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Concise report

The effect of tocilizumab on bone mineral density in patients with methotrexate-resistant active rheumatoid arthritis

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Abstract

Objective. The aim of this study was to analyse the effects of therapy with tocilizumab (TCZ), an anti-IL-6 receptor antibody, on BMD of the lumbar spine and femoral neck in patients with RA.

Methods. Eighty-six patients with active RA (indicated by a 28-joint DAS ESR >3.2) despite treatment with MTX 12 mg/week were included in this open-label prospective study and started on TCZ (8 mg/kg every 4 weeks). All patients used a stable dosage of MTX and were not allowed to use steroids or bisphosphonates during the study period. BMD of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry at baseline and 52 weeks after initiating TCZ.

Results. Seventy-eight patients completed this study. BMD of the lumbar spine and femoral neck remained stable after 1 year of TCZ treatment. In 33 patients who had osteopenia at baseline, there was a significant increase in BMD of the lumbar spine [mean 0.022 (S.D.) 0.042, $P < 0.05$] and femoral neck [0.024 (0.0245), $P < 0.05$].

Conclusion. TCZ affects BMD in patients who had active RA despite treatment with MTX. BMD of the lumbar spine and femoral neck in patients with normal BMD at baseline was stable. TCZ increased the BMD of patients who had osteopenia at baseline.

Key words: rheumatoid arthritis, bone mineral density, tocilizumab, anti-interleukin-6 receptor antibody, osteopenia.

CLINICAL SCIENCE

Introduction

RA is associated with systemic bone loss [1–3]. Rheumatologists should have strategies to prevent bone loss in RA patients [4]. IL-6 is a major cytokine involved in the pathology of RA and may also promote osteoporosis [5, 6]. Tocilizumab (TCZ) is an IL-6 receptor inhibitor that is highly effective in the treatment of RA [7, 8]. Several reports have suggested that TNF inhibitors prevent bone loss [9, 10], however, there is no evidence that TCZ affects BMD. This study aimed to analyse the effects of TCZ treatment on BMD of the lumbar spine and femoral neck in patients with RA.

Methods

This was an open-label, prospective study. It was blinded to the BMD technician and the physician who observed and recorded the patient's disease activity. This study was approved by the ethics committee of Hiroshima Clinic. Informed patient consent was obtained from all subjects who participated in this study.

Patients

Study participants were recruited from patients who were diagnosed with RA according to the ACR diagnostic criteria [11] and were observed at Hiroshima Clinic, Hatta Clinic or Sky Clinic between October 2010 and

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June 2012. RA patients were eligible if they had active disease [28-joint DAS with ESR (DAS28-ESR) > 3.2] [12] during the previous 12 weeks despite prior treatment with MTX at 12 mg/week. All patients were biologic naive. Patients were excluded if they were <18 years of age, pregnant or had received steroids, bisphosphonates or PTH.

Study protocol

TCZ 8 mg/kg was administered by i.v. infusion every 4 weeks for a total of 52 weeks. Clinical and laboratory assessments were performed every 4 weeks during the same visit as the i.v. infusions. BMD was measured at baseline and after 52 weeks using the same machine. Clinical, laboratory and BMD assessments were performed in the Rheumatology Department of Hiroshima Clinic, Japan. Permitted concomitant drugs included stable doses of NSAIDs. No IA injections of any joints were permitted. No changes in MTX dosage were permitted during the study period.

Evaluation of RA activity and clinical response

Disease activity and clinical response were defined by the European League Against Rheumatism (EULAR) response criteria [12]. The patients were evaluated with the DAS28 every 4 weeks. After 12 weeks of TCZ treatment the patients were given the option to voluntarily leave the study.

BMD measurement

BMD of the lumbar spine (L1–L4) and femoral neck was measured with DXA (Lunar iDXA, General Electric, Fairfield, CT, USA). The least significant detectable difference of the lumbar spine and femoral neck was ±0.02.

Primary endpoint

The primary endpoint was comparison of the BMD of the lumbar spine and femoral neck at baseline and 52 weeks after TCZ treatment.

Other endpoints

Additional study endpoints included the following: a comparison of the BMD of the lumbar spine and femoral neck at baseline and 52 weeks after TCZ treatment for patients who had osteopenia at baseline, a comparison of disease activity (DAS28) at baseline and 52 weeks after TCZ treatment and a correlation between the change in BMD and the clinical response.

Statistical analysis

This study utilized the intention-to-treat analysis per protocol. Comparison of the changes in BMD and RA disease activity were analysed using paired *t* tests. Correlations between the changes in BMD and clinical response were assessed using Pearson's product–moment correlation coefficients, and withdrawn cases were selected using the worst-case scenario. SPSS version 15.0 (IBM, Armonk, NY, USA) was used for all statistical analysis.

Results

Patient characteristics

Eighty-eight patients were enrolled in this study. Two patients were withdrawn prior to receiving treatment due to ineligibility [1] owing to patient mental retardation (an inability to understand the informed consent) and at the patient's request. A total of 86 patients with active RA (DAS28 > 3.2) despite MTX started TCZ treatment (8 mg/kg i.v. every 4 weeks). Characteristics at baseline, including age, gender, RA disease activity, disease duration and BMD are shown in Table 1. A total of 78 patients completed the full 52 weeks of the study. Eight patients were withdrawn: five due to lack of efficacy, two due to infection and one for unknown reasons (Table 1).

