Table 3. Results of multivariate analysis for survival and local recurrence

	Survival			Local recurrence		
	Risk ratio	p value	95% CI	Risk ratio	p value	95% CI
Acridine orange therapy group						
Tumor size	1.12	0.001	1.05–1.2	1.12	0.02	1.01–1.23
Age	0.98	0.22	0.96–1	1.02	0.06	1–1.05
Sex	1.04	0.93	0.37–2.87	1.02	0.97	0.34–3.04
Recurrence cases	1.16	0.79	0.37–3.67	1.54	0.47	0.47–5.01
AJCC IV	24.2	0.0001	6.5–89.5	2.23	0.18	0.67–7.36
AO-RDT	0.68	0.47	0.24–1.93	0.71	0.55	0.23–2.18
Intraregional margin	2.22	0.29	0.49–9.88	0.55	0.29	0.17–1.69
Wide-margin resection group						
Tumor size	1.1	0.0006	1.04–1.16	1.13	0.009	1.05–1.2
Age	1	0.46	0.98–1.02	1	0.58	0.98–1
Sex	0.6	0.17	0.28–1.25	0.98	0.97	0.43–2.2
Recurrence cases	1.97	0.21	0.68–5.64	9.25	0.0001	3.54–24.2
AJCC IV	12.7	0.0001	5.9–27.4	2.37	0.16	0.69–8.1
BTx versus RTx	0.58	0.21	0.24–1.36	0.9	0.82	0.36–2.22

CI = confidence interval; AJCC = American Joint Committee on Cancer staging; AO-RDT = radiodynamic therapy with acridine orange; BTx = brachytherapy; RTx = radiation therapy.

Table 4. Local recurrence percentages in histological subtypes in acridine orange therapy

Histological diagnosis	Local recurrence cases (%)
Acridine orange therapy (n = 51)	
Synovial sarcoma	0/9 (0%)
MFH	3/8 (38%)
Rhabdomyosarcoma	1/7 (14%)
Leiomyosarcoma	3/6 (50%)
Extraskeletal myxoid chondrosarcoma	2/4 (50%)
PNET	1/4 (25%)
Fibrosarcoma	1/4 (25%)
Liposarcoma	1/4 (25%)
Other	1/5 (20%)

MFH = malignant fibrous histiocytoma; PNET = primitive neuroectodermal tumor.

[11, 14, 35, 46]. If the surgical margin can be reduced without local recurrence, postsurgical limb function can be maintained. To reduce the surgical margin, we have developed a therapeutic approach involving the use of acridine orange therapy [18–20, 26–28, 32, 47]. We therefore examined the survival, local recurrence, and limb function outcomes in patients treated with a less radical surgical approach and adjunctive acridine orange therapy compared with those who underwent a conventional wide-margin resection.

Our study had a number of limitations. First, because the present trial was not a randomized study comparing acridine orange therapy and wide-margin resection surgery, these therapies were difficult to compare strictly. However, the number of patients was reasonably large, and the distribution of AJCC stages, tumor sizes, and histological subtypes was similar within each group. Furthermore, a poorer survival and a larger number of local recurrences would be expected in the group with a marginal resection if the adjunctive acridine orange therapy was ineffective, yet we did not find this to be the case. Second, in the conventional wide-margin group, a large number of patients received postoperative radiation, presumably lowering the risk of local recurrence. Because positive-margin status after surgery is a risk factor for local recurrence [11, 15, 36, 41, 48], we used postoperative radiation therapy or brachytherapy in the wide-margin resection group if the surgical margin was positive or nearly positive. However, the long-term effects of radiation therapy (those effects occurring more than 1 year after the completion of therapy) generally involve fibrosis, necrosis, edema, fractures, and contractures, all of which can substantially impair limb function. Although postoperative radiation therapy in the wide-margin resection group would likely cause dysfunction because of long-term radiation effects, whether postoperative radiation therapy in the wide-margin resection group promoted better local tumor control or survival could not be decided based on the present study because the results of the two groups were not different with regard to local control or survival with the exception of limb function. Furthermore, acridine orange therapy was used in tumors that were in contact with major vessels, requiring

conventional radiation therapy for a wide-margin resection. Third, for the acridine orange therapy group, we selected patients whose tumors were in contact with major nerves or vessels. The surgical margin of tumors in contact with major nerves or vessels tended to be closer to enable the preservation of the nerves or vessels; to avoid the risk associated with closer margins, preoperative chemotherapy was more frequently performed in the acridine orange group than in the wide-margin resection group (Table 2). Although the invasion of blood vessels by soft tissue sarcomas is a risk factor for a poor prognosis, chemotherapy for soft tissue sarcomas can improve the outcome [25]. On the other hand, the percentage of patients with AJCC Stage IV in the acridine orange therapy group (25%) was higher than that in the wide-margin resection group (12%) (Table 1). For these advanced tumors, preoperative chemotherapy tended to be performed more frequently. If the adjunctive acridine orange therapy for these aggressive AJCC Stage IV tumors had been ineffective, a poorer survival and a larger number of local recurrences would have been expected. Furthermore, because of the criteria used as indicators for acridine orange therapy, rhabdomyosarcomas, synovial sarcomas, PNETs, or tumors that are commonly located in contact with major joints, nerves, or vessels and that occur in young patients tend to be selected for acridine orange therapy. Although these tumors in contact with critical structures are associated with a risk of local recurrence because of the relatively close margin, these tumors included so-called "chemosensitive tumors" such as rhabdomyosarcoma or PNET. Although chemotherapy for soft tissue sarcomas can improve the survival or local recurrence outcomes, such advanced tumors requiring chemotherapy were more frequently selected to undergo acridine orange therapy. The important point of this comparison study is to show similarity between the two groups in terms of the overall survival and local recurrence outcomes.

We found similar overall survival and local recurrence periods in the acridine orange therapy group and the wide-margin resection group. The 10-year overall survival rate for the acridine orange therapy group and the wide-margin resection groups were 68% and 63%, respectively, and the 10-year local recurrence rate was 29% for each group. The overall 5-year survival rates in a large series of patients with high-grade soft tissue sarcomas of the limb or trunk reportedly range from 66% to 76% (Table 5) [9, 33, 36, 41]. Therefore, the clinical results for acridine orange therapy are comparable to those for wide-margin resection.

Perhaps more importantly, patients with microscopically positive surgical margins have an increased risk of local recurrence. Indeed, the margin status after surgical resection is an independent prognostic factor for local recurrence [11, 15, 36, 41, 48]. Regarding the surgical margin, although clinical judgment and interpretation of the MRI findings identify an apparent tumor margin, the judgments are obviously subjective. If MR images could detect a single or small number of tumor cells, the resection of tumors with a safe or adequate surgical margin would be easy. However, surgeons must decide on the surgical margins based on MRI or other imaging findings that cannot detect a single cell, relying instead on their experience and the available evidence. Determining appropriate

Table 5. Significant prognostic factors for survival in patients with soft tissue sarcoma from large series

Author/institution	Number	Population characteristics	Overall survival	Prognostic factors for poor survival
Pisters et al/MSKCC [35]	1041	Soft tissue sarcoma, limb	76% (5-year)	Size > 10 cm
				High grade
				Deep location
				Histological subtype: leiomyosarcoma, malignant peripheral nerve sheath tumor
				Positive surgical margin
Gustafson/SSG [9]	508	Soft tissue sarcoma, limb or trunk	66% (5-year)	Size > 10 cm
				High grade
				Deep location
				Tumor vascular invasion
Trovik et al/SSG [41]	559	Soft tissue sarcoma, limb or trunk	72% (5-year)	Size > 7 cm
				High grade
Parsons et al/SEER [33]	6215	Soft tissue sarcoma, limb (nonmetastatic)	75.6% (10-year)	Size > 5 cm
				High grade
				Histological subtype: leiomyosarcoma

MSKCC = Memorial Sloan-Kettering Cancer Center; SSG = Scandinavian Sarcoma Group; SEER = public-use release of the Surveillance, Epidemiology, and End Results tumor registry.

safety margins can be difficult. Although we selected patients whose tumors did not exhibit "invasiveness" or "nonmassive invasiveness" on preoperative MR images, these terms do not necessarily imply that they are less aggressive. Furthermore, in our comparison of acridine orange therapy and wide-margin resection surgery, we found no difference in the overall survival or local recurrence despite the different surgical margins used in the two groups. One explanation for this finding is that acridine orange therapy has the advantage of making the tumor cells visible during surgery. Even if the tumor cannot be visualized because of its small size or deep-seated nature, the tumor cells can subsequently be killed using low-dose radiation therapy with acridine orange. Still, the preoperative judgment of surgical margins is not as perfect as the surgeons may believe, and the surgical margins for musculoskeletal tumors sometimes result in a partial intralesional or marginal margin. So, these advantages in acridine orange therapy and the results of this study indicate that acridine orange therapy is useful for local control after a closer margin or positive margin tumor resection and for preserving limb function in patients with high-grade soft tissue sarcomas.

