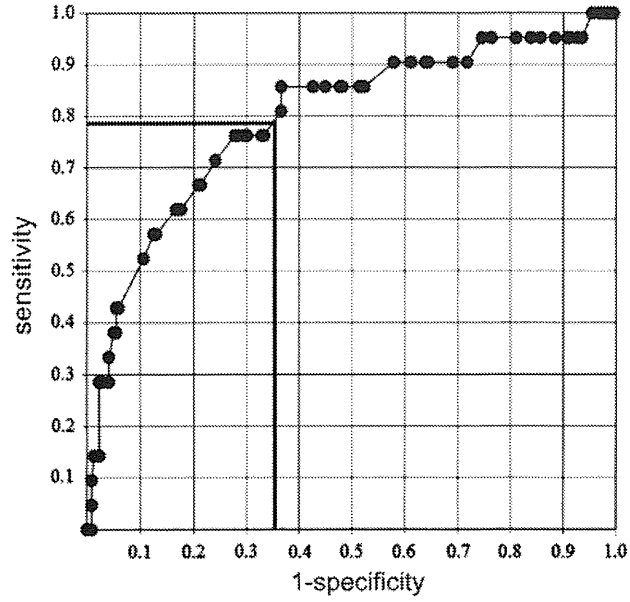

Fig. 1 ROC curve for TPR associated with CSM morbidity in patients with LSS. The area under ROC curve for TPR was 0.796. When the cut-off value of TPR was assumed to be 0.78, sensitivity of CSM in patients with LSS was 0.86, specificity was 0.63 and accuracy was 0.65. ROC: receiver operating characteristic, TPR: Torg-Pavlov ratio, CSM: cervical spondylotic myelopathy, LSS: lumber spinal stenosis

In this study, TPR was 0.71 ± 0.09 in the CSM group and 0.81 ± 0.10 in the non-CSM group; the predictive value of TPR for CSM was 0.78. Yue et al. [12] compared TPR between 28 patients with CSM and 88 control patients (non-spondylotic and non-myelopathic patients) and reported that TPR was significantly smaller ($P < 0.001$) in CSM patients (mean 0.72 ± 0.08) compared with control patients (mean 0.95 ± 0.14). TPR of the CSM group in this report was consistent with that reported by Yue but TPR of the non-CSM group was considerably small. It was assumed that there were many patients with cervical spinal stenosis in those with LSS.

Lee et al. [13] examined the cervical and lumbar spines of 440 cadavers and found that spinal stenosis in one part of the spine positively predicted stenosis in other areas of the spine 15.3–32.4% of the time. A retrospective analysis of 200 patients requiring cervical disc surgery was performed to determine the frequency of coexistent lumbar disc or spine abnormalities and it was found that 30.5% of the patients had already undergone lumbar disc surgery [7]. Moreover, Lee et al. [8] analyzed the incidence of asymptomatic cervical cord compression in 93 LSS patients and found that 23.7% of the patients had moderate or severe cervical cord compression by whole spine MRIs. It has been presumed that patients who develop LSS or CSM have a tendency to developmental spinal stenosis. There were 21 (8.86%) patients with coexistent CSM

among the 237 LSS patients in the present study. Kokubun et al. [14] reported that the annual rate of surgeries for CSM per 100,000 residents was 5.7. Compared with his report, our CSM morbidity rate is definitely high.

In our series, there were 17 males (81.0%) and 4 females (19.0%) with coexistent CSM in LSS patients, the CSM morbidity rate in patients with LSS was significantly higher in males than that in females. The principal cause of the gender gap in CSM morbidity is considered to be the fact that male TPR (0.76 ± 0.08) is significantly smaller than female TPR (0.85 ± 0.10). Hukuda et al. [15] analysed the canal/body ratio of healthy young adult men and women and found that it was significantly smaller in men than in women. They concluded that a significantly small canal/body ratio in men might implicate the male prevalence of CSM. 63.6% of CSM occurring in men was reported by Lees [16], 70.8% by Clarke [17], and 67.4% by Nurick [18]. It is believed that TPR is associated with the gender gap of CSM morbidity.

