Fig. 1 K-MAX® cementless artificial hip prostheses. **a** Cementless femoral stem (K-MAX® HS-6): a double wedge-shaped, metaphyseal filling-type stem. **b** Cementless acetabular component (K-MAX® Q5LP): a low-profile porous-coated acetabular component with four peripheral fins and three screw holes

Table 2 Laboratory tests

Tests	Items
Hematologic test	Red blood cell count
	Hemoglobin
	Hematocrit value
	White blood cell count
	Differential blood count
	Platelet count
Blood chemistry	Alanine aminotransferase
	Albumin
	Alkaline phosphatase
	Aspartate aminotransferase
	Blood creatinine
	Blood urea nitrogen
	C-reactive protein
	Electrolytes (sodium, potassium, chlorine)
	Gamma-glutamyltransferase
	Lactate dehydrogenase
	Total bilirubin
	Total cholesterol
	Total serum protein
	Uric acid
Urine	Glucose
	Protein
	Urobilinogen

Q5LP) (Fig. 1). These components are made of vanadium-free titanium alloy, and a bottom coating was applied to the porous area with apatite–wollastonite glass ceramic. For the bearing coupling, a 26-mm-diameter cobalt–chromium–molybdenum alloy ball and an poly(MPC)-grafted CLPE liner were employed. All poly(MPC)-grafted CLPE liners were manufactured from compression-molded PE sheet stock (GUR 1020 resin). The sheet stock was treated with a dose of 50 kGy gamma-ray irradiation in N_2 gas and annealed at 120 °C for 7.5 h in N_2 gas. After cooling, the liners were machined to have a 26-mm inner diameter and an elevated lip. For the poly(MPC) grafting, they were immersed in an acetone solution containing benzophenone and subsequently dried to remove the acetone. The liners were then immersed in the aqueous MPC solution, and the graft polymerization on the bearing surface was performed using ultraviolet-ray irradiation. Finally, the liners were packaged and sterilized by a dose of 25 kGy gamma-ray irradiation in N_2 gas. The surgery was performed through a posterior approach by or under the guidance of five principal investigators. Patients underwent the routine thromboprophylaxis regimen and postoperative rehabilitation program of each institution.

The patients were seen postoperatively at 3 months, 6 months, and 1 year. Orthopedic surgeons other than the operators of the index surgery followed the patients pre- and postoperatively at each institution. They measured clinical performance using the evaluation chart of hip joint function authorized by the Japanese Orthopaedic Association (JOA score) [9]. The JOA score consists of four categories, i.e., pain, range of motion, gait, and activities of daily living, with 40 points attributed to pain and 20 points to the other three categories. The sums of points from these four categories can be used as an approximate estimate for the hip function of an individual; 100 points is a perfect score and is regarded as normal.

Anteroposterior pelvic radiographs were made immediately after surgery and postoperatively at 3 weeks, 3 months, 6 months, and 1 year. Laboratory tests, including full blood counts and blood chemistry (Table 2), were performed before surgery and postoperatively at 1 and 3 weeks, 3 and 6 months, and 1 year.

Two radiologists and an orthopedic surgeon, all of whom worked at different institutions from the five participating hospitals, performed the radiographic analysis while blinded to clinical information. These experts compared radiographs taken at 3 weeks to those taken at 1 year to detect relevant findings, such as implant migration, periprosthetic osteolysis, and heterotopic ossification. The migration of the implants was defined as changes of

≥3 mm in the position of the implants [10]. Periprosthetic osteolysis was defined as a new cystic lucency localized on the endosteal surface of the bone. Heterotopic ossification was graded according to Brooker et al. [11].

All adverse events occurring during the course of this clinical trial were recorded. An adverse event was defined as any unfavorable event that occurred in the subjects during the study period. Particular attention was paid to severe adverse events, defined as: (1) those leading to death, (2) those threatening life, (3) those requiring the patient to be hospitalized or submit to an extended stay in the hospital stay, (4) those resulting in permanent or severe impairment, (5) those resulting in permanent or severe dysfunction, (6) those inducing congenital abnormalities in the offspring, and (7) those representing medically serious conditions.

Statistical methods

The paired *t* test was used to compare the JOA scores recorded before surgery and at 1 year after surgery.

Results

No patients were lost to follow-up at 1 year postoperatively. A total of 111 adverse events were recorded in 54 subjects, including four severe adverse events (Table 3). However, no adverse events were found to be correlated with the implanted poly(MPC)-grafted CLPE liners.