Variables associated with poor long-term function after radiation therapy include large tumors, high-dose radiation, long radiation fields, and wound complications [39, 46]. In the acridine orange therapy group, we performed acridine orange radiodynamic therapy after surgery in 34 patients, but no complications requiring surgical intervention occurred [3]. Acridine orange radiodynamic therapy is a unique technique that has the potential to be useful as a high-dose radiation therapy without adverse complications. X-ray energy can excite acridine orange like a visible beam, and tumor cells exposed to acridine orange are killed even if they are deeply seated [10]. X-ray energy is accelerated by acridine orange in a manner such that low-dose radiation has an effect similar to that of high-dose radiation without the associated complications. Consequently, limb function can often be preserved in patients who receive acridine orange therapy.

Survival and local recurrence are affected by the tumor subtype and AJCC stage, as many previous articles have mentioned. Gustafson [9] suggested that a diagnosis of synovial sarcoma was a risk factor for reduced survival, but acridine orange therapy produced good local control and survival rates for patients with synovial sarcoma or rhabdomyosarcomas. Consequently, if acridine orange therapy is further refined and basic studies involving large numbers of patients are performed, this therapy could became an effective treatment for soft tissue sarcomas.

Our data suggest that acridine orange therapy may be useful for local control after reduction surgery in patients with soft tissue sarcoma compared with a conventional wide-margin resection. Even if the surgical margin is positive, acridine orange therapy can control local recurrence as conventional wide-margin resection. A less radical approach in combination with adjunctive acridine orange therapy can provide comparable survival, local recurrence, and limb function to a conventional wide-margin resection. Thanks to the preservation of normal tissue, better limb function can also be anticipated after acridine orange therapy compared with after a wide-margin resection.

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SHORT COMMUNICATION

Day zero ambulation under modified femoral nerve block after minimally invasive surgery for total knee arthroplasty: preliminary report

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Abstract Ambulation in the early postoperative period of total knee arthroplasty is crucial, in order to avoid complications and obtain preferable outcomes. Although a femoral nerve block can provide enough postoperative analgesia after total knee arthroplasty, falling, or other accidents due to motor paresis, are potentially adverse events in patients who have received a conventional femoral nerve block. We devised a modified femoral nerve block to spare voluntary knee extension ability, and clinically applied it to patients who received total knee arthroplasty under minimally invasive surgery. In our new-approach nerve blockade technique, the main targets of the sensory nerves are the saphenous nerves which branch out from the femoral nerve trunk. All the patients rated pain at bed rest between 0 and 3 on a numerical rating scale 3 h after the operation. In addition, the rectus femoris muscle was not affected at all, and the surgically invaded vastus medialis oblique muscle was completely anesthetized. Patients were able to not only actively raise their extremities with their knee in extension, but also to flex the knee in the air without pain or aggravation. On day 0, the patients were able to walk around, with the leg that had been operated upon not giving way. Our anesthetic approach can provide better pain relief than a conventional femoral nerve block, while the patients achieve ambulation on the day of the procedure, following minimally invasive knee surgery.

Keywords Total knee arthroplasty · Femoral nerve block · Early ambulation · Ultrasound-guided nerve block

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Early postoperative ambulation after knee surgery is important to obtain clinically preferable outcomes [1]. Whereas minimally invasive total knee arthroplasty (TKA) enables early ambulation and rehabilitation after surgery, conventional postoperative analgesia with regional blocks such as lumbar epidural analgesia and femoral nerve blocks may disturb weight-bearing ambulation in the early postoperative period. In addition, TKA belongs to the highest risk group of procedures for deep venous thrombosis (DVT), along with other various postoperative complications [2]. Therefore, ambulation in the early postoperative period after TKA is especially important. We preserve motor function for early weight-bearing ambulation after minimally invasive surgery (MIS)-TKA by the use of a modified femoral nerve block (mFNB), which does not block major knee extensors, unlike the standard femoral nerve block.

After approval was granted by the institutional ethics committee of Mie University (Mie, Japan), we enrolled 25 patients with osteoarthritis and rheumatoid arthritis who were to receive a primary unilateral cemented TKA (Columbus total knee system; Aesculap, 78532 Tuttlingen, Germany) under MIS (via a mid-vastus approach), performed using a navigation system (Orthopilot navigation system 4.2 Version; Aesculap). We obtained written informed consent for the procedure from each patient.

General anesthesia was induced with propofol 1 mg/kg, rocuronium (0.6 mg/kg), and remifentanil (0.5 μg/kg/min) and it was maintained with propofol target-controlled infusion (2.0–2.5 μg/ml) and remifentanil (0.15–0.2 μg/kg/min) within 50–60 on the bispectral index without additional rocuronium. The patients had an intraoperative air tourniquet at the pressure of 300 mmHg applied. Immediately after the surgery, a 38-mm broadband (13–6 MHz) linear array transducer (HFL38x; Sonosite, Bothell, WA, USA) coupled to a portable ultrasound machine (M-turbo®; Sonosite) was placed perpendicular to the neurovascular bundle in the apex of the femoral triangle where the sartorius muscle overlaps the superficial femoral artery, and the mFNB was conducted by an in-plane technique with a needle guidance system. An 18-G BIBraun contiplex® Tuohy needle (BIBraun Aesculap Japan, Tokyo, Japan), 10 cm in length, was set into the needle guide and attached to the transducer with its exclusive fixator (CIVCO Infiniti™ Needle Guidance System IA; USA).

As it is sometimes impossible to discern the femoral nerve from other structures at this level, contraction of the vastus medialis oblique (VMO) only should be a prerequisite at this time (Fig. 1). Muscle contraction of the VMO was detected by manual pulsation, using stimuli of 0.4–0.6 mA (BIBraun Stimuplex® HNS 12, Melsungen, Germany) [3, 4]. In total, 20 ml of 0.75 % ropivacaine was injected around the neural structure. During ropivacaine injection, the spot just proximal to the injection site was compressed by the thumb of the assistant so that local anesthetics did not flow proximalward.

Four of our patients were men and 21, women, with a mean (SD) age of 74 (6) years, height of 151 (8) cm, and weight of 62 (11) kg. The mean (SD) duration of surgery was 155 (30) min. All patients were able to raise their operated leg, straighten it, and actively flex and extend the knee immediately after emerging from general anesthesia. In the recovery room 3 h after the surgery, pain at rest was rated from 0 to 3 on a numerical rating scale (0 = no pain and 10 = worst pain imaginable). The patients were also able to stand on the operated extremity alone. Hence, without adjuvant analgesics, they were able to walk around independently, or with the slight assist of a walking frame,

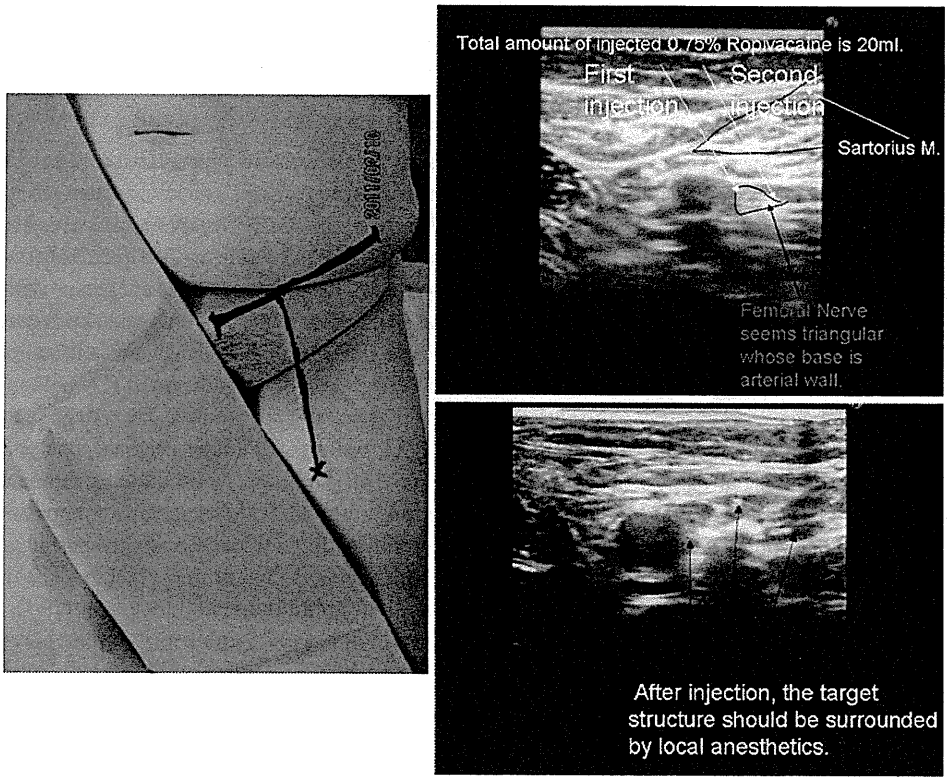

Fig. 1 In this very obese female, the femoral crease where a conventional femoral block is preferably performed is far away from the inguinal band, which is an important anatomical landmark. The '*X*' mark is where the block is performed. The *oblique line* to the inguinal crease is the one drawn between the pubic tubercle and the anterior superior iliac spine. The *line almost vertical* to the crease is in line with the femoral nerve trunk. The femoral nerve seems triangular, with its base being the arterial wall. *White arrows* indicate the injection site. First, local anesthetic was injected between the artery and the base of the triangular structure. Second, the remaining anesthetic was injected around the apex of the structure. After the injection, the target structure should be surrounded by local anesthetic and the femoral nerve fibers should appear bloated and dispersed. *M* muscle

and without knee braces. During ambulation, the patients displayed respiratory and hemodynamic stability, and did not complain of severe pain. Ambulation did not increase drainage bleeding.