In a previous study, it was reported that many patients with CSM developed symptoms in their 50s. In this study, age was not related to the development of CSM. Chen et al. reported that TPR of their CSM group was significantly smaller than that of the control group among individuals aged <55 years as well as older than 55 years [19]; his results are consistent with our results, indicating that age is not related to the development of CSM. This study enrolled patients with LSS, in whose ages morbidity of CSM is higher than in younger ages, and there was no significant difference in age between the CSM and non-CSM groups.

Because our study subjects were LSS patients, patients' backgrounds were obviously biased and this could be one reason no other factors were found to be predictive of CSM unlike other researches. Moreover, 237 LSS patients were examined but CSM morbidity was only 8.86% and we could not analyse males and females separately. Given the significant difference in TPR of healthy males and females previously reported, it is possible that there are different TPR cut-off values for patients with LSS. The CSM morbidity was high among our LSS patients compared with the general population. Further clinical studies of CSM in patients with LSS thus appear necessary.

Conclusion

The CSM morbidity was higher among our LSS patients compared with the general population and TPR was identified as a predictive factor of CSM. The predictive value of TPR for CSM was 0.78. In this study, TPR was 0.71 ± 0.09 in the CSM group and 0.81 ± 0.10 in the non-CSM group. Furthermore, there was no significant difference between the CSM and non-CSM groups in age, spondylolisthesis or spondylosis, LSS symptom types and number of stenosis segments with LSS. Therefore, we can use TPR for predictive factor of CSM in patients with LSS.

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BASIC RESEARCH

Anatomic Mapping of Short External Rotators Shows the Limit of Their Preservation During Total Hip Arthroplasty

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Abstract

Background The direct anterior approach in THA requires no detachment of muscle insertions. However, damage to the short external rotator muscles may occur when attempting to elevate the femur for exposure. Although the anatomic insertions of these muscles are approximately known, there are no quantitative data regarding their locations.

Questions/purposes We therefore asked where and how the tendons attach to the inner aspect of the greater trochanter.

Methods In 20 cadaveric hips we identified the attachments of the short external rotator tendons on the medial aspect of the greater trochanter. Mapping of the attachment site was performed by defining coordinate axes; the total width and height of the greater trochanter represented 100% and distances of the attachment from the anteroinferior reference point were given.

Results The mean anterior border location of the conjoined tendon (obturator internus, gemellus superior, and gemellus inferior) attachment was located at 29% (13 mm from the anteroinferior reference point), its posterior border at 53% (23 mm), its mean superior border at 70% (15 mm), and its mean inferior border at 24% (5 mm). The mean anterior border of the piriformis tendon attachment was located at 57% (25 mm), its mean posterior border at 78% (34 mm), its mean superior border at 64% (17 mm), and its inferior border at 55% (12 mm). There was considerable variation in these attachment sites among individuals.

Conclusions The insertion of the conjoined tendon extends to the anterosuperior aspect of the greater trochanter. Together with the considerable variation of the attachment site, external rotator muscles remain at risk of being damaged during the capsular release.

Introduction

Minimally invasive THA (MIS-THA) that minimizes soft tissue dissection reportedly reduces blood loss [3], does not increase complication rates [3, 6, 13], and improves early walking ability compared with conventional THA [3, 4]. Among the MIS-THA methods, the direct anterior approach (DAA) was modified from the Smith-Petersen approach and has become one of the standard procedures for primary THA [5, 13]. The DAA, which uses an intermuscular plane among the sartorius, rectus femoris, and tensor fasciae latae, does not dissect muscles around the hip and conserves the posterior tissue to a large extent, leading to improved stability and a reduced postoperative dislocation rate [6, 8, 11–13]. As a consequence, reduction of the dislocation rate and early postoperative functional recovery can be expected [10].