No reoperations were performed for any reasons. Dislocations occurred in two patients. The first, a 69-year-old woman (case 79), suffered a dislocation 14 days after the index surgery and was treated by manual reduction. The second, also a 69-year-old woman (case 38 in Table 3), suffered four dislocations and was treated with an abduction brace. Deep vein thrombosis occurred in three patients and was successfully treated in each case with anticoagulants.

The average of the JOA scores improved from 43.2 ± 9.7 preoperatively to 91.7 ± 9.1 postoperatively at 1 year (mean ± standard deviation) ($p < 0.01$). The change was most apparent in the category of pain (Table 4). Neither implant migration nor periprosthetic osteolysis was detected on radiographic analysis (Fig. 2). There was evidence of Brooker grade 3 heterotopic ossification in one individual without any clinical manifestations.

Laboratory tests detected abnormal changes in six patients (Table 5), including elevations in white blood cell counts and in a number of blood enzymes, such as lactase dehydrogenase. Four of these abnormal changes (cases 5, 9, 21, and 45) were the result of slight hepatic dysfunction; of these, three (cases 5, 9, 21) occurred within 1 week postsurgery and resolved spontaneously to the preoperative value without any treatments. Hence, these changes may have been drug-induced hepatic dysfunction resulting from the perioperative medication. One change (case 45) was a slight elevation of blood gamma-glutamyltransferase (36 U/L; normal <30), which was seen at the 1 year follow-up. This individual had a habit of alcohol drinking but was otherwise healthy. The other two changes (cases 39 and 54) also resolved spontaneously to the preoperative value and were not accompanied with hip symptoms.

Table 3 Severe adverse events

Case	Sex	Age (years)	Adverse events	Comments
6	Female	64	Breast neoplasm	Hospitalization for treatment
38	Female	69	Recurrent dislocation of total hip replacement	Extension of hospital stay and another hospitalization
44	Female	66	Local recurrence of rectal cancer	Hospitalization for treatment
54	Female	73	Transient myocardial ischemia	Occurred just after surgery due to blood loss during surgery. Fully recovered

Table 4 Preoperative and postoperative Japanese Orthopaedic Association score

Category	Pre-operative	Postoperative		
		3 months	6 months	1 year
Pain	11.5 ± 6.2	35.7 ± 5.3	37.9 ± 3.8	38.6 ± 3.6
Range of motion	11.6 ± 3.3	15.9 ± 2.4	16.7 ± 2.1	17.5 ± 2.3
Gait	8.8 ± 3.3	13.4 ± 4.6	16.3 ± 4.4	17.6 ± 4.3
Activities of daily living	11.4 ± 2.8	15.9 ± 3.0	17.1 ± 2.7	18.1 ± 2.5
Total	43.2 ± 9.7	80.8 ± 10.7	87.9 ± 9.2	91.7 ± 9.1

Data are presented as the mean ± SD

Discussion

The production of a novel bearing surface for an artificial joint with a new material is a challenge. Even if the results of preclinical tests are favorable, unexpected complications may occur in clinical use [12–14]. Here, we introduce a new material, i.e., a ploy(MPC), for use in an artificial hip joint.