There are some reports that early postoperative ambulation in TKA patients prevents locomotive complications and the formation of DVT [5, 6]. Therefore, retaining the practical motor function of the lower extremities immediately after surgery through proper anesthetic management is crucial.

MIS in TKA encourages early rehabilitation. However, conventional regional anesthetic techniques result in motor paralysis, which will sometimes lead to the knee giving way, or the patient falling immediately after surgery [7]. Hence, our anesthetic management is of significance for this surgery.

One of the important clinical assessments used for a decision on when to start weight-bearing ambulation is whether or not the patient can elevate the operated leg with no extension lag [8]. Among the quadriceps muscles, the rectus femoris is the muscle which contributes the most to knee extension. The motor branch of the rectus femoris branches out about 2 fingerwidths below the inguinal ligament from the femoral nerve trunk. It is not anesthetized in our method, due to there being "no patellar motor response" to stimuli [9]. The main targets of our nerve blockade technique are the motor branches of the VMO and the saphenous nerve. The motor branches of the VMO diverge distal to the other motor branches. Then, with continuous electrical stimuli at this point, the VMO contracts alone; namely, this is "a medial motor response" to stimuli. In the mini mid-vastus approach, the distal part of the muscle belly of the VMO is split in line with the fibers. Therefore, blocking the motor branches of the VMO alleviates ascending myogenic pain from the surgically invaded VMO, especially in knee flexion, whether this is voluntary or involuntary. Blocking the saphenous nerves also alleviates the pain of operatively invaded skin and soft tissues. Unlike the standard femoral nerve block, with our technique, abdominal subcutaneous fat does not interfere with the procedure during the process. Compared with the standard femoral nerve block, however, our mFNB was inferior in revision TKA, as the revision procedure usually requires extended proximal skin incision or surgical invasion to the rectus femoris tendon.

In the present study, we performed the mFNB procedure after the surgery to facilitate immediate rehabilitation by alleviating postoperative pain. For the future, we are considering the use of preoperative tubing for the mFNB procedure, although there are some obstacles to overcome, such as the unveiled anatomy of the adductor canal, and the non-rigid connective tissue of the thigh, which makes catheter placement unstable and unpredictable.

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BRIEF REPORT

Clinical outcome in patients with rheumatoid arthritis switched to tocilizumab after etanercept or infliximab failure

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Abstract The present study retrospectively assessed the efficacy of tocilizumab in patients with rheumatoid arthritis (RA) who failed to respond to treatment with etanercept or infliximab. A retrospective study of 33 RA patients who did not respond to etanercept or infliximab was conducted. Responses of subjects switching from etanercept to tocilizumab (n=17) were compared with those switching from infliximab to tocilizumab (n=16). Treatment with disease-modifying antirheumatic drugs before the switch, especially methotrexate (MTX), was maintained. Disease activity was assessed by the Disease Activity Score 28-C Reactive Protein (DAS28-CRP), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). Patients who switched from etanercept were significantly less likely to have used MTX and were significantly older than patients who switched from infliximab. In both groups, there was a significant reduction from baseline in DAS28-CRP, SDAI, and CDAI values at 24 weeks with no significant differences between groups. However, at week 52, DAS28-CRP, SDAI, and CDAI values in the group switched from etanercept were significantly worse than those in the group switched from infliximab. All patients switched from infliximab were using MTX. In the evaluation between patients who switched from etanercept monotherapy, etanercept plus MTX, and infliximab plus MTX, a significant improvement from baseline was seen in DAS28-CRP, SDAI, and CDAI for all patients at 24 weeks with no significant differences between groups. Disease activity was maintained at 52 weeks in the group that switched from etanercept plus MTX and infliximab plus MTX. However, the efficacy of tocilizumab was decreased in the group that switched from etanercept monotherapy. Switching from etanercept plus MTX or from infliximab plus MTX to tocilizumab plus MTX improved response to therapy, but switching from etanercept monotherapy to tocilizumab monotherapy did not improve response to therapy.

Keywords Etanercept · Interleukins-6 · Infliximab · Rheumatoid arthritis · Tocilizumab · Tumor necrosis factor inhibitors

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Introduction

Tumor necrosis factor-α (TNF-α) inhibitors are remarkably effective in the treatment of rheumatoid arthritis (RA) [1–4]. These drugs changed the treatment goal for RA to include not only the inhibition of joint destruction but also the induction of remission [5]. However, responses are insufficient in 20–40 % of patients with RA.

Some patients who experience treatment failure with their TNF-α inhibitor may benefit from a therapeutic switch to another TNF-α inhibitor [6–8]. Virkki et al. [9] reported that, among patients who switched from TNF-α inhibitor therapy due to lack of efficacy, switching to another TNF-α inhibitor may be most beneficial among those who experienced a secondary lack of efficacy with the initial agent (i.e., loss of clinical response after initially demonstrating a

clinical response). However, switching from etanercept to adalimumab maintained, but did not improve, the response achieved before the switch.

The European League Against Rheumatism recommendations state that patients who do not respond to an initial TNF-α inhibitor should receive a different TNF-α inhibitor or a different class of biologic agent (abatacept, rituximab, or tocilizumab) [10]. Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, was the first biologic agent of a different class approved in Japan.

The present study adds to the existing data by comparing the response of RA patients who showed lack of efficacy to either etanercept or infliximab and switched to treatment with tocilizumab. It also assesses differences among patients who did or did not receive methotrexate (MTX) as part of their treatment regimen.

Patients and methods

All patients commencing tocilizumab therapy for RA at our institution from April 2008 to March 2011 were reviewed retrospectively. All patients fulfilled the 1987 American College of Rheumatology criteria for RA. Patients with a history of treatment failure due to loss of efficacy with previous etanercept or infliximab treatment were eligible for inclusion. Patients who fulfilled any of the contraindications or precautions for tocilizumab were excluded. All patients provided written, informed consent, and the local ethics committee approved the study.

Study design

During recruitment, patients in the tocilizumab group started infusions of 8 mg/kg (body weight) of tocilizumab every 4 weeks for 52 weeks. Treatment with disease-modifying antirheumatic drugs (DMARDs) before the switch, especially MTX, was maintained.

Efficacy assessments

Baseline clinical efficacy assessments are shown in Table 1. Disease activity was assessed by the same rheumatologist at baseline (time of the switch) and 24 and 52 weeks later. Clinical responses to therapy were evaluated using the Disease Activity Score 28-C Reactive Protein (DAS28-CRP; high disease activity, >4.1; moderate disease activity, >2.7 to ≤4.1; low disease activity, ≤2.7; remission, <2.3) [11]; the Simplified Disease Activity Index (SDAI; high disease activity, >26; moderate disease activity, >11 to ≤26; low disease activity, ≤11; remission, <3.3); and the Clinical Disease Activity Index (CDAI; high disease activity, >22; moderate disease activity, >10 to ≤22; low disease activity, ≤10; remission, <2.8) [12]. The last observation carried forward (LOCF) was applied when patients discontinued treatment or when data were unavailable.