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Each author certifies that his or her institution either has waived or does not require approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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When performing DAA, detachment of the joint capsule at appropriate sites is indispensable to obtain a clearer visual field during surgery [8, 11]. However, despite careful capsular release and rasping, damage to muscles may occur [9], possibly eliminating one of the advantages of the approach. Furthermore, because of the limited surgical visual field in MIS-THA, there is a risk of prolonged operation time, unexpected soft tissue injury, unfavorable implant placement position, and fracture [1]. Anterior elevation of the proximal femur for a clearer visual field and femoral rasping may minimize these complications, and releasing of the posterolateral capsule or superior capsule has been advocated [7, 11]. However, such capsular dissection and femoral rasping may pose a risk of damaging the short external rotators. Therefore it is essential for surgeons to have detailed anatomic knowledge of the muscle attachment sites to minimize soft tissue damage during the anterior approach. Although the anatomy of the short external rotator muscles is approximately known [15], there is no detailed quantitative information regarding the location of their tendon insertions.

We therefore asked where and how the tendons attach to the inner aspect of the greater trochanter on defined horizontal and vertical axes.

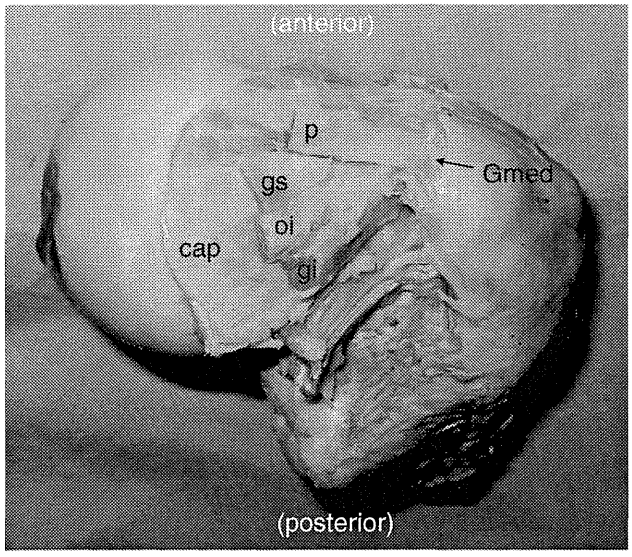

Fig. 1 A posterosuperior view of the cadaveric dissection of the right hip shows the short external rotator muscles. p = piriformis; gs = gemellus superior; oi = obturator internus; gi = gemellus inferior; Gmed = gluteus medius; cap = capsule.

Materials and Methods

We obtained 20 hips (11 right hips and nine left hips) from 16 embalmed cadavers (11 males and five females) donated for medical education and research. The cadaver specimens had a mean age of 84 years (range, 61–100 years) at the time of death and had no history of hip disease. Details of the antemortem weight and mobility status were not available, but the estimated height was 168 ± 8 cm for the male and 149 ± 6 cm for the female cadavers. Measured collodiaphyseal angle and neck anteversion were 126.0° ± 6.0° and 12.3° ± 5.1°, respectively. We removed the skin, fat, and soft tissues until only the gluteus medius, gluteus minimus, piriformis, obturator internus, obturator externus, gemellus superior, gemellus inferior, and capsular structures remained. After arthrotomy around the acetabular rim, the femur was disarticulated and the muscles were dissected so as to leave sufficient structures at the femoral insertion (Fig. 1). We then dissected the gluteus medius, obturator internus, gemellus superior, gemellus inferior, obturator externus, and remaining capsule with special attention to the connection between the tendons (Fig. 2A). When the tendons were integrated close to the insertion sites, the tendons were identified and separated