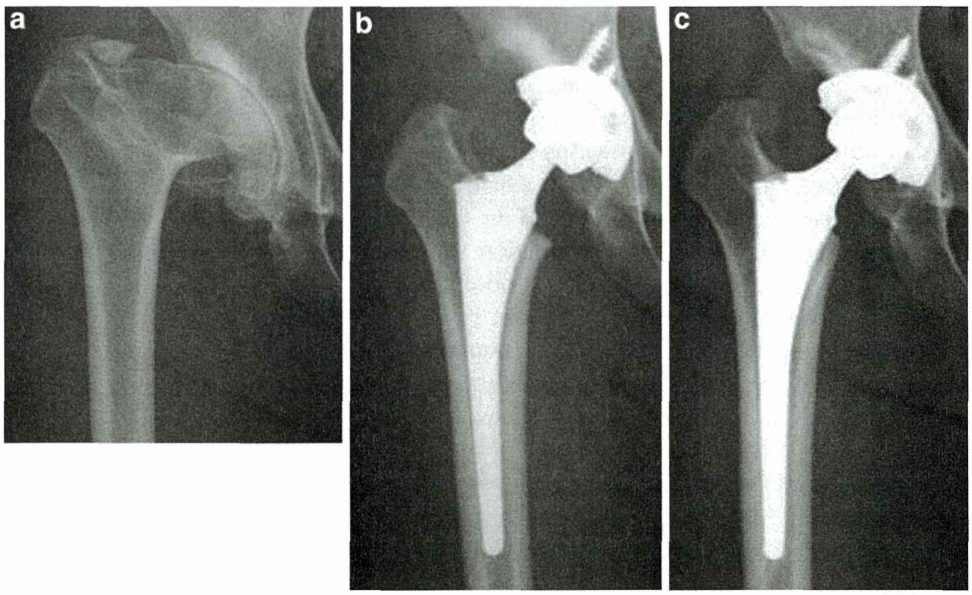

Fig. 2 Radiographs of a representative case. **a** Before surgery: radiographs show end-stage osteoarthritis of the right hip joint with severe deformity of the proximal femur. **b**, **c** Postsurgery (**b** 3 weeks postsurgery, **c** 1 year postsurgery: radiographs show no findings related to implant migration or periprosthetic osteolysis

Table 5 Patients with abnormal laboratory data

Case no.	Sex	Age (years)	Adverse events	Outcome	Presumed causes and comments
5	Female	54	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
9	Female	62	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
21	Female	66	Elevation of enzymes related to liver function	Normalization of enzyme levels	Drug-induced hepatic dysfunction
39	Female	57	Elevation of lactate dehydrogenase and C-reactive protein	Normalization of lactate dehydrogenase level. The value of C-reactive protein was 0.61 mg/dL at 1 year postoperatively	Preoperative value of C-reactive protein was 0.9 mg/dL without relevant findings of infection
45	Female	45	Elevation of gamma-glutamyltransferase	The value of gamma-glutamyltransferase was 36 U/L (normal <30) at 1 year postoperatively	Related to alcohol drinking
54	Female	54	Elevation of white blood cell count and C-reactive protein	Normalization of white blood cell count and C-reactive protein without specific treatment	The cause of transient abnormal data was not specified. Elevation of these values accompanied no hip symptoms

We investigated 80 consecutive patients who were implanted with poly(MPC)-grafted CLPE liners as a component of an artificial hip joint. Both the clinical assessment using the JOA score and the radiographic examinations demonstrated comparable results to other contemporary artificial hip joints [15–17].

Although more than 100 adverse events were encountered, none of which were correlated to the poly(MPC)-grafted CLPE liners. Abnormal changes in laboratory chemistry data were detected in six patients. These changes resolved spontaneously except in one individual. In this case, the elevation of the gamma-glutamyltransferase may be related to the habit of alcohol intake.

MPC is a synthesized phospholipid and is composed of a methacryloyl group and a zwitterionic phosphorylcholine group; the former is a polymerization reaction group, and the latter is a polar group. Ishihara et al. developed a new technique to graft poly(MPC) onto the PE surface using a photoinduced reaction. In this reaction, a covalent bond is first formed between the carbon atoms of the PE and a methacryloyl group of the MPC molecule. This MPC molecule then links with another MPC molecule. Through

the repetition of this polymerizing reaction, the PE surface is covered with a poly(MPC) layer having a thickness of 100–150 nm. The poly(MPC) has branch-like structures of phosphorylcholine, which change the characteristics of the bearing surface to be hydrophilic. The poly(MPC) layer presumably results in a significant reduction in the friction of the CLPE liners through a hydration–lubrication mechanism and makes the bearing surface more robust under multi-directional loadings. Moreover, phosphorylcholine is a constituent of the human cell membrane. Thus, poly(MPC)-grafted particles are not recognized as foreign bodies by macrophages and, consequently, the wear particles produced from the poly(MPC)-grafted CLPE liners have a reduced risk of resulting in serious foreign body reactions.

This study has several limitations. First, it was not a randomized controlled trial. The primary reason for not performing a randomized controlled trial was our conclusion that it would be extremely difficult to conduct such a trial for a THR, a well-established surgical procedure, in Japan. Although some individuals are willing to join a clinical trial for a new product because of its potential benefits, many often regard the process in which an implant is chosen by a chance mechanism as too experimental. Second, 80 individuals and 1 year of follow-up may be not a sufficient period of time to exclude the possibility of rare adverse reactions related to these new bearings. Thus, a long-term follow-up study (UMIN000003681) is currently underway for an extended investigation, including the measurement of PE wear.