Safety assessments

Safety assessments included physical examinations, pre- and post-dose electrocardiograms, and laboratory analyses

Table 1 Baseline characteristics of patients

Previous treatment	IFX (n=16)	ETN (n=17)	p value
Sex (female n, %)	14 (88)	12 (71)	0.2350
Age (years)	53.9±13.4	65.6±7.2	0.0028*
Disease duration (years)	6.8±7.4	8.1±4.9	0.1585
Stage (I/II/III/IV)	0/4/10/2	0/1/13/3	0.3068
Class (1/2/3/4)	0/12/4/0	0/12/5/0	0.7761
Concomitant MTX (n, %)	16 (100)	7(41.2)	0.0002**
Mean dosage of MTX (mg/week)	6.0±1.5	2.5±3.1	0.0146*
Concomitant PSL (n, %)	15 (93.8)	17 (100)	0.2952
Mean dosage of PSL (mg/day)	5.6±1.7	4.9±1.1	0.0893
Tender joint count	6.3±6.5	6.3±7.0	0.9278
Swollen joint count	7.6±7.0	4.1±3.2	0.2117
ESR (mm/h)	39.4±27.4	59.4±27.2	0.0417*
CRP (mg/dl)	2.2±3.2	4.5±3.8	0.0105*
Patient global assessment	56.1±28.2	73.6±23.8	0.0584
Physician global assessment	45.1±21.4	39.8±15.5	0.4930
DAS28-CRP	4.5±1.6	5.0±1.3	0.2345
SDAI	26.2±18.2	26.2±14.4	0.4177
CDAI	24.0±16.5	21.7±11.3	0.9139

Data are expressed as mean±SD. p value between previous treatment with ETN and IFX

ETN the group that switched from etanercept, *IFX* the group that switched from infliximab, *MTX* methotrexate, *PSL* prednisolone, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28-CRP* Disease Activity Score 28-C Reactive Protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index

*p<0.05 by Wilcoxon rank sum test; **p<0.05 by Pearson's test

of hematology, serum biochemistry, coagulation, immunologic parameters, and urine. Adverse events were recorded throughout the study.

Statistical analysis

Differences between groups in terms of swollen and tender joint counts, patient global assessment, physician global assessment, erythrocyte sedimentation rate (ESR), CRP, DAS28-CRP, SDAI, and CDAI scores were assessed using the Wilcoxon signed rank test, Wilcoxon rank sum test, analysis of variance, Pearson's test, or Tukey–Kramer's honestly significant difference (HSD) test. The LOCF was applied when patients discontinued treatment or when data were unavailable. A P value less than 0.05 was considered statistically significant.

Results

Patients' characteristics

Seventeen patients who switched from etanercept to tocilizumab were compared with 16 patients who switched from infliximab. All patients had experienced a secondary loss of efficacy (i.e., loss of clinical response after initially demonstrating a clinical response). Baseline characteristics revealed that patients in the group switched from etanercept were significantly older and had significantly increased ESR and CRP values compared with patients in the group switched from infliximab. However, disease activity as assessed by DAS28, SDAI, and CDAI was not significantly different between groups. The percentage of patients using MTX and the mean dosage of MTX were significantly lower in the group switched from etanercept than in the group switched from infliximab. All patients who switched from infliximab were receiving MTX. Thus, we compared patients who switched from etanercept monotherapy group (without MTX), the etanercept plus MTX group and the infliximab (plus MTX) group. Of the ten patients not receiving MTX in the etanercept monotherapy group, five had experienced GI symptoms, three had experienced liver dysfunction, one had experienced an allergy, and one had experienced interstitial pneumonia during previous treatment with MTX. MTX was discontinued and other DMARDs or etanercept therapy was maintained. Baseline characteristics revealed that patients who switched from infliximab were significantly younger than patients who switched from etanercept monotherapy. The mean dosage of MTX was almost the same between

Table 2 Baseline characteristics of patients

Previous treatment	IFX (MTX+) (n=16)	ETN (MTX−) (n=10)	ENT (MTX+) (n=7)	p value
Sex (female, n, %)	14 (88)	6 (60)	6 (86)	0.2187
Age (years)	53.9±13.4	68.7±6.4	61.1±6.0	0.0055*
Disease duration (years)	6.8±7.4	7.7±5.6	8.6±4.0	0.8132
Stage (I/II/III/IV)	0/4/10/2	0/1/9/0	0/0/4/3	0.0824
Class (1/2/3/4)	0/12/4/0	0/9/1/0	0/3/4/0	0.0956
Concomitant MTX (n, %)	16 (100)	0 (0)	7 (100)	<0.0001**
Average dosage of MTX (mg/week)	6.0±1.5	0.0±0.0	6.0±1.2	<0.0001*
Concomitant PSL (n, %)	15 (93.8)	10 (100)	7 (100)	0.5782
Mean dosage of PSL (mg/day)	5.6±1.7	4.9±1.4	4.9±0.4	0.4297
Tender joint count	6.3±6.5	7.7±8.7	4.3±3.0	0.5968
Swollen joint count	7.6±7.0	3.7±3.2	4.6±3.2	0.1923
ESR (mm/h)	39.4±27.4	61.3±30.1	56.6±24.3	0.1285
CRP (mg/dl)	2.2±3.2	5.1±4.4	3.7±2.7	0.1378
Patient global assessment	56.1±28.2	76.6±20.4	69.4±29.1	0.1534
Physician global assessment	45.1±21.4	39.2±17.3	40.7±13.7	0.7164
DAS28-CRP	4.5±1.6	5.1±1.6	4.8±1.0	0.6238
SDAI	26.2±18.2	28.1±17.1	23.6±10.0	0.8603
CDAI	24.0±16.5	23.0±13.4	20.0±8.1	0.8158

Data are expressed as mean±SD. p value between previous treatment with ETN (MTX−), ETN (MTX+) and IFX (MTX+). Age: ETN (MTX−) vs. IFX (MTX+), p=0.0040 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX−) vs. ETN (MTX+), p=0.3197; ETN (MTX+) vs. IFX (MTX+), p=0.2945; average dosage of MTX: ETN (MTX−) vs. IFX (MTX+), p<0.0001 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX−) vs. ETN (MTX+), p<0.0001 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX+) vs. IFX (MTX+), p=1.0000

ETN (MTX−) the group that switched from etanercept monotherapy, *ETN (MTX+)* the group that switched from etanercept plus methotrexate, *IFX (MTX+)* the group that switched from infliximab plus MTX

*p<0.05 by ANOVA; **p<0.05 by Pearson's chi-square test

subjects who switched from etanercept plus MTX and subjects who switched from infliximab (Table 2). In addition, the percentage of patients using prednisolone and the mean dosage of prednisolone did not differ significantly among groups (Tables 1 and 2).

Clinical assessments

Fifteen patients completed 52 weeks of tocilizumab treatment after switching from etanercept (88.2 %) or infliximab (94.1 %). In the group that switched from etanercept, two patients discontinued treatment because of lack of efficacy. Neither patient was able to take MTX due to adverse events experienced when MTX was added to their former treatment. In the group that switched from infliximab, one patient discontinued treatment because of an adverse event (heart failure).

Following the switch from infliximab to tocilizumab, a significant improvement from baseline was seen in DAS28-CRP, SDAI, and CDAI for the entire study population at 24 and 52 weeks. Following the switch from etanercept to tocilizumab, a significant improvement from baseline was seen in DAS28-CRP, SDAI, and CDAI for the entire study population at 24 weeks. In the group that switched from etanercept, there was a significant reduction from baseline in DAS28-CRP and SDAI, but no significant reduction in CDAI values (p=0.0008, 0.011, and 0.052, respectively) at 52 weeks. There was a significant increase in DAS28-CRP, SDAI, and CDAI values in the group that switched from infliximab

Table 3 Clinical assessments of tocilizumab therapy

		BL	24W	p value vs. BL	52W	p value vs. BL
Clinical assessments of tocilizumab therapy among subjects who switched from etanercept or infliximab						
DAS28-CRP	ETN	5.0±1.3	3.0±1.5	<0.0001**	3.5±1.3	0.0008**
	IFX	4.5±1.6	2.6±0.7	<0.0001**	2.7±0.7	<0.0001**
	p value ETN vs. IFX	0.2345	0.4936	–	0.0158*	–
SDAI	ETN	26.2±14.4	13.5±12.5	0.0007**	17.2± 9.2	0.0110**
	IFX	26.2±18.2	9.3±5.5	<0.0001**	9.2 ± 4.8	0.0002**
	p value ETN vs. IFX	0.4177	0.4493	–	0.0335*	–
CDAI	ETN	21.7±11.3	12.5±9.7	0.0032**	16.0±10.3	0.0520
	IFX	24.0±16.5	9.1±5.4	<0.0001**	8.9±4.6	0.0003**
	p value ETN vs. IFX	0.9139	0.4601	–	0.0265*	–
Clinical assessments of tocilizumab therapy in the group that switched from etanercept monotherapy, etanercept plus methotrexate group, and infliximab plus MTX group						
DAS28-CRP	ETN MTX−	5.1±1.6	3.1±1.9	0.0078****	3.9±1.5	0.0547
	ETN MTX+	4.8±1.0	2.8±0.6	0.0156****	3.0±0.6	0.0156****
	IFX MTX+	4.5±1.6	2.6±0.7	<0.0001****	2.7±0.7	<0.0001****
	p value	0.6238	0.6080	–	0.0139***	–
SDAI	ETN MTX−	28.1±17.1	14.7±16.2	0.0273****	20.6±15.1	0.2324
	ETN MTX+	23.6±10.0	11.8±4.6	0.0313****	12.2±5.7	0.0156****
	IFX MTX+	26.2±18.2	9.3±5.5	<0.0001****	9.2±4.8	0.0002****
	p value	0.8603	0.4014	–	0.0158***	–
CDAI	ETN MTX−	23.0±13.4	13.0±12.4	0.0488****	18.6±12.2	0.6426
	ETN MTX+	20.2±8.1	11.8±4.6	0.0313****	12.2±5.7	0.0156****
	IFX MTX+	24.0±16.5	9.1±5.4	<0.0001****	8.9±4.6	0.0003****
	p value	0.8158	0.4695	–	0.0161***	–