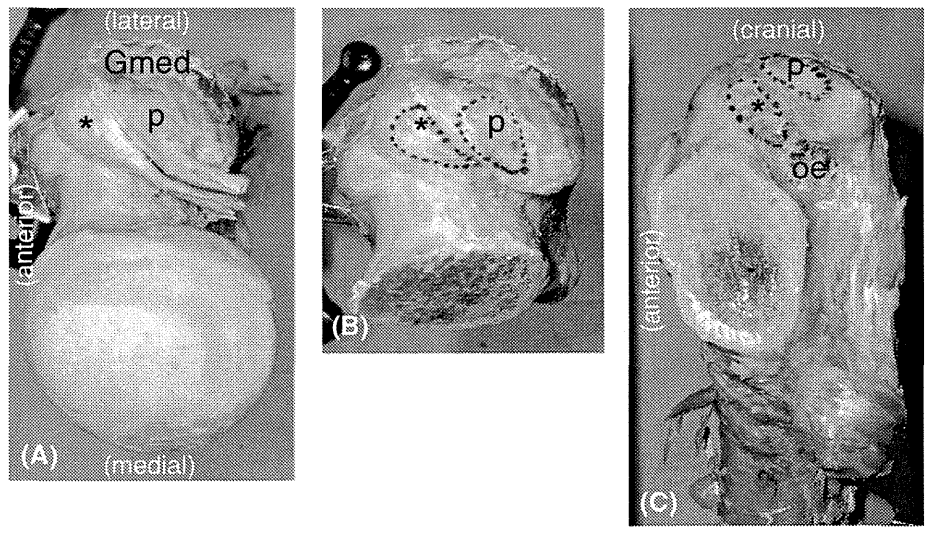

Fig. 2A–C The attachment site of the short external rotator muscles indicates their relative localization. (**A**) A superior view, (**B**) superior view and footprint of the tendon insertion, and (**C**) mediolateral view and footprint of the tendon insertion are shown. *Conjoined tendon of the gemellus superior, obturator internus, and gemellus inferior; p = piriformis; oe = obturator externus; Gmed = gluteus medius.

bluntly based on their fiber orientation down to the attachment on the greater trochanter or trochanteric fossa. Subsequently, we partially cut the tendons with scissors to identify their footprints at the insertion and their peripheries were carefully marked with a pen. Osteotomy of the femoral neck at the saddle then was done (Fig. 2B-C).

We measured the major and minor axes of the elliptical or scaphoid-shaped footprint of the tendon attachment using calipers. We then took high-resolution scaled digital photographs of each dissected specimen in a mediolateral direction from 50 cm away at a right angle to the femoral shaft. We determined eight points (anterior, posterior, superior, inferior, and midpoints between each of them) on the contour of the attachment footprint and recorded them using Adobe Photoshop CS2 software (Adobe Systems Inc, San Jose, CA, USA). In the mediolateral view of the femur, the proximal shaft axis was defined as the proximal femoral axis (Fig. 3A). At the level of the femoral neck saddle, an axis perpendicular to the proximal femoral axis was defined as the X-axis (AP axis). We defined an axis at the anterior border of the greater trochanter on the saddle level, parallel to the proximal femoral axis, as the Y-axis (vertical axis) (Fig. 3B). Their intersection was defined as 0. For mapping of the tendon attachment, the AP position was expressed in percentages with the anterior border as 0% and the posterior border as 100%. The vertical position of the tendon attachment was expressed with the saddle height as 0% and the vertex of the greater trochanter as 100% (Fig. 3B). The distance of each border in millimeters from the 0 reference point also was measured and the value was standardized with the mean width and height of the greater trochanter of the cadavers.

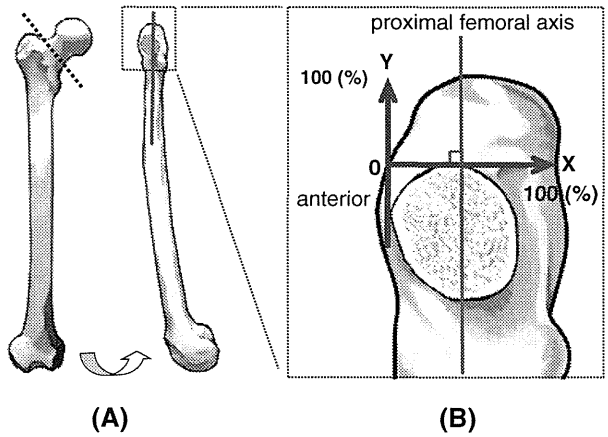

Fig. 3A–B The femoral axis and coordinate axis used for measurement are shown. In the mediolateral view of the femur, the anterior border of the greater trochanter parallel to the proximal femoral axis was defined as the Y-axis and its perpendicular axis at the saddle level was defined as the X-axis. (**A**) An AP view of the right femur is shown on the left and a mediolateral view is shown on the right. (**B**) The coordinate axis for measurement of tendon attachment is shown.