Primary endpoint: change in BMD of the lumbar spine and femoral neck after 52 weeks of treatment with TCZ

After 52 weeks of TCZ treatment, the BMD of the lumbar spine and femoral neck remained stable. The change in BMD from baseline to 1 year was as follows: lumbar spine, 0.006 (S.D. 0.072), $P = 0.12$; femoral neck, 0.001 (S.D. 0.042), $P = 0.27$ (Table 2).

Secondary endpoints

BMD of the lumbar spine and femoral neck changed only in patients who had osteopenia at baseline. Thirty-three of 86 patients had osteopenia at baseline. After 52 weeks of TCZ treatment the BMD of the lumbar spine [0.022 (S.D. 0.042), $P < 0.05$] and femoral neck [0.024 (S.D. 0.012), $P < 0.05$] had significantly increased (Table 2).

BMD and RA disease activity

The changes in BMD of the lumbar spine and femoral neck after 1 year did not correlate with decreases in DAS28 or the EULAR response ($R = 0.102$, $P = 0.421$).

Table 1 Characteristics at baseline

Demographics	
Age, mean (S.D.), years	56 (18)
Female, *n* (%)	53 (78)
BMI, mean (S.D.), kg/m^2	26.8 (9.5)
Disease activity (DAS28), mean (S.D.)	5.3 (1.4)
Disease duration, mean (range), months	54 (4–87)
IgM RF positive, *n* (%)	58 (85)
Anti-CCP positive, *n* (%)	57 (84)
Lumbar spine	
BMD, mean (S.D.), g/cm^2	0.980 (0.17)
T-score, mean (S.D.)	−0.78 (1.28)
Z-score, mean (S.D.)	0.02 (1.13)
Femoral neck	
BMD, mean (S.D.), g/cm^2	0.825 (0.14)
T-score, mean (S.D.)	−0.79 (1.32)
Z-score, mean (S.D.)	0.04 (1.14)

Table 2 Lumbar spine and femoral neck BMD at baseline and week 52

		BMD at baseline, mean (s.d.), g/cm^2	BMD at week 52, mean (s.d.), g/cm^2	*P*-value
Lumbar spine	All patients	0.980 (0.17)	0.986 (0.21)	0.12
	Normal BMD at baseline	1.096 (0.13)	1.091 (0.14)	0.24
	Osteopenia at baseline	0.821 (0.16)	0.843 (0.18)	0.02
Femoral neck	All patients	0.825 (0.14)	0.826 (0.12)	0.27
	Normal BMD at baseline	0.931 (0.15)	0.919 (0.14)	0.19
	Osteopenia at baseline	0.674 (0.25)	0.698 (0.21)	0.03

Discussion

The findings of this study suggest that TCZ had an impact on the BMD of the lumbar spine and femoral neck. The BMD remained stable in patients with normal BMD at baseline, while patients who were osteopenic at baseline experienced an increase in BMD. This suggests that TCZ helped patients with normal BMD maintain an adequate bone density, while increasing the BMD in patients whose BMD was not sufficient. TCZ treatment helps patients with normal BMD to maintain adequate BMD for 1 year. However, it should also be noted that it is very likely that without TCZ treatment, because of the short period of observation (1 year), BMD could have remained stable. In fact, the improvement of BMD in patients with osteopenia was quite small. What is required is a randomized controlled study including an MTX-only group for a minimum of 1 year, but for ethical reasons that cannot be done.

The patient population, disease duration and age is typical of RA populations. In many countries, rheumatologists are not used to TCZ being a first-line biologic drug (all patients were biologic naive), however, this makes it more straightforward to investigate the effect of TCZ on BMD. In this study we excluded patients with osteoporosis and patients on bisphosphonates or PTH since we were investigating only the effect of TCZ on BMD. Patients using steroids were excluded for the same reason.

Changes in BMD did not correlate with improvement in DAS28. TNF inhibitors have been noted to improve BMD [9, 10], and changes in BMD caused by MTX or TNF inhibitors have been correlated with an improvement in disease activity. The following aspects of our study may have caused our results to be discordant with the previous findings: a small study population, mostly adequate BMD at baseline, minor changes in BMD following treatment and the almost universal response to treatment (good responder 25.3%, moderate responder 62.5%) with very few non-responders (12.2%). While it is possible that the effect of TCZ on BMD was not correlated with disease activity, further studies are required to elucidate the relationship. Additionally, studies that identify the effect of TCZ on non-inflammatory diseases, such as primary osteoporosis, may be beneficial. In this study we evaluated the effect of TCZ on BMD. Further studies will be needed to determine the effect of TCZ on bone quality.

Rheumatology key messages

- Tocilizumab (TCZ) affects BMD in patients who had active RA despite treatment with MTX.
- BMD in RA patients with normal BMD at baseline was stable over 1 year.
- TCZ increased the BMD of patients who had osteopenia at baseline over 1 year.

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