DAS28-CRP at 52 weeks: ETN (MTX−) vs. IFX (MTX+), p=0.0109 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX−) vs. ETN (MTX+), p=0.1418; ETN (MTX+) vs. IFX (MTX+), p=0.7952; SDAI at 52 weeks: ETN (MTX−) vs. IFX (MTX+), p=0.0121 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX−) vs. ETN (MTX+), p=0.1733; ETN (MTX+) vs. IFX (MTX+), p=0.7485; CDAI at 52 weeks: ETN (MTX−) vs. IFX (MTX+), p=0.0119 (p<0.05 by Tukey–Kramer's HSD test); ETN (MTX−) vs. ETN (MTX+), p=0.2348; ETN (MTX+) vs. IFX (MTX+), p=0.6262

BL baseline, *ETN* the group that switched from etanercept, *IFX* the group that switched from infliximab, *DAS28-CRP* Disease Activity Score 28-C Reactive Protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *ETN MTX−* the group that switched from etanercept monotherapy, *ETN MTX+* the group that switched from etanercept plus MTX, *IFX MTX+* the group that switched from infliximab plus MTX, *MTX* methotrexate

*p<0.05 by Wilcoxon rank sum test (ETN vs. IFX); **p<0.05 by Wilcoxon signed rank test (vs. baseline); ***p<0.05 by ANOVA; ****p<0.05 by Wilcoxon signed rank test

compared with the group that switched from etanercept at 52 weeks (p=0.0158, 0.0335, and 0.0265, respectively) (Table 3).

Next, we compared patients who switched from etanercept monotherapy (without MTX) with the etanercept plus MTX group and the infliximab (plus MTX) group. For all groups, a significant improvement from baseline was seen in DAS28-CRP, SDAI, and CDAI values for the entire study population at 24 weeks with no significant differences between groups (Table 3). Disease activity was maintained at 52 weeks in the group that switched from etanercept plus MTX and the group that switched infliximab plus MTX. However, the efficacy of tocilizumab was decreased in the group that switched from etanercept monotherapy at 52 weeks. In addition, the disease activity of the group that switched from etanercept monotherapy at 52 weeks was significantly higher than that in the group that switched from infliximab plus MTX therapy.

In the group that switched from infliximab plus MTX group, the percentage of patients who achieved clinical remission and low disease activity defined by DAS28-CRP, SDAI, and CDAI were 56.3–68.8 % at 24 weeks and 62.5 % at 52 weeks. Those percentages in the group that switched from etanercept plus MTX were 57.1 % at 24 weeks but decreased to 28.6–42.9 % at 52 weeks. Percentages in the group that switched from etanercept monotherapy were lower at 52 weeks (20 %) compared with 24 weeks (50–60 %) (Fig. 1a–c).

Safety

After tocilizumab therapy was started, two adverse events occurred in the group that switched from etanercept: palpitations and pharyngitis. Five adverse events occurred in the group that switched from infliximab: heart failure, common cold, urinary tract infection, diarrhea, and stomatitis. One patient with heart failure withdrew from tocilizumab therapy. During tocilizumab therapy, the incidence of adverse events was 11.8 % (two of 17 patients) in the group that switched from etanercept and 31.3 % (five of 16 patients) in the group that switched from infliximab. The group that switched from infliximab tended to experience more adverse events, but differences were not significant.

Abnormal laboratory profiles (increased cholesterol, liver disorder, decreased leukocyte count) occurred in 13 patients in both groups. None of the abnormalities required treatment.

Discussion

Biological agents targeting TNF-α have been shown to be effective in the treatment of RA. Nevertheless, approximately one third of patients discontinue TNF-α treatment due to

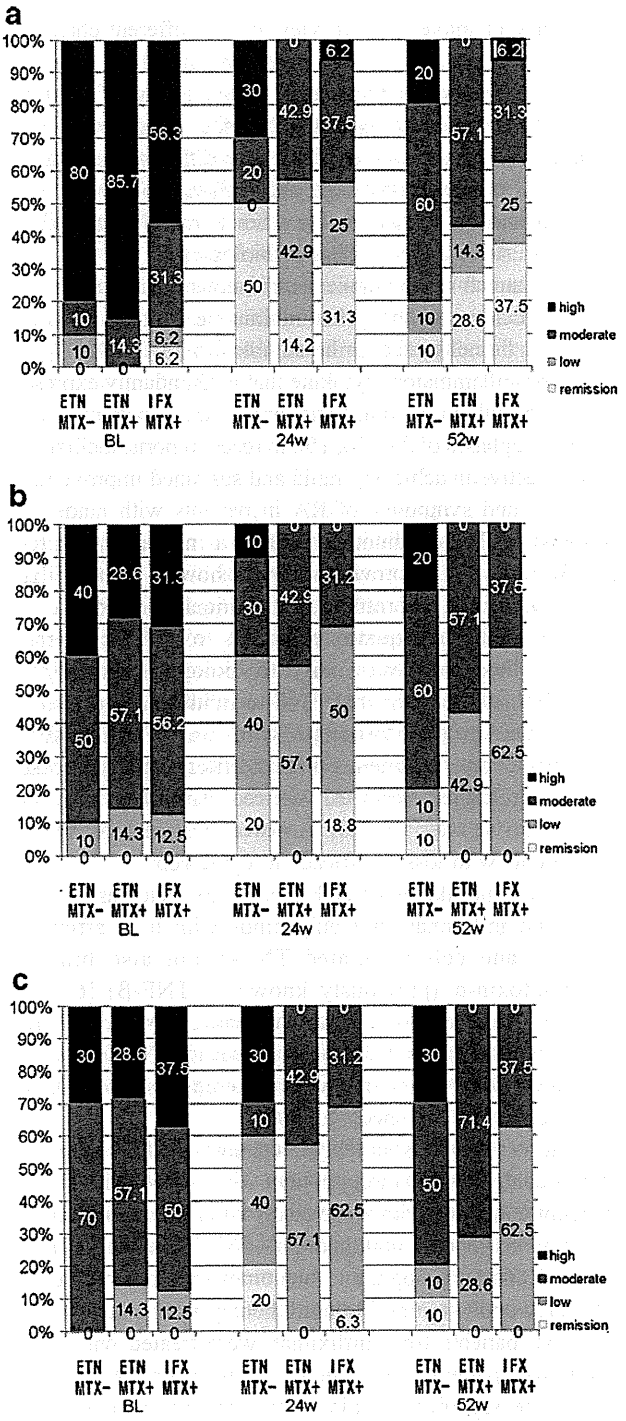

Fig. 1 Incidence of disease activity with tocilizumab therapy in subjects that switched from etanercept monotherapy, etanercept plus methotrexate (MTX), and infliximab plus MTX (**a** DAS28-CRP, **b** SDAI, **c** CDAI). *BL* baseline, *DAS28-CRP* Disease Activity Score 28-C Reactive Protein, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *ETN MTX−* the group that switched from etanercept monotherapy, *ETN MTX+* the group that switched from etanercept plus MTX, *IFX MTX+* the group that switched from infliximab plus MTX group

inefficacy or intolerance. In view of the different characteristics of the available TNF-α inhibitors, switching from one TNF-α inhibitor to another may be helpful in case of treatment failure with the initial agent. On the other hand, several new biological drugs are now available with different mechanisms of action (rituximab, abatacept, and tocilizumab). Hyrich et al. reported that the best alternative when a first TNF-α inhibitor fails is to start a different class of biologic [7].

Tocilizumab is a humanized anti-human IL-6 receptor (IL-6R) monoclonal antibody that inhibits the binding of IL-6 to IL-6R on the cell surface or the soluble form of IL-6R [13]. IL-6 is a proinflammatory cytokine that is abundantly expressed and detectable in the joints and circulation of patients during the active phases of RA [14, 15]. In recent reports, tocilizumab was effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF-α inhibitors and had a manageable safety profile [16, 17]. A previous report showed that tocilizumab was safe, tolerable, and clinically effective for patients with inadequate responses to TNF-α therapy and for those who were naïve to biologic therapy [18].

Infliximab was the first TNF-α inhibitor approved in Japan. One problem associated with use of infliximab in therapeutic drug regimens is that its efficacy often decreases during prolonged treatment, whereas etanercept has good drug survival rates [19, 20]. However, treatment is difficult in patients with loss of efficacy to etanercept.