We used Spearman's rank correlation to identify relationships among the anterior border of the tendon attachment site, neck anteversion angle, and the width and height of the greater trochanter.

Results

Three muscles of the short external rotators, obturator internus, gemellus superior, and gemellus inferior, formed a conjoined tendon and attached anteriorly of the medial aspect of the greater trochanter. On the coordinate axes, the anterior border of the conjoined tendon attachment site ranged from 19% (9 mm) to 43% (23 mm), the posterior border ranged from 39% (18 mm) to 60% (30 mm), the superior border ranged from 48% (8 mm) to 86% (21 mm), and the inferior border ranged from 4% (1 mm) to 40% (9 mm) (Table 1). The footprint of the conjoined tendon insertion was elliptical or scaphoid-shaped with a mean size of 12.8 (± 2.5) mm × 4.3 (± 1.2) mm. As shown in the superimposed drawing of the attachment site of each specimen (Fig. 4A), there was variation in the position of the conjoined tendon attachment in the horizontal and vertical directions. The attachment site of the piriformis was posterosuperior to that of the conjoined tendon. On the coordinate axes, the anterior border of the piriformis attachment site ranged from 42% (16 mm) to 77% (36 mm), the posterior border ranged from 59% (23 mm) to 97% (46 mm), the superior border ranged from 65% (10 mm) to 99% (24 mm), and the inferior border ranged from 34% (7 mm) to 79% (17 mm) (Table 1). The size of the attachment footprint was 10.3 (± 1.6) mm × 4.7 (± 1.1) mm and the superimposed attachment sites indicated the degree of their variation (Fig. 4B). The obturator externus attached independently to a fossa located posteroinferior to the other short external rotator muscles (Fig. 4C). Its

Table 1. Mapping of attachment sites

Tendon	Attachment border		Mean ± SD (range) (%)
Conjoined tendon*	X axis	Anterior	29.1 ± 6.4 (18.8–43.2)
		Posterior	52.8 ± 5.1 (38.9–59.9)
	Y axis	Superior	70.2 ± 8.4 (48.1–85.7)
		Inferior	24.3 ± 10.1 (3.8–40.2)
Piriformis	X axis	Anterior	57.4 ± 10.2 (42.1–76.9)
		Posterior	78.4 ± 11.9 (59.4–97.3)
	Y axis	Superior	64.3 ± 9.4 (64.9–98.5)
		Inferior	55.1 ± 11.3 (34.3–74.8)
Obturator externus	X axis	Anterior	61.3 ± 6.5 (48.6–70.1)
		Posterior	75.9 ± 5.8 (65.6–83.0)
	Y axis	Superior	10.6 ± 12.7 (−19.0–33.3)
		Inferior	−18.7 ± 18.6 (−59.0–6.3)

* Obturator internus, gemellus superior, and gemellus inferior.