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Intraoperative Measurements of Femoral Anterior Tangent (FAT) Line for Determining the Rotational Alignment of Femoral Component of Total Knee Arthroplasty

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ABSTRACT

Previously, we reported using CT images that the anterior surface of the femur immediately proximal to the trochlea and its tangent line (femoral anterior tangent line; FAT line) could be used as a good index of the femoral rotation. In this study, we developed a jig that allowed us to measure the FAT line during surgery, and we examine the relation between preoperative and intraoperative measurement values. The results indicated that the average intraoperative measurement value of the 'surgical' FAT line was 9.8° ± 3.2° internally rotated using surgical transepicondylar axis reference. This value significantly correlated to preoperative FAT line/clinical transepicondylar axis angle. These findings demonstrated that FAT line is a useful index for appropriate rotational alignment of femoral component, both before and during TKA.

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The rotational alignment of the femoral component is essential for the optimal patellar tracking, ligament balancing, and functional outcome of the total knee arthroplasty (TKA). Several indexes have been reported to decide the appropriate rotational alignment of the femoral component, including the posterior condylar axis (PCA), the antero-posterior (AP) axis (Whiteside's line), and the transepicondylar axis (TEA). Because these indicators have advantages and disadvantages, they are often used in combination at present, to increase the accuracy of the determination of the femoral rotational alignment.

Previously, we reported that the anterior surface of the femur immediately proximal to the trochlea and its tangent line (femoral anterior tangent line; FAT line) could be used as a good index for the rotational alignment of femoral component [1]. The analysis of the preoperative computed tomography (CT) images of 150 knees with osteoarthritis indicated that FAT line was consistently determined to be approximately 12° internally rotated to the clinical TEA. In this previous study, determination and measurement of the FAT line were performed by the CT imaging and image analysis software. It remained to be answered whether FAT line is measurable during TKA and become an accurate reference axis for the intraoperative determination of the rotational alignment of femoral component.

The purpose of this study is to determine 'surgical' FAT line intraoperatively and measure an angle relative to TEA using a newly develop jig. We analyzed the correlation of the intraoperative measurement to preoperative CT scan-based measurement and demonstrated the usefulness of the FAT line during surgery.

Materials and Methods

The patient population included 43 patients (47 knees) who had TKA because of osteoarthritis of the knee. There were 6 men and 37 women, and average age was 75.1 ± 5.7 years old (average ± standard deviation; range, 62–83). This study was implemented in accordance with the ethical principles of the Declaration of Helsinki, as well as relevant regulations promulgated by the Institutional Review Board. In these patients, both preoperative and postoperative CT images were available. A CT scan of the lower extremity was performed as a routine preoperative examination for TKA in full extension at 1 mm intervals. The scan direction was aligned perpendicularly to the longitudinal axis of the femur. The postoperative CT was taken approximately four weeks later after TKA surgery. The estimated mean dosage of the radiation of CT (knee) by the scanner was 4 mSV.

The measurement of each axis on CT was performed as described in previous report [1]. The anterior femoral surface around the upper pole level of patella was examined on the serial CT slices. Next,

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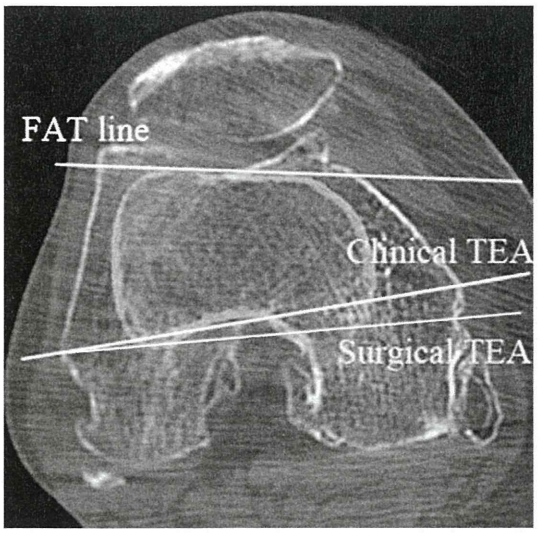

Fig. 1. The anterior femoral surface immediately proximal to the trochlea with the FAT line is superposed to the femoral condyle CT slice. The lines indicate the FAT line, clinical and surgical TEA.