Etanercept, like other TNF-α inhibitors such as adalimumab and infliximab, not only binds with high affinity to soluble and cell-associated TNF-α but also binds to lymphotoxin-α (previously known as TNF-β) [6]. It is possible that loss of efficacy in patients switched from etanercept to tocilizumab occurs because TNF-β may be activated when treatment with etanercept is stopped, and disease activity may become worse.

Another reason is that the percentage of MTX usage was significantly lower among patients who switched from etanercept compared with those who switched from infliximab. In previous reports, continuation of MTX resulted in better clinical and/or radiographic outcomes than discontinuation of MTX upon starting biologic therapy in RA patients [21, 22]. All patients from infliximab were treated with MTX. Moreover, patients who switched from etanercept monotherapy were significantly older than patients who switched from infliximab plus MTX. It has been reported that older age, longer disease duration, more structure damage, and decreased function are associated with poorer responses to anti-TNF therapy [23]. Thus, tocilizumab demonstrated clinically meaningful efficacy over 52 weeks in patients with an inadequate response to infliximab plus MTX and etanercept plus MTX, but not etanercept without MTX.

In recent reports and recommendations, therapy for RA needs to change and be maintained to at least achieve low disease activity by composite scores and, ideally, remission [24]. Although the mean dosage of MTX was almost same among patients who switched from infliximab plus MTX and those who switched from etanercept plus MTX, the percentages of patients who achieved clinical remission and low disease activity tended to be higher among those who switched from infliximab plus MTX compared with those who switched from etanercept plus MTX.

In this small retrospective study, RA patients who did not respond fully to TNF-α inhibitors experienced improved disease control with a switch to tocilizumab. Switching from etanercept plus MTX or from infliximab plus MTX to tocilizumab plus MTX improved response to therapy, but switching from etanercept monotherapy to tocilizumab monotherapy did not improve response to therapy.

Most adverse events that arose in both groups were mild or moderate. Our results suggest that tocilizumab plus MTX may provide safe and effective treatment options for some patients when infliximab plus MTX or etanercept plus MTX has been ineffective.

Conclusion

Tocilizumab plus MTX demonstrated acceptable safety and tolerability and clinically meaningful efficacy over 52 weeks in patients with an inadequate response to infliximab plus MTX or etanercept plus MTX. The efficacy of tocilizumab monotherapy was decreased due to secondary loss of efficacy in the treatment of patients switching from etanercept monotherapy.

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Disclosures None.

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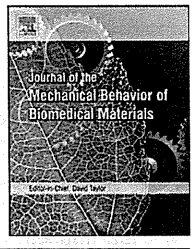

Failure analysis of sandwich-type ceramic-on-ceramic hip joints: A spectroscopic investigation into the role of the polyethylene shell component

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ABSTRACT

The mechanisms leading to systematic failure in modular acetabular components with a sandwich insertion (alumina/polyethylene/titanium) have been reconsidered in light of the newly collected Raman spectroscopic results. Raman assessments were conducted on the polyethylene shells, which belonged to a series of six failed sandwich implants with *in vivo* lifetimes ranging between 2 and 9 yr. With only one exception, all implants commonly showed dislodgment of the polyethylene shell during radiographic analyses prior to revision surgery. The polyethylene shell slipped out of the backing titanium shell, while always remaining integer to the ceramic liner. Four implants fractured at the ceramic liners, but their fractures occurred according to distinctly different patterns, which could be rationalized and classified. The insertion of the polyethylene layer, originally conceived to reduce the rigidity of the ceramic-on-ceramic bearing and to prevent impingement between the ceramic liner rim and the femoral neck, played a role in implant failure with its initial (asymmetric) thickness reduction due to creep deformation (eventually followed by cup rotation and backside wear). The results of the present spectroscopic investigation suggest that a simplistic failure classification of the sandwich-type implant as a "ceramic fracture failure" could be misleading and might represent a confounding factor in judging about the reliability of modern ceramic implants.

1. Introduction

Through the relatively long history of alumina ceramic-on-ceramic hip bearings, the cases of fracture reported with relatively high rates could systematically be associated to design failures (Tateiwa et al., 2008). French statistics from the early seventies (Hamadouche et al., 2002; Hannouche et al., 2003; Sedel, 2000) reported a 2% fracture rate for alumina-on-alumina implants due to an unreliable fixation method adopted on the cup side. In Germany, an early design with a skirted head mated with a bulky monoblock screw cup (i.e., also referred to as the Mittelmeier design) led to fracture incidences up to 0.8% (Cameron, 1991; Huo et al., 1996; Peiro, 1991) and was abandoned by the maker in 1991. More recently, in Japan, a high fracture incidence rate in alumina ceramic-on-ceramic implants has been found for a particular "sandwich" design, which included the insertion of an adaptive layer of ultra-high molecular weight polyethylene (UHMWPE) between the ceramic liner and the metal shell (Oonishi, 1992). In the period between 1998 and 2001 (after

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which the maker interrupted the supply), about 5500 implants using this hip system were replaced. Since then, several authors (Amino, 2002; Ha et al., 2006; Hasegawa et al., 2003; Kitajima and Hotokebuchi, 2003; Park et al., 2006; Suzuki, 2003) reported about catastrophic fractures at the alumina-bearing surface (ABS) of the implants from the cup side for the same sandwich-type hip implant. Owing to the phenomenological aspects of the described cases, all the failures of sandwich-type implants have commonly been referred to in the published literature as "ceramic failures" (Ha et al., 2006; Hasegawa et al., 2003; Park et al., 2006; Suzuki, 2003). Suzuki et al. (2003) mainly described problems of fracture and dislocation with the ceramic liner for the same implant studied in this paper (i.e., the ABS of the sandwich implant), while Amino (2002) reported on 5500 cases of ABS cup (January 1998–July 2000) with 16 fractures by January 2002. Kitajima and Hotokebuchi (2003) also reported more than 60 fractures by January 2003 for the ABS of the sandwich implant. These studies, reporting about a large percent of failures in sandwich-type hip implants, investigated the same implant object of the present investigation. Similarly, fractures of modular ceramic acetabular components with a sandwich polyethylene insertion (from a different maker) were recently also reported by German surgeons (Kircher et al., 2009).

While fracture of the ceramic liner component certainly represents the most evident and catastrophic phenomenon observed in a sandwich-type implant retrieved after failure, there are two important details suggesting that the actual origin of the implant failure might not necessarily reside in a poor structural behavior of the ceramic cup component. Despite the improved quality of recent ceramic implants as compared to their previous generations, it is obviously impossible to completely eliminate the risk of fracture in brittle ceramic components such as hip heads and liners. However, thoroughly compiled data reviews (excluding sandwich-type implants) indeed show that the fracture rate of third-generation alumina-bearing couples occurs at extremely low levels (Kircher et al., 2009; Tateiwa et al., 2008). On the other hand, ceramic cups usually possess by far more load-bearing capacity than the mating ceramic heads, not only because cups are mainly loaded in compression but also because, unlike balls that necessarily contain taper edges, the cup morphology can be accurately designed in order to conspicuously avoid stress intensification. Accordingly, among the sporadic events of fracture reported in the literature (Krikler, 1997; Maccauro and Piconi, 2000; McLean et al., 2002; Piconi et al., 1999; Pulliam and Trousdale, 1997; Suzuki, 2003), a large majority of cases are concerned with fractured ceramic heads rather than with ceramic liners. It follows that, if the poor strength (or brittleness) of alumina ceramic would actually have been the main cause of failure in sandwich-type implants, one could hardly explain why fracture systematically occurred on the less-stressed liner side, as reported in the majority of sandwich-type failures (Hasegawa et al., 2003; Amino, 2002), instead of hitting the most stressed regions at the corners of the head taper, which is made of the same material.

The so-called sandwich cup configuration, with its ceramic liner locked into an adaptive layer of polyethylene, was originally conceived in order to reduce the rigidity of the ceramic-on-ceramic coupling and to prevent impingement between the rim of the ceramic liner and the metal neck of the femoral stem. Various surgeons, who reported about the sandwich implant failures, observed that the liner had rotated during gait by about 90° inside the metal shell and the ball head has been displaced in superolateral direction (Hasegawa et al., 2003; Yamamoto et al., 2004). The ball head eventually entered into contact with the metal shell in the superolateral area and in a number of cases the ceramic liner fractured. In one case, fracture and fragmentation of the ceramic cup were reported (Hasegawa et al., 2003), while in another report the liner was found yet unfractured despite the implant having undergone liner rotation (Yamamoto et al., 2004). In reviewing the published literature, one might intuitively feel consensus toward authors hinting that the fault of sandwich implant failure arises from brittleness of the ceramic components (Ha et al., 2006; Park et al., 2006). The squatting attitude of Asian patients was also suggested as becoming an exacerbating factor in the fracture process (Ha et al., 2006). However, a clear and final explanation of the implant failure mechanism(s) is still missing in the literature.

