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Case Report

Improvement of Knee Joint and Laboratory Markers of a Rheumatoid Arthritis Patient Treated with Tocilizumab

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Abstract

Here, we report on the case of 27-year-old women with rheumatoid arthritis [RA] whose symptoms improved after the administration of tocilizumab [TCZ] following long-term biological disease-modifying anti-rheumatic drugs treatment. The clinical changes in her signs and symptoms were confirmed by radiographic analysis of the affected knee joint and laboratory markers including C-reactive protein, matrix metalloproteinase-3, amino-terminal telopeptides of type 1 collagen [NTX], osteocalcin, interleukin-6, anti-cyclic citrullinated peptide, carboxy-terminal telopeptides od type 2 collagen [CTX-2], Dikkopf-1 [DKK-1], and osteoprotegerin [OPG] levels. Changes in disease activity score [DAS] 28-erythrocytes sedimentation rate were also estimated during the clinical physical observation. Initially, she was prescribed bucillamine, methotrexate [MTX] and salazosulfapyridine [SASP], however her RA activity was not improved. Therefore, the prescription was changed to predonisolone, and mizoribine. However, her RA activity was still not controlled and she was referred to our hospital. At our clinic, etenercept and MTX were prescribed, but her RA activity was not controlled. After 1 year, although adalimumab and MTX were prescribed, these agents were not effective in controlling the RA. Finally, TCZ, PD and SASP were prescribed. These medications greatly suppressed her RA activity, which correlated with the improvement of NTX, CTX-2, DKK-1 and OPG levels. Physical changes were also confirmed radiographically, including a widening of the joints space and enlargement of range of motion. Thus, her state of RA was greatly improved by TCZ.

Keywords: Rheumatoid Arthritis; Joint Space Narrowing; Tocilizumab; Carboxy-Terminal Telopeptides of type 2 collagen; Dickkopf-1; Osteoprotegerin

Abbreviations:

RA : Rheumatoid arthritis:

cs-DMARD : Conventional Synthetic Disease-Modified Anti-Rheumatic Drug;

b-DMARD : Biological Disease-Modified Anti-Rheumatic Drug;

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MTX : Methotrexate; SASP : Salazosulfapyridine; PD : Predonisolone;

TNF :Anti-Tumor Necrotic Factor;

ADA : Adalimumab; ETN : Etanercept;

CTX : 2-Carboxy-Terminal Telopeptides of Type 2

Collagen;

TCZ : Tocilizumab; IL-6 : Interleukin-6;

NTX : Amino-Terminal Telopeptides of Type 1 Col-

lagen;

DKK-1 : Dickkopf-1;
OPG :Osteoprotegerin;
OC : Osteocalcin;
CRP : C-Reactive Protein;

MMP : Matrix Metalloproteinase;

LTIA : Latex Turbidimetric Immunoassay;

CARF : Anti-Galactose-Deficient Immunoglobulin G

Antibody;

RANKL : Receptor Activator of Nuclear Factor kap-

pa-β Ligand;

CCP : Anti-Cyclic Citrullinated Peptide; CLEIA : Chemiluminescent Immuno Assay;

DAS : RA Disease Activity Score;

ESR : Erythrocyte Sedimentation Rate;

ROM : Range of Motion

Introduction

Rheumatoid arthritis [RA] progression has been markedly improved by the application of biological anti-RA agents, which suppress RA activity and also repair affected joint space under certain conditions. The revised guidelines also indicate the application of newly introduced biological disease-modifying anti-rheumatic drugs [b-DMARD] [1], as RA progresses; however, the use of the anti-tumor necrosis factor [TNF] antibody has been decreasing as reported in the latest version of the guidelines [2]. In a study wherein b-DMARDs were administered to RA patients with a high rheumatoid factor and anti-cyclic citrullinated peptide [CCP] antibody titer, 18 of 250 RA cases showed improvement in their joint spaces (7.2%) [3]. RA is often accompanied with high values of C-reactive protein [CRP], receptor activator of nuclear factor kappa-β ligand [RANKL], carboxy-terminal telopeptides of type 2 collagen [CTX-2], Dickkopf-1 [DKK-1] and sclerostin levels, as well as exacerbated cartilage destruction [4]. All b-DMARDs suppress matrix metalloproteinase [MMP]-3, with regard to the early stage of cartilage destruction the CTX-2 level is believed to reflect the pathophysiology [5]. Recently DKK-1 has been noted for new bone formation [6]. One of the recent b-DMARDs, tocilizumab [TCZ], which suppresses interleukin-6 [IL-6], is expected to induce new bone formation after osteosclerosis in RA [7].