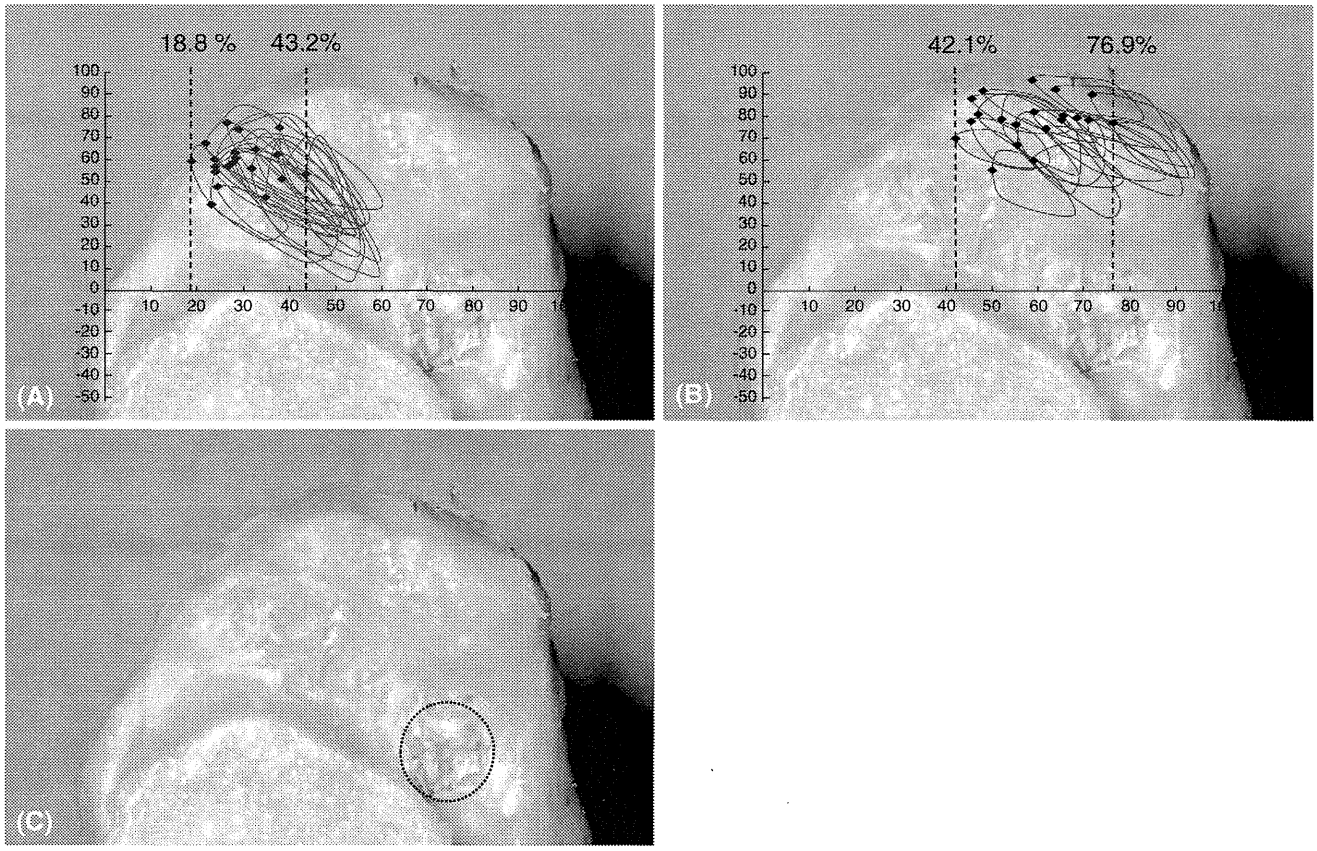

Fig. 4A–C Superimposed footprints of the attachment of the short external rotator muscles on the inner aspect of the greater trochanter are shown. (**A**) The attachment of the conjoined tendon (obturator internus, gemellus superior, and gemellus inferior) for 20 hips is shown. The plot highlights the most anterior part of the attachment in each specimen to show its variation of 18.8% to 43.2% from the anterior border of the greater trochanter. (**B**) The attachment of the piriformis for 20 hips is shown. The plot highlights the most anterior part of the attachment in each specimen. (**C**) The dotted line indicates the attachment site of the obturator externus to a fossa.

attachment site was relatively constant; on the coordinate axes, the anterior border ranged from 49% (20 mm) to 70% (34 mm), the posterior border ranged from 66% (23 mm) to 83% (39 mm), the superior border ranged from −19% (−2 mm) to 33% (7 mm), and the inferior border ranged from −59% (−7 mm) to 6% (1 mm) (Table 1).

No significant correlation was found between the anterior border (X value) of the conjoined tendon attachment and neck anteversion angle ($p = 0.12$), the width of the greater trochanter ($p = 0.25$), or the height of the greater trochanter ($p = 0.82$). In addition, the anterior border (X value) of the piriformis attachment did not show significant correlation with neck anteversion angles ($p = 0.73$), the width of the greater trochanter ($p = 0.74$), or the height of the greater trochanter ($p = 0.36$).