We revisit here several cases of sandwich-type implant failure by focusing on the specific role played by the polyethylene shell component in the overall process of implant failure. Our opinion is that the published descriptions of ceramic liner fracture in sandwich-type implants are indeed phenomenologically correct. However, we shall also attempt to provide some clear experimental proofs supporting the thesis that the structural inadequacy of the alumina components was not the principal factor originating failure in

Table 1 – Clinical details of the six cases of sandwich-type implant failure examined in this study.

Case	Gender	Follow-up	Cause	Pristine PE thickness [μm]	Side	Inclination [deg.]	Anteversion [deg.]
I	Female	4 yr 8 months	Dislodgement fracture	3000	Left	42	−5
II	Female	9 yr 3 months	Dislodgement	5000	Right	43	16
III	Female	9 yr 8 months	Dislodgement	5000	Right	50	24
IV	Female	2 yr 11 months	No-dislodgement destruction	2000	Left	59	41
V	Female	4 yr 11 months	Dislodgement fracture	2000	right	45	25
VI	Female	9 yr	Dislodgement fracture	3000	left	51	51

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sandwich-type implants. On the other hand, the structural defeat associated to creep deformation on the polyethylene side of the implants played a major role, as a consequence of the flawed joint design.

2. Experimental procedures

2.1. *Patients and implants*

Six cases of sandwich-type implant failure were examined, whose clinical details are summarized in Table 1. All retrieved implants were of the sandwich-type ABS HA Shell (CH 46)/ABS Liner (28-46)/Ball Head (28N:-4)/Perfix Stem #12-M, produced by Kyocera Co., had cementless fixation, and belonged to female patients. The fact that all samples belonged to female patients, however, was just due to a fortuitous circumstance and it is believed not to limit the possibility of extending the outputs of the present investigation to eventual cases of male patients. The *in vivo* implantation lifetime of the devices ranged between 2 yr 11 months and 9 yr 8 months, for an average followup of 6 yr 9 months. No traumatic event, as possible cause of failure, was encountered in all patients. The time delay between symptoms of failure and revision typically ranged between few days and few weeks. Except for the shortest followup (Case IV in Table 1), all the studied retrievals showed dislodgment of the liner at the time of revision surgery. However, in two of the six studied retrievals (Cases II and III) the ceramic liner did not fracture. Among the four cases in which the ceramic liner fractured, Case IV was completely different from the other cases because it showed fragmentation of the ceramic liner into many small pieces. Anteversion and inclination angles for all the studied cases are listed in Table 1, as obtained from radiographic analyses immediately after primary surgery. As far as inclination angles are concerned, a range comprising between 30° and 50° is considered to be a safe zone for avoiding dislocation, while for anteversion the angular range is between 5° and 25° (Lewinnek et al., 1978; Widmer and Zurfluh, 2004). Therefore, only Case IV, for which radiographic analyses showed an inclination angle of 59° (cf. Table 1), should be considered affected by the effects of an excessive inclination. Values of anteversion angle, which could not be considered in the safe zone, included Cases I, IV and VI. In particular, the anteversion angle $\approx -5°$ of Case I clearly represented an implantation error.

2.2. *Raman spectroscopic assessments on retrievals and their preliminary calibrations*

Raman spectra were collected with a triple monochromator spectrometer (T-64000, ISA Jobin-Yvon/Horiba Group, Tokyo, Japan) equipped with a charge-coupled detector (i.e., a high-resolution CCD camera). The laser power at the UHMWPE surface was typically 90 mW. The laser excitation source was a monochromatic blue line emitted by an Ar-ion laser at a wavelength of 488 nm. Spectral integration times were typically 5 s for unpolarized spectra. Each recorded spectrum was averaged over three successive measurements at each selected location. The confocal configuration of the probe adopted throughout the present experiments corresponded to a ×100 objective lens; numerical objective aperture, confocal pinhole diameter, and focal length of the objective lens were set as NA=0.9, Φ=100 μm and f=0.3 mm, respectively. All Raman spectra were non-destructively recorded at room temperature. Intensity and full-width at half-maximum (FWHM) of the 1130 cm^{-1} Raman band of polyethylene were retrieved by fitting the CCD raw data to the mixed Gaussian/Lorentzian curves with commercially available software (Labspec, Horiba Co., Kyoto, Japan). Variations of FWHM with respect to a virgin sample reflected the microstructural modifications induced by body weight, namely by the uniaxial residual strain piled up in

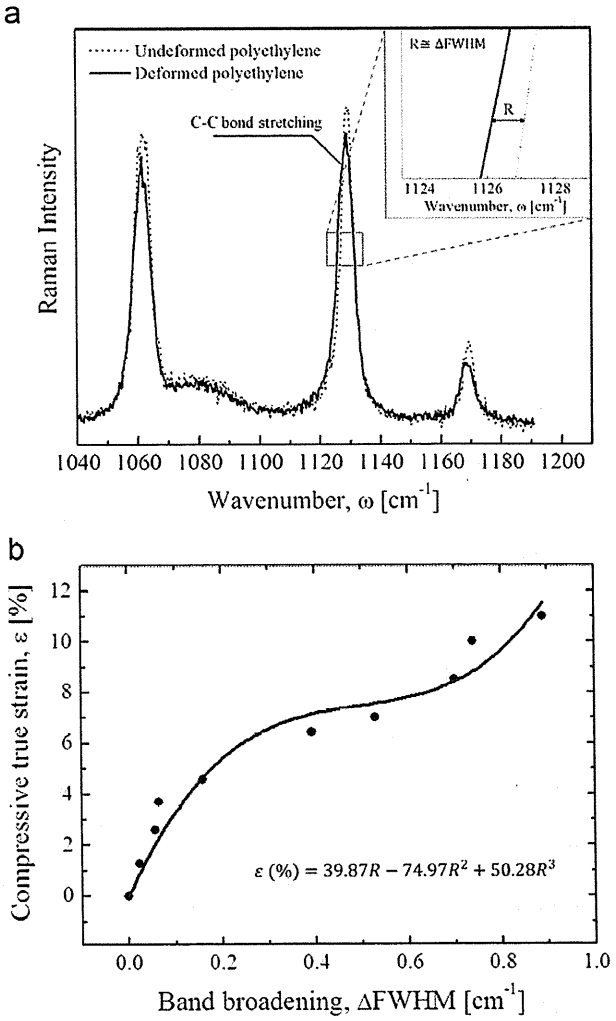

Fig. 1 – (a) Raman spectra are shown of the investigated polyethylene layer belonging to the sandwich-type implants in its unstrained and compressively strained state. In the inset, an enlargement of the spectral region is given where band broadening was measured. Note that R≈ΔFWHM because broadening occurred mainly from the low-frequency side of the band and (b) plot of band broadening vs. compressive true strain as obtained by preliminary calibration tests of uniaxial compression on undeformed samples. The cubic equation best-fitting the experimental plot is given in the inset.

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the polymeric structure. The width of the Raman band located at 1130 cm^{-1} (A_g+B_{1g} mode or symmetric stretching of C–C bonds (Tashiro et al., 1988; Wong and Young, 1994)) was selected as a sensor for residual strain in the polymeric network because it reflects the degree of disorder of the polymeric network and its degree of molecular orientation, which are both directly affected by strain. Fig. 1(a) shows the Raman spectrum of the undeformed polyethylene of the sandwich-type implant under investigation vs. that of the same material deformed with a true strain of 11%. A clear broadening could be observed (cf. also inset) for the C–C bond-stretching band located at around 1130 cm^{-1}. Band broadening, characterized by the variation of FWHM, could be rationalized as a function of true residual strain by means of a cubic dependence, as given in the calibration plot of Fig. 1(b) (cf. best-fitting equation in inset). In the latter plot, uniaxial strain (in a known amount) was intentionally introduced into a pristine (undeformed) sample and Raman band-broadening measured after 24 h recovery since successive sample unloading. The plot, thus, reports about the dependence of broadening of the C–C stretching Raman band on the amount of the compressive (uniaxially applied) residual strain permanently stored in the material. The increase of structural disorder under compressive strain in turn reflects in a broadening of the Raman band due to both inter- and intra-lamellar slip processes in fractions depending on the amount of strain. Additional phenomena leading to broadening of the Raman bands have also been indicated, including crystallite fragmentation, fibril formation, and chain disentanglement (Hiss et al., 1999). These microstructural modifications generally appear at relatively high strain levels, while broadening of the 1130 cm^{-1} band rigorously obeys a linear dependence only at low strain levels, as shown in band-width/strain calibrations in previous papers (Kumakura et al., 2009; Kyomoto et al., 2007; Pezzotti et al., 2011). The threshold for deviation from a linear behavior, namely for the activation of multiple microscopic mechanisms of deformation, strongly depends on the polymer microstructure and, thus, varies from material to material. A comparison between the polyethylene material investigated in this paper and the newest brands of polyethylene materials with engineered microstructures more recently launched in the orthopedic market is definitely beyond the scope of this paper. However, we wish here to qualitatively mention about a comparison (not shown here) we could make based on plots similar to those shown in Fig. 1(b). The comparison demonstrated that the polyethylene material used in the sandwich-type implants was a relatively "soft" one, presumably due to its lower crystallinity and lower degree of cross-linking as compared to modern polyethylene materials. According to the complex deformation behavior followed by the material investigated in this paper, transformation of band broadening data into strain values was performed by means of the cubic calibration curve obtained in Fig. 1(b).