a CT slice immediately proximal to the femoral trochlea, which showed widest anterior width without trochleal prominence, was selected. A line tangential to the anterior femoral surface as FAT line was determined. CT slices on which the medial or lateral epicondyles were most prominently detectable were also selected to measure the clinical and surgical TEA (Fig. 1). From postoperative CT images, the rotational angle of the femoral component relative to the clinical TEA was measured (Fig. 2). The rotational alignment of the femoral component was determined with reference to the line connecting the center of the medial and lateral pegs. As for decision of the clinical TEA, we measured in the same method as the preoperative CT. The cases that were unsure of the medial and lateral eminence of femoral condyle due to the metal halation were excluded in this study.

Axis measurements on the CT images were performed using computer software (Photoshop; Adobe SYSTEMS, San Jose, CA) and absolute values of each axis (FAT line, TEA, and the rotational alignment of postoperative femoral component) were recorded. Thereafter, the angle between the FAT line and the TEA and the angle between the postoperative femoral component and the TEA were calculated. The rotational angle to the TEA was arbitrarily expressed as a positive value for the internal rotation and as a negative value for the external rotation. The data are presented as the mean ± SD.

For intraoperative measurement of the 'surgical' FAT line, we developed a jig that allows us to measure the FAT line angle against axes on the distal femur. The jig consisted of anterior rectangular bar for the surgical FAT line, distal femoral block, and posterior condylar paddle (Fig. 3). In the present case series, the angle between the surgical FAT line and femoral block with reference to surgical TEA was measured.

The Pearson correlation test was used to analyze the correlation between preoperative clinical TEA/FAT line angle and intraoperative surgical FAT line angle (Stat View 5.0; Abacus Concepts, Berkley, CA). The level of significance was set at a value of 0.05.

Results

On measurement of the preoperative CT, FAT line was 12.2° ± 3.9° internally rotated to the clinical TEA. In 20 knees (20/47 knees; 43%) in which the surgical TEA was able to be determined, the FAT line was 7.3° ± 4.0° internally rotated to the surgical TEA. These measurement values were largely similar to those of the preceding study involving 150 knees [1].

The average intraoperative measurement value of the surgical FAT line angle was 9.8° ± 3.2°. This value significantly correlated to preoperative FAT line/clinical TEA angle (Fig. 4: $r = 0.72$, $P = .01$).

The postoperative CT revealed that the femoral component was aligned at 2.8° ± 1.9° internally rotated to the clinical TEA.

Discussion

There was significant correlation between intraoperative angle of the surgical FAT line against the reference TEA and preoperative FAT/clinical TEA angle using CT images. In addition, the proper rotational angle of the femoral component was obtained according to the intraoperative measurement of surgical FAT line. From these results, the surgical FAT line should become very useful as the index for the rotational alignment of the femoral component.

In the preceding study using preoperative CT, we demonstrated that the anterior surface of the distal femur can be a landmark for the rotational alignment and named it a FAT line [1]. However, it was not clear whether determining the FAT line was feasible during operation, or if that was possible, whether an obtained value was consistent with the preoperatively expected value. It was also necessary to assess whether the femoral component was aligned in accordance with the intraoperative measurement value after operation.

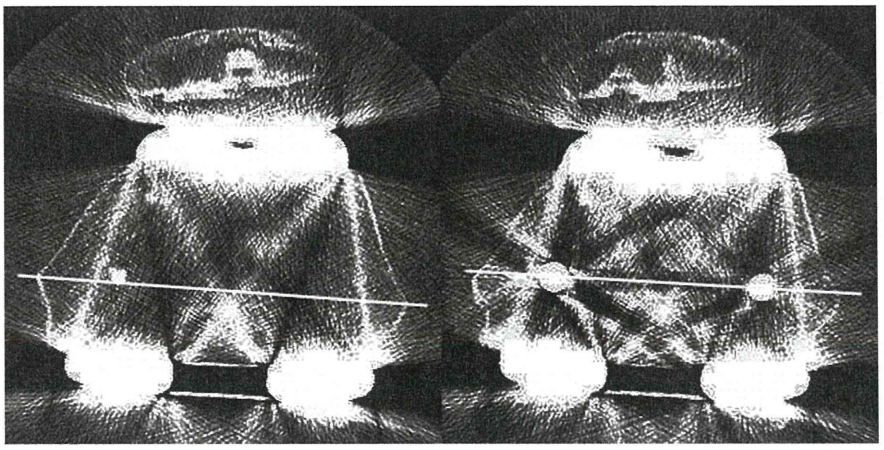

Fig. 2. CT slices used to confirm the rotational alignment of the femoral component after operation are shown. The rotational alignment of the component is defined as the line connecting the center of the medial and lateral pegs.