In the present report, the use of TCZ greatly improve the RA status including widening of the affected joint space, and the improvement of laboratory markers. The patient has returned to her workplace and could resume normal work.

Analysis of the laboratory markers

We measured the following markers: CRP (Sekisui Medical, Tokyo, Japan) by latex turbidimetric immunoassay [LTIA], MMP-3 (Fine Chemical, Toyama, Japan) by LTIA, anti-galactose-deficient immunoglobulin G antibody (CARF; EIDIA, Tokyo, Japan) by electrochemiluminesent immune assay, CCP (Igaku Seibutsugaku Laboratory, Japan) antibody by chemiluminescent immunoassay [CLEIA], amino-terminal telopeptides of type 1 collagen (NTX; Alere Medical, Tokyo, Japan) by enzyme linked immunosorbent assay (ELISA), CTX-2 (Nordic Bioscience Diagnostics, Denmark) by ELISA, osteocalcin (OC: LSI Mediance, Tokyo, Japan) by enzyme immune assay, Dickkopf-1 (DKK-1: R&D Systems Inc., Minneapolis, MN, USA) by ELISA, IL-6 (Fuji Rebio, Tokyo, Japan) by CLEIA. and osteoprotegerin (OPG: Immundiagnostik, AG, Deutschland) by ELISA. The RA disease activity score (DAS 28-erythrocyte sedimentation rate [ESR] was also monitored.

Analysis of the treatment medication

The following treatment medications were analyzed: bucillamine (Japanese conventional DMARD, Santen Pharmaceutical, Co. Osaka, Japan), methotrexate (MTX, Santen Pharmaceutical, Co. Osaka, Japan), salazosulfapyridine (SASP, Santen Pharmaceutical Co. Osaka, Japan), predonisolone (PD, Shionogi, Osaka, Japan), leflunomide (Sanofi, Toulouse, France), mizoribine (Japanese immunosuppressive DMARD, Asahikasei Pharmaceutical, Tokyo, Japan), etarnercept (ETN, human soluble anti- TNF alpha and beta receptor antibody, Pfizer, Groton, USA), adalimumab (ADA, anti-TNF alpha antibody, AbbVie, North Chicago, IL, USA), TCZ (anti-IL-6 antibody, Chugai Pharmaceutical, Co., Ltd. Tokyo, Japan)

Case Report

A 27 year-old female nurse had RA for over 8 years. Her past history included treatment with bucillamine, MTX, and SASP; however her RA activity was not controlled. She was then treated with PD (5-10 mg/day), leflunomide (20 mg/day) and mizoribine (100 mg/day). However, her RA activity was still not well controlled and she was referred to our Orthopaedic Clinic at Sakai Hospital, Kinki University Faculty of Medicine.

In our outpatient clinic, ETN (50 mg/week) and MTX (4 mg/week) were prescribed. However, she still had RA activity along with a mild depressive feeling; moreover, she was unable to appropriately perform her daily duties as a nurse.

After one year, a new anti-TNF alpha antibody, ADA (40 mg/every 2 weeks) and MTX (8 mg) were prescribed. During this stage, we measured several laboratory markers to confirm her RA activity, including the CTX-2 level. Since her RA activity and CTX-2 levels did not show any good response to these prescriptions, TCZ was used instead of ADA. Finally, she was prescribed PD (7.5 mg/day), SASP (500 mg/day) and TCZ (400 mg/month). These treatments suppressed her RA activity and improved her NTX, CTX-2, DKK-1 and OPG levels. After 3 months her condition was good and she returned to her initial workplace and could work well.

Changes in the laboratory markers are shown in Table 1. It is clear that DAS 28-ESR values markedly reduced after starting TCZ. Similarly significant changes were also observed in the MMP-3, CTX-2, DKK-1, and IL-6 levels.

Radiographic analysis of the knee joint

As shown in Figure 1, a radiographic weight bearing film of the left knee joint before starting TCZ shows a narrow joint space, osteoatrophy around the joint, and osteonecrosis. These were estimated quantitatively using joint space measurement. In addition the position of the patella was lower, which caused pain and loss of power of the quadriceps muscle was confirmed by physical examination. The knee joint range of motion [ROM] was -10/100.







Lateral view

Figure 1. Anteroposterior and lateral radiographs of the affected knee joint in June 2009 before the administration of tocilizumab.

The width of the joint space is 1.04mm (medial) and 2.49mm (lateral).

After 3 years of TCZ regiment administration, the joint space measurement had improved (Figure 2) and the joint ROM (0/130) showed improvement as well. Furthermore, neosyn-

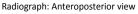
thesis of the chondral space was observed. The joint space had expanded from 1.04 mm to 2.67 mm (medial joint space) and from 2.49 mm to 2.98 mm (lateral side) due to TCZ treatment.