Exploiting the high transparency of polyethylene, non-destructive in-depth scans allowed us to retrieve detailed sub-surface profiles of spectral properties at selected locations along the entire thickness of the polyethylene shells. In the experimental practice, an automated sample stage with sub-micrometric step precision was employed, making it possible to record spectra at each depth focusing below the sample surface, and to map spectral features with lateral line scanning on the sample surface and along the sub-surface. Maps 30 × 30 μm were typically recorded at 50 different depths for each polar angle of the shell, and the collected spectra (900 spectra for each map) averaged to give the representative molecular vibrational modes of the polyethylene structure at each selected in-depth location. Measurements of sub-surface profile properties were eventually repeated at nine polar angles along a circumferential path in a plane containing the axis of symmetry of the cup and passing through the main-wear zone. The locations were thus separated by an angular displacement of 22.5°. Mapping rather than single-point measurements was made in an attempt to improve the statistical validity of the strain assessments at each selected location of the investigated

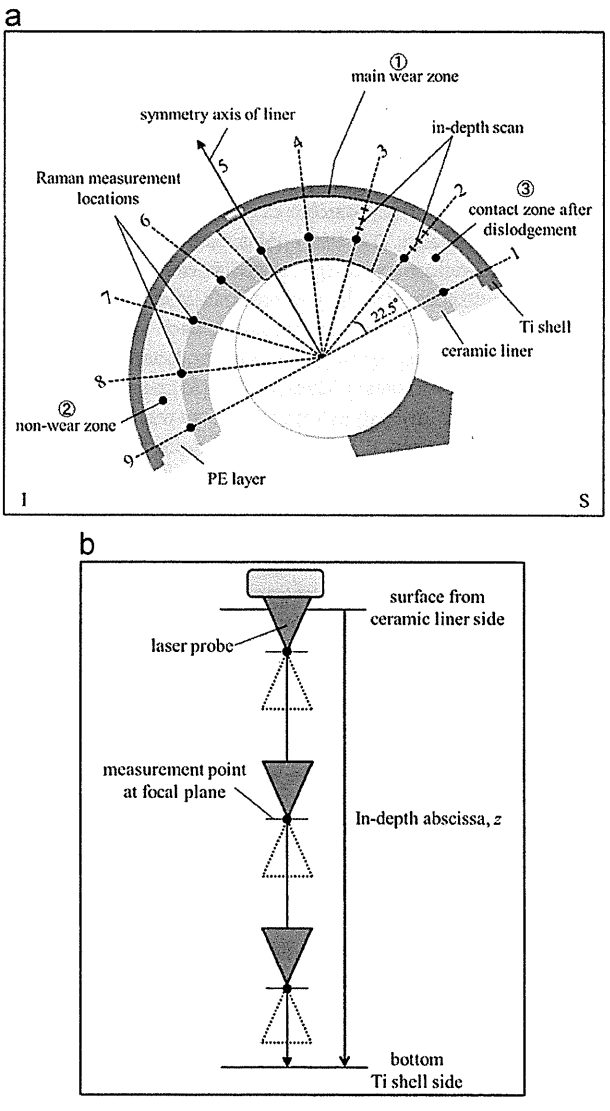

Fig. 2 – (a) Schematic draft describing the geometrical characteristics of the sandwich-type implant studied and the protocol followed in the quantitative analysis of creep displacements in its polyethylene layer and (b) explanatory draft of the in-depth defocusing experiments used for assessing the residual strain profile developed along the thickness of the UHMWPE layer at a given location as shown in (a).

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retrievals. The draft in Fig. 2(a) shows the geometrical locations of the Raman measurements, while the in-depth (or defocusing) scan protocol followed at each measurement location is given in Fig. 2(b). Strain data at each polar location were translated into thickness variations due to creep by integrating the in-depth strain profile over the in-depth abscissa through the entire thickness of the polyethylene layer at each measurement location. The method is schematically explained in Fig. 2(b), and the related computational procedures were previously shown (Kumakura et al., 2009). In this study, the total number of collected Raman spectra on all retrievals was in the order of $\approx 2.5 \times 10^6$ for a total measurement time of ≈ 2100 h. Finally, it should be noted that the Raman method for assessing creep displacements in acetabular cups is relatively new (Kumakura et al., 2009; Pezzotti et al., 2011) and yet lacks a direct validation according to more conventional methods based on profilometry analyses. However, such latter analyses, considered as the golden standard method in hip arthroplasty, can only record total thickness reductions and are, thus, comprehensive of both creep displacements and wear thickness consumptions. This makes a direct comparison between profilometry and Raman results difficult, the latter ones including only creep displacement contributions. Nevertheless, an indirect confirmation of the Raman method for creep analysis was provided in a previous study (Pezzotti et al., 2011), in which some of the retrieved cups were exposed for very short periods of time in the human body and, thus, mainly underwent creep deformation. In such cases, a good correspondence could be found between Raman analyses of creep displacements and thickness reductions measured by standard methods.

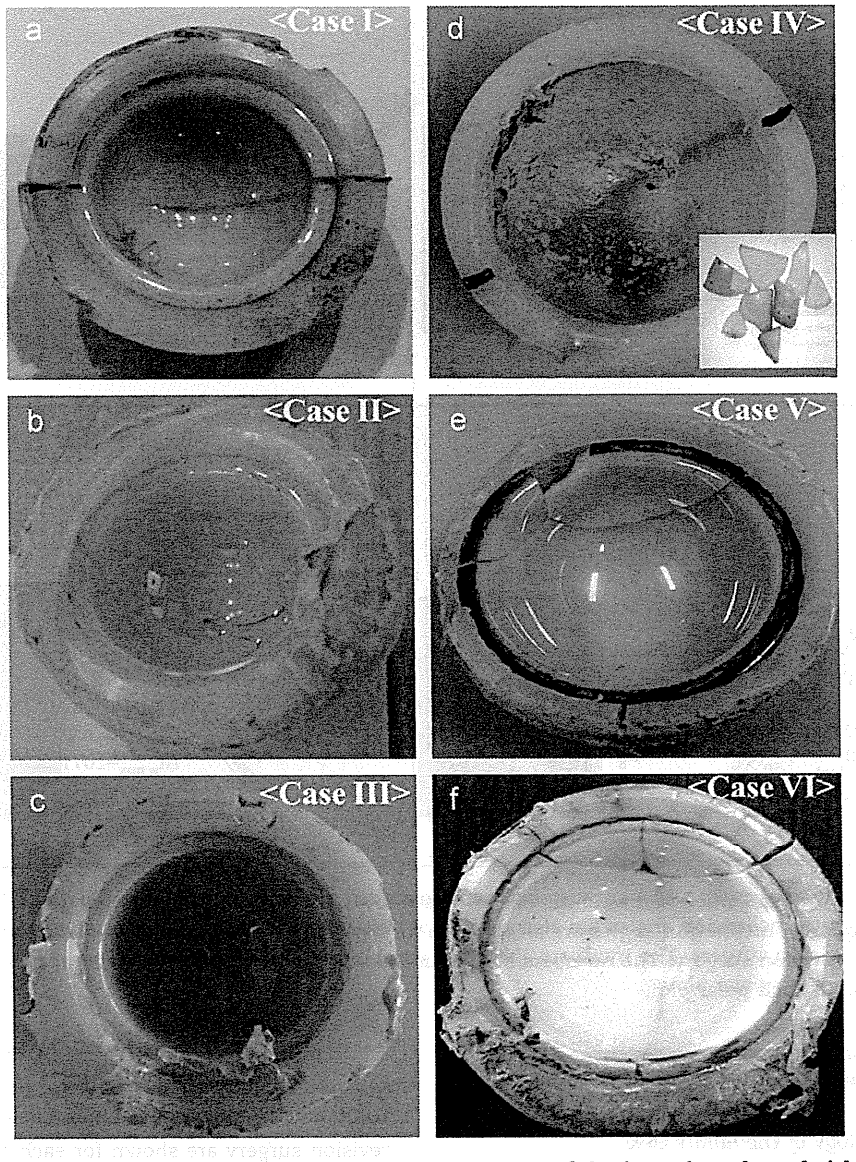

Fig. 3 – Photographs of the ceramic-cup/polyethylene-shell components of the investigated sandwich-type implants after being retrieved from the patients' body. In Case IV, destruction of the ceramic liner occurred *in vivo* (cf. photograph of the ceramic broken pieces in the inset of (d)).

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