Discussion

Detailed knowledge of the anatomy of tendon attachment is a prerequisite for less invasive THA and attempts should be made to preserve soft tissue, including the short external rotator muscles. MIS-THA using an intermuscular approach has been reported [2, 13]. However, unless capsular dissection and femoral rasping are performed carefully, the short external rotators might be injured. It therefore is important to have improved knowledge of the anatomic positions of the tendon attachment sites.

Readers should know the limitations of our study. First, our study was limited by sample size as a result of the difficulty in obtaining a large number of embalmed cadavers. Second, we did not have detailed information regarding body size and could not correlate quantitative anatomy with body size. However, the position of the tendon attachment site, when shown as a relative value on the coordinate axes, apparently was not influenced by skeletal size difference. Third, with a smaller sample size of female and bilateral hip cadavers, our study was underpowered to analyze possible gender differences or intraspecimen variance. Additional study is needed to investigate such variance, if any. Fourth, the study is limited to the measurement of morphologic hip features in

Japanese subjects. It is possible that ethnic difference in bony geometry may be associated with variation of the tendon attachment. However, we believe these quantitative data supplement what generally is known about the locations of the short external rotator muscle attachments.

The general gross anatomy and approximate insertion of the short external rotator muscles to the greater trochanter have been approximately known, but detailed quantitative locations of the attachment sites are not known. Standard anatomy textbooks only indicate the insertion to be the upper medial side of the greater trochanter [15] and do not provide specific information regarding the attachment site. Windisch et al. [17] provided details regarding the anatomy of the musculotendinous junction and fusion of short external rotator muscles. Solomon et al. [14] reported that the piriformis inserted onto the greater trochanter through a conjoint tendon with the obturator internus. Nevertheless, the location of the attachment of each tendon on the inner aspect of the greater trochanter still remained obscure. Our observations show the accurate location of the greater trochanteric attachments of the short external rotator muscles (a conjoined tendon, piriformis, and obturator externus) and their positional relation for the first time.

We found both attachment sites of the conjoined tendon and piriformis were considerably more variable among individuals than had been thought. Based on the mapping data, the conjoined tendon of the short external rotators may attach as anteriorly as 19% (or 9 mm from the anteroinferior reference point) of the horizontal width of the greater trochanter and as low as 4% (1 mm) of the medical height of the greater trochanter from the saddle in certain individuals. These observations suggest preservation of the short external rotator muscles may not always be possible during capsular release in the DAA. The piriformis also can be damaged depending on its attachment variation during capsular release or femoral rasping. This is consistent with the study of Meneghini et al. [9] that showed the need for transection of the piriformis or the conjoined tendon of the obturator internus and gemelli in 50% of the cases during the anterior Smith-Petersen approach.

Thus, the short external rotators, especially the conjoined tendon, are at a high risk of being damaged and their detachment might be inevitable during the superior and/or posterior capsular release that is necessary to mobilize the femur during DAA in certain cases. The importance of preservation of the short external rotators for postoperative hip stability has been documented for other approaches such as the posterior approach [16]. The question remains whether a partial release of the short external rotator muscle during DAA would affect the postoperative stability of the hip. In addition, further study is needed to see the potential influence of morphologic features of a diseased hip, such as coxa vara and valga, on alteration of anatomic tendon attachment.

We report the quantitative locations of the anatomic attachment of the short external rotators of the hip. We showed that the tendons are at a risk of being damaged during capsular release. Improved anatomic knowledge of the short external rotators will assist surgeons in accurately locating these structures.

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ORIGINAL ARTICLE

Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: Tsurumai Biologics Communication Registry (TBCR) Study

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Abstract Biologic agents have proven to be effective against rheumatoid arthritis (RA) in clinical trials and post-marketing surveillance (PMS) studies. However, limited follow-up periods and strict criteria for recruitment might lead to an underestimation of adverse events. To document the long-term course of patients with RA treated with biologics in clinical settings, we established the Tsurumai Biologics Communication Registry (TBCR). First, we retrospectively collected data of patients registered for any biologic PMS study or clinical trial at participating

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institutes. Thus far, thirteen institutes have joined the registry and 860 patients have been identified. Comparing baseline characteristics by age and initiation year of biologics, young patients had significantly less joint damage and dysfunction and a higher dose of concomitant methotrexate (MTX) compared to older patients. Older age and functional class were significantly related to the incidence of adverse events that resulted in discontinuation of the 1st biologic treatment. The TBCR is in its initial stages, and information on all patients newly starting biologic therapy at participating institutes is being collected prospectively. Differences in baseline characteristics by age and initiation year of biologics need to be carefully evaluated in order to report on drug-related survival and long-term prognosis, using follow-up data in the near future.