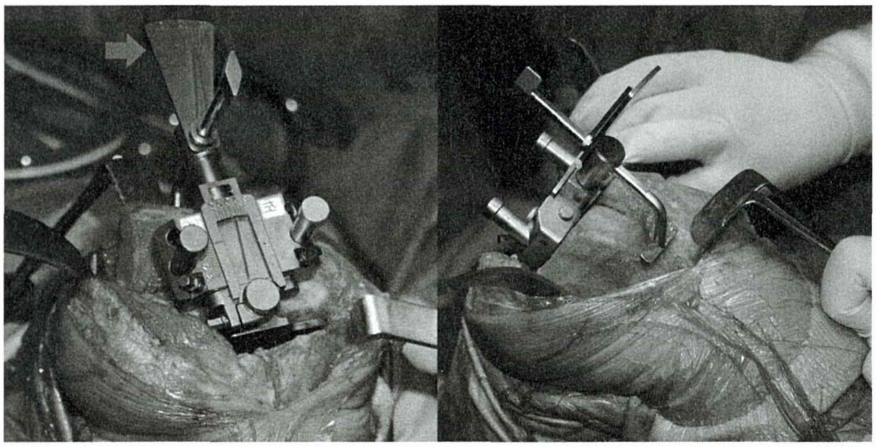

Fig. 3. The new jig used to measure the surgical FAT line angle is shown. The angle between the FAT line and transepicondylar axis reference is indicated (arrow).

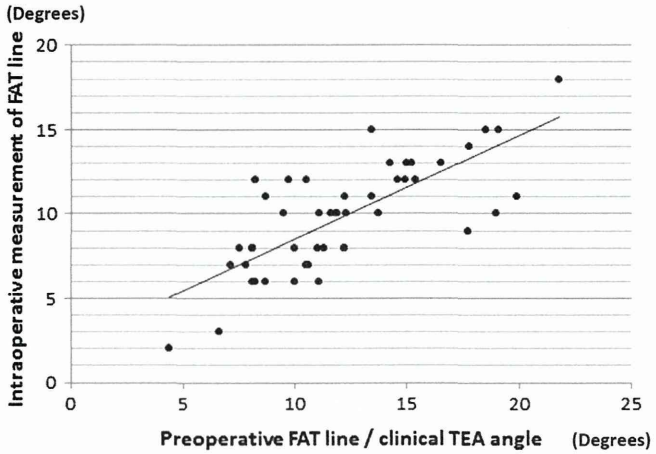

Fig. 4. Relationship between the preoperative measurement value of FAT/clinical TEA angle and the intraoperative surgical FAT line angle. The intraoperative value of the surgical FAT line angle using the jig is observed to correlate with the value of preoperative FAT/clinical TEA angle ($r = 0.72$, $P = .01$).

The intraoperative measurement value of the surgical FAT line angle was 9.8° ± 3.2°. This was smaller by an average of 2.3° than the preoperative value of the angle composed of the FAT line and clinical TEA (12.2° ± 3.9°). In addition, the intraoperative measurement value was larger by an average of 2.5° than the preoperative value of the angle to the surgical TEA. In other words, the femoral component was expected to be rotated approximately 2.3° internally from the clinical TEA and approximately 2.5° externally from the surgical TEA that were determined on the preoperative CT images. According to postoperative CT images, the component was internally rotated 2.8° ± 1.9° to the clinical TEA, well reflecting the preoperative and intraoperative measurement values. Moreover, the alignment targeted during operation was achieved.

Previous report has proposed that the anterior surface of the distal femur should become a rotational alignment reference axis during navigation surgery [2]. As another similar index, Won et al and Morizane et al reported a trochlear line that connects the most anterior projections of the lateral and medial femoral condyles for the determination of rotational alignment of femoral component [3,4]. However development of arthritis would easily deform the patello-femoral joint and the bone spurs make the intra-operative measurement difficult. In addition, the anterior trochlear line is not measurable as an index for the revision surgery. In contrast, FAT line can be measureable in most of cases with osteoarthritic deformity and cases with bone defect [1].

