Evaluation of Anti-interleukin-6 Therapy In Patients With Rheumatoid Arthritis Using FDG-PET/CT

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Introduction: In recent years, the treatment of newly developed biologics have changed the therapeutic strategy for treating rheumatoid arthritis (RA). A humanized anti-interleukin-6 receptor (anti-IL-6R) antibody, tocilizumab (TCZ), is one of these new drugs. The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) immediately decrease after the initiation of TCZ therapy. Therefore, clinical physicians are sometimes confused with regard to how to judge the efficacy of TCZ therapy, especially within six months of the initiation of treatment.

Positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) can be used to evaluate the activity of RA. Because 18F-FDG PET can be used to precisely recognize an increase in synovitis in affected joints, imaging studies with 18F-FDG PET have been performed to assess the metabolic activity of synovitis in RA patients and evaluate the disease activity of RA. In addition, PET enables the quantitative measurement of RA joints using the standardized uptake value (SUV).

Hence, in the present study, we evaluated whether the findings of FDG-PET matched the conventional assessments of the Disease Activity Score in 28 Joints (DAS28), DAS28-CRP, simplified disease activity index (SDAI) and clinical disease activity index (CDAI) at three and six months after initiating TCZ therapy in RA patients.

Methods: Patients and methods

The institutional review board of our hospital approved the protocol for this study, and informed consent was obtained from each patient. Seventeen patients (5 males, 12 females; average age: 59.9 ± 11.7 (30-82) years) were enrolled in this study. All patients were diagnosed according to the American College of Rheumatology (ACR) criteria revised in 1987, and all had a history of a clinically inadequate response to previous treatment with non-biological disease modifying antirheumatic drugs (DMARDs) and biological agents, only including TNF inhibitor.

The average disease duration was 12.7 ± 10.4 (1 - 41) years. After undergoing a baseline assessment with whole-body 18F-FDG PET combined with computed tomography (CT) (FDG-PET/CT), the subjects received TCZ therapy. FDG-PET/CT was performed at three and six months after the initiation of treatment. Clinical parameters, including the ESR and serum CRP and matrix metalloproteinase-3 (MMP-3), were obtained. The degree of disease activity was assessed using the DAS28, DAS28-CRP, SDAI and CDAI.
Whole-body PET scans were performed 60 minutes following the intravenous injection of 18F-FDG (5 MBq/kg) after the patient had fasted for more than six hours. Data acquisition was carried out in 3D mode using a PET-CT scanner (Biograph 16, Siemens Medical Solutions, Inc.). The patients were scanned from the head to the toe in the arms-down position. The PET images were interpreted by the experienced nuclear physicians, who recorded an increased FDG uptake in the bilateral shoulder, elbow, wrist, hip, knee and ankle joints. For the semiquantitative analysis of the PET images, functional images of the SUV were produced. The therapeutic response was evaluated based on the changes in the total value of the maximum SUV of the affected joints (total SUV) and the DAS28, DAS28-CRP, SDAI, CDAI, ESR, CRP and MMP-3 scores. We used either all 12 joints evaluated on FDG PET or eight (bilateral shoulder, elbow, wrist and knee) joints to calculate the total SUVmax.

**Statistical analysis**

Spearman's rank correlation test was applied to evaluate the correlations between the different parameters recorded in this study. Based on a power analysis, the estimated total sample size was at least 16 patients (correlation $\rho_{H1} = 0.65$, $\alpha = 0.05$, $\beta = 0.20$). Wilcoxon's signed-rank sum test was used to assess the differences in the effects of treatment. The IBM SPSS Statistics 21 software program was used for the analysis, and values of $P < 0.05$ were considered to be statistically significant.

**Results:** The disease activity, as assessed according to the composite measurements, DAS28-CRP and SDAI, which included the CRP level, was significantly decreased at three months and six months. Similarly, the CDAI, which did not include the serum CRP level, was also decreased at three months and six months after the initiation of TCZ treatment. The serum MMP-3 level was also significantly decreased at three and six months after starting treatment.

In addition, the total SUV values decreased at three months ($18.1 \pm 7.9 / 15.3 \pm 6.6$) and at six months ($21.8 \pm 8.3 / 14.5 \pm 8.6$) compared to those observed at baseline ($24.8 \pm 9.5 / 20.8 \pm 7.7$) (12/8 joints, respectively).

According to the correlation analyses, the $\Delta$SUV (3M-0M) values were positively correlated with the $\Delta$DAS28 (3M-0M) ($r = 0.615$, $p = 0.009$ / $r = 0.610$, $p = 0.009$), $\Delta$DAS28-CRP (3M-0M) ($r = 0.696$, $p = 0.002$ / $r = 0.723$, $p = 0.001$), $\Delta$SDAI (3M-0M) ($r = 0.652$, $p = 0.005$ / $r = 0.652$, $p = 0.005$ / $r = 0.637$, $p = 0.006$) and $\Delta$CDAI (3M-0M) ($r = 0.662$, $p = 0.004$ / $r = 0.640$, $p = 0.006$) values (12/8 joints, respectively). There were also significant correlations between the $\Delta$SUV6M-0M values and the $\Delta$DAS28 (6M-0M) ($r = 0.775$, $p < 0.001$ / $r = 0.749$, $p = 0.001$), $\Delta$DAS28-CRP (6M-0M) ($r = 0.828$, $p < 0.001$ / $r = 0.775$, $p < 0.001$), $\Delta$SDAI (6M-0M) ($r = 0.686$, $p = 0.002$ / $r = 0.623$, $p = 0.008$) and $\Delta$CDAI (6M-0M) ($r = 0.711$, $p = 0.001$ / $r = 0.686$, $p = 0.002$) values (12/8 joints, respectively).

**Discussion:** FDG-PET utilizes molecular imaging to obtain images, not of the morphology, but of the metabolism of cells. In this study, we evaluated the effects of TCZ therapy three and six months after the initiation of treatment using the SUVmax of FDG-PET/CT semiquantitatively. Our results indicate that inflammatory synovitis was suppressed in the RA joints at both three and six months after starting TCZ treatment, and that the composite measurements conventionally used by rheumatologists, with or without the serum CRP level or ESR, properly reflect the disease activity in RA patients with TCZ therapy.
The precise mechanism underlying the blockage of FDG uptake in synovial cells under biological treatment remain unclear. One potential mechanism is a decrease in the number of synovial cells in inflamed joints due to the therapy. In addition, the suppression of neoangiogenesis and cellular infiltration may also reduce the FDG uptake in affected joints. There was a significant decrease in the serum MMP-3 level, which is thought to primarily reflect the volume of the RA synovium at both three and six months after the initiation of TCZ treatment. These results indicate that TCZ therapy reduced the volume of the synovium in the RA patients at three and six months after the initiation of treatment, and that MMP-3 is one of the physiological indicators of the clinical course of RA under TCZ therapy.

There are some limitations. First, we did not have an untreated comparison group in this study. Second, we did not evaluate the small joints in the RA patients because such assessments require additional devices and long examination times. Further prospective studies will need to be performed to evaluate the FDG uptake in the joints of RA patients using FDG-PET/CT.

**Significance:** The disease activity estimated on FDG-PET/CT matched the conventional parameters following the TCZ therapy in RA patients. FDG-PET/CT might be a useful tool for monitoring the response to anti-IL-6 therapy in RA patients.

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