Discussion

Before 2013, the guidelines for RA [1] indicated that the b-DMARD to be used for first-line treatment was anti-TNF antibodies; TCZ was listed as the second-line treatment among b-DMARD preparations. We have previously performed small clinical trials in order to compare the compliance of TNF alpha antibodies with that of TCZ. The TCZ group (four failed infliximab [IFXs], six failed ETNs, and one failed ADA) showed high compliance (81.8%), but the TNF alpha antibodies group (one failed IFX, nine failed ETNs, and one failed ADA) showed very low compliance (36.4%).

The present case revealed that there is a significant correlation between the laboratory markers and DAS 28-ESR, which was confirmed by the radiographic weight-bearing films of the patient's knee joint (Figure 2). A significant finding of the present case report was the improvement in the signs and symptoms of RA, which was confirmed by the improvement in laboratory markers. Thus, through the administration of TCZ to suppress IL-6 levels, the laboratory markers related to cartilage tissue destruction were also decreased: MMP-3 decreased by one-fifth, CTX-2 decreased by one-third, DKK-1 decreaed by one-half of the original levels. Moreover, the laboratory markers related with osteogenesis showed an increasing tendency: osteocalcin increased from 8.4 ng/ml to 10.0 ng/ml and OPG increased from 85.2 pmol/L to 97.7 pmol/L (Table 1).







Lateral view

Figure. 2. Anteroposterior and lateral radiographs of the affected knee joint in May 2012 after the administration of tocilizumab.

The width of the joint space is 2.67mm (medial) and 2.98mm (lateral).

Biologics	Date	DAS 28-ESR	MMP-3	CTX-2	DKK-1	OPG	NTX	OC	IL-6	Anti-CCP
			ng/ml	ng/mmol	pg/ml	pmol/L	$nmolBCE/mmol \cdot Cre$	ng/ml	ng/ml	mg/dl
Pre-ETN	9 March 2009	5.98	384	543			53	6.9		76
Post-ETN	2 July 2009	5.31	389	913			37.6	6.3		50
Pre-ADA	8 October 2009	5.89	425	1432			41.8	7.5		66
Post-ADA/Pre-TCZ	12 January 2010	5.51	262	1599	3100	85.2	40.4	8.4	32.9	68
TCZ:1	5 April 2010	1.32	66	584	1710	89.2	37.9	8.6	11.1	52
TCZ:2	5 July 2010	1.29	60	617	2050	88.2	26.4	9.5	8.4	55
TCZ:3	7 March 2012	1.21	49	592	1630	97.7	28.9	10	6.6	48

Table 1. Changes of the laboratory markers during in the clinical course.

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It is clear that DAS 28-ESR values markedly reduced after starting TCZ. Significant decreased changes were also observed in the MMP-3 (- 213), CTX-2 (-1007), DKK-1 (-1470), and IL-6 (-26.3) levels and increased in OPG (+12.5) and OC (+1.6).

In this case, we measured eight laboratory markers in RA patients treated with TCZ. Our patient recovered well with the administration of TCZ, which was accompanied by an improvement in laboratory markers. In particular, DKK-1 was useful marker and it may help to indicate clinical signs and symptoms, in conjunction with radiographic analysis.

TCZ is effective against RA whereas other b-DMARD preparations are ineffective. TCZ administration induces a suppressive effect on IL-6 levels and joint destruction [9] [10]. Furthermore, TCZ also suppresses the levels of OPG which binds to RANKL [11]. These suppressive effect is also reported for the levels of DKK-1, which induces the inhibition of bone destruction in RA [6]. IL-6 promotes the differentiation of osteoclasts via RANKL, and/or the production of MMP-3 in chondrocytes, which induce cartilage destruction. TCZ binds to the IL-6 receptor and blocks signal transduction in osteoclasts and/or chondrocytes. During this process, TCZ treatment activates the Wnt signal, promotes the remodeling of bone, and causes a decrease in DKK-1. Thus, TCZ repairs cartilage destruction. These multiple functions of TCZ were confirmed in the present case.

Conclusion

A 27 year-old women had RA for over 4 years without any improvement and was referred to our hospital. We confirmed the clinical changes in her signs and symptoms by radiographic analysis and laboratory markers. She did not respond to treatment with bucillamine, MTX, SASP, PD, mizoribine, or ETN. Therefore, we prescribed TCZ, PD and SASP that greatly

suppressed her RA activity; this was correlated with the improvement in NTX, CTX-2, DKK-1 and OPG levels. Moreover, her joint space was widened and her ROM was enlarged. Thus, TCZ was very effective in controlling her RA state.

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