Our current study demonstrated the validity of measurements of the FAT line on the basis of a series of its assessments before, during, and after operation. Although the preoperative assessment of the FAT line might remain necessary because of its variation among patients, the surgical FAT line is a useful index for appropriate rotational alignment of femoral component during most TKA operations.

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ORIGINAL ARTICLE

A review of tocilizumab treatment in 122 rheumatoid arthritis patients included in the Tsurumai Biologics Communication Registry (TBCR) Study

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Abstract
Objectives Biologics have transformed the treatment of rheumatoid arthritis. Clinical remission is now the goal. We sought to verify whether the administration of tocilizumab—a biologic—can help to achieve current treatment goals.
Methods Using data from the Tsurumai Biologics Communication Registry for 122 patients treated with tocilizumab, we evaluated changes in DAS28-ESR at 12 months after initiation, and also evaluated remission rates defined using conventional and new Boolean-based remission criteria. We divided 50 patients who had received tocilizumab as a first-line treatment into two groups [disease duration at baseline of 12 months or less ($\leq$12 M) and more than 12 months (>12 M)].
Results At 12 months after initiation, there was no difference in DAS28-ESR, and remission rates based on the conventional criterion were also comparable (50 % in both groups). However, under the new criterion, remission was 50.0 % in the $\leq$12 M group against 12.5 % in the >12 M group ($p = 0.0181$). Among the individual components of the new remission criterion, the small proportion of patients in the >12 M group with a patient global assessment (PtGA) of $\leq$1 had a particularly strong influence on the remission rate for that group, but this component was not as important for the $\leq$12 M group.
Conclusions When used as a first-line biological drug for patients with early-stage RA ($\leq$12 M), tocilizumab appears to provide high rates of remission under the Boolean-based remission criterion, which were strongly affected by the PtGA.

Keywords Interleukin-6 · Multicenter study · Remission · Rheumatoid arthritis · Tocilizumab

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by chronic and destructive inflammation of the joints. The major transformation in treatment brought about by the advent of biologics over the last few years in particular has evoked a number of responses: the European League Against Rheumatism (EULAR) has published *Recommendations for the management of RA with synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs)* [1]; the American College of Rheumatology (ACR) and EULAR have jointly drawn up new classification criteria defining rheumatoid arthritis as "having at least one joint with definite clinical synovitis, with the synovitis not better explained by another disease" [2]; and the concept of

"treat-to-target (T2T)" [3] has emerged, which defines clinical remission as the goal of treatment and seeks to educate the many people involved in treating RA that tight control is the cornerstone of treatment. Then, in 2011, new criteria aiming for even higher levels of remission than those defined by the ACR and EULAR—the simplified disease activity index (SDAI), the clinical disease activity index (CDAI), and the Boolean definition—were proposed [4]. As a consequence of all this, the aim is for RA to be diagnosed sooner, and the goal of treatment is to meet the new remission criteria.

Tocilizumab (TCZ), developed in Japan, is the first anti-interleukin-6 (IL-6) receptor monoclonal antibody that targets IL-6. TCZ, which can now be used in the USA in patients who have shown inadequate response to anti-tumor necrosis factor (TNF) agents, can also be used in Japan as a first-line biologic treatment, and is applicable to some 30 % of patients in the clinical setting [5–7].

Using data from the Tsurumai Biologics Communication (TBC) Registry (a database of patients treated with biologics in the Department of Orthopedics in the Faculty of Medicine at Nagoya University and 20 affiliated institutions), we carried out an investigation to confirm the therapeutic response to TCZ, and we then considered its efficacy when used according to the ACR and EULAR recommendations and the T2T concept; we also examined the remission status achieved with the drug as determined using the new and the conventional remission criteria.

Patients and methods

Patients

The subjects included in this study were 122 patients diagnosed with RA under the 1987 ACR criteria [8] who were treated with TCZ from June 2008 to September 2009 according to data held by the TBCR [9, 10], and whose clinical progress could be followed for a period of 12 months or longer. The study was approved by the Ethics Committee of Tokyo KoseiNenkin Hospital, the Faculty of Medicine, Nagoya University (approval number: 1164) and other associated hospitals, and personal information about the patients was strictly protected.