Keywords Rheumatoid arthritis · Biologics · Methotrexate · Registry · Age

Introduction

Biologic agents have proven to be effective against rheumatoid arthritis (RA) in a number of clinical trials and post-marketing surveillance (PMS) studies. In Japan, PMS for biologics including infliximab, etanercept, adalimumab, and tocilizumab has provided variable information for clinical practice [1, 2]. However, limited follow-up periods and strict criteria for recruitment might lead to an underestimation of adverse events. Long-term clinical data are necessary to evaluate the effectiveness of biologics in the clinical setting. To this end, we developed the Tsurumai Biologics Communication Registry (TBCR), a prospective, observational, multicenter registry of patients with RA starting biologic therapy; the registry became active in October 2008. The aim of this registry is to document the course and outcome of RA patients newly starting biologic therapy in Japan.

Treatments using biologics are expensive. Considering the significant economic burden on society, the efficacy, safety, and cost-effectiveness of biologics need to be determined. Age is one of the most important factors that influence health outcomes and socioeconomic status. Information from clinical trials and other registries is also becoming increasingly available. Thus, assessing changes in patient characteristics will prove to be invaluable for a better understanding of the clinical outcomes of treatment with biologics. In this study, we describe the study protocol of the TBCR and evaluate the baseline characteristics of patients who initiated treatment with biologics by October 2008 and registered with the TBCR. We evaluated the patients' baseline characteristics stratified by age and initiation year of biologics, as well as determining the incidence of adverse events within 1 year from the initiation of biologics.

Patients, materials, and methods

Registration of patients treated with biologic agents

Thirteen institutes throughout Japan have joined this project. All institutes have already conducted PMS for at least one of infliximab, etanercept, adalimumab, or tocilizumab, continued the follow-up of registered patients after the completion of PMS, and continue to register patients with RA newly starting biologic therapy after PMS. Therefore, we collected retrospective data of patients registered for any biologic PMS or clinical trial at each of the participating institutes. We identified a total of 1,037 patients with RA who began biologic therapy at the participating institutes, and we transferred all their information from each institute's established database to the new TBCR database. We also initiated recruitment of all patients who had newly started biologic therapy since October 2008.

Baseline data

Baseline data were collected in two ways. Data for patients registered through the established database system at each institute were obtained from the institutional databases. Data for patients recruited after TBCR implementation were collected from hospital charts at each institute. Documented variables at baseline were as follows: demographic variables, including sex, age, years of disease duration; Steinbrocker stage of joint damage and class of dysfunction in daily life [3]; disease activity assessed by the 28-joint disease activity score using C-reactive protein (DAS28-CRP), including swollen and tender joint counts; visual analog scale (VAS) scores for patient's global assessment of health status; serum CRP levels; and concomitant treatment with methotrexate (MTX). In addition to these variables, we have been collecting physicians' global assessment scores and information on concomitant treatment with prednisolone (PSL), Health Assessment of Questionnaire disability index (HAQ-DI) scores, and serum matrix metalloproteinase-3 (MMP-3) levels of newly registered patients since October 2008 for baseline data.

Follow-up

Registered patients are followed until they discontinue biologic therapy; the reasons for discontinuation are recorded: serious adverse events, non-serious adverse events, insufficient effectiveness, patient's convenience, etc. If a patient changes biologics, collected data include disease activity (DAS28-CRP), physician's global assessment, MMP-3, and information regarding current biologic use and concomitant treatment. Follow-up is continued by rheumatologists during regular visits at each institute. Data