TCZ therapy

The dose of tocilizumab administered for RA in Japan and Europe is 8 mg/kg, but the dose used in the United States is only 4 mg/kg. In this study, 8 mg/kg TCZ was administered every 4 weeks in accordance with the TCZ treatment guidelines of the Japan College of Rheumatology [11]. This dose, 8 mg/kg, was maintained from initiation to the end point. The methotrexate (MTX) dose administered was left to the judgment of the attending physician.

Therapeutic response

The response to TCZ was evaluated at 6 and 12 months after initiating treatment. The evaluation looked at changes in disease activity, using DAS28-ESR; remission was defined as DAS28-ESR <2.6 based on the revised EULAR criteria [12, 13]. Among the new criteria used to define remission (SDAI, CDAI, and the Boolean definition), we selected the Boolean criterion all ≤1 [tender joint count (TJC) ≤1, swollen joint count (SJC) ≤1, patient global assessment (PtGA) ≤1 cm, and C-reactive protein (CRP) ≤1 mg/dL] to denote remission [4].

Validation of recommendations and treat-to-target

To evaluate clinical response, we divided the 122 patients into 50 who had received TCZ as a first-line biological drug and 72 who were treated initially with an anti-TNF agent but had received TCZ as a second- or third-line biologic treatment. Then, under the presumption that treatment with TCZ starts early according to the concept of T2T, we further divided the 50 who had received TCZ as first-line treatment into a group of those with a disease duration at baseline of 12 months or less (≤12 M) and a group of those with a disease duration at baseline of more than 12 months (>12 M) (Fig. 1).

Validation of the new remission criterion

The percentages of the 122 patients who achieved remission under the new remission criterion (Boolean definition: all ≤1) and under the conventional remission criterion (DAS28-ESR <2.6) were calculated, and the baseline factors contributing to remission were identified for both situations. In order to examine differences in the remission rates seen with the new and the conventional criteria, we also analyzed the baseline characteristics in patients who had achieved remission under the conventional criterion but not under the new criterion, and those who had achieved remission according to both sets of criteria.

Statistical analysis

Efficacy in patients who discontinued administration was investigated on a last-observation-carried-forward basis. Fisher's exact test, Pearson's chi-square test, and the Wilcoxon rank sum test were used for comparisons between the two groups. The Wilcoxon signed-rank test was used to check for changes at 12 months after the initiation of TCZ treatment compared with baseline values

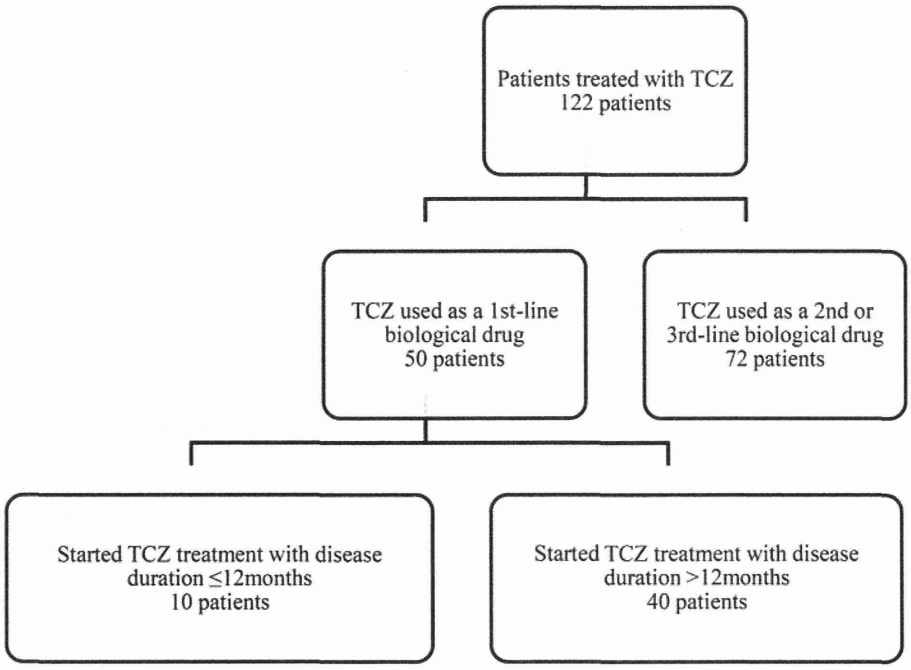

Fig. 1 Breakdown of the patients. *TCZ* tocilizumab

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