Introduction

An increase in the incidence of HF has been reported in patients with RA. The risk of HF was previously shown to be approximately 2-fold higher in patients with RA than in the general population, and is known to markedly contribute to mortality in these patients\(^1\)\(^-\)\(^2\). The increased incidence of cardiovascular (CV) events\(^3\) and higher prevalence of diastolic dysfunction\(^4\) may account for the development of HF in patients with RA. A disease duration of more than 10 years, rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (CCP) antibody positivity, the presence of severe extra-articular manifestations, and higher levels of C-reactive protein (CRP) have been associated with an increase in the risk of CV events\(^3\), all of which are listed as poor prognostic factors and are among the main considerations for biologics. Nevertheless, TNF-α inhibitor therapy is contraindicated in patients with New York Heart Association (NYHA) class III/IV HF\(^5\)\(^-\)\(^6\). We herein described a 46-year-old male patient with active RA and severe congestive HF, who has been administered TCZ for 5 years without adverse events.

Case report

A 41-year old male was transferred to our hospital in July 2008 because of multiple joint and chest pain. A general examination in the emergency room indicated the acute exacerbation of both RA and congestive HF. A cardiac examination, including ultrasonography and cardiac angiography, revealed diffuse hypokinesis with a left ventricular ejection fraction (LVEF) of 16.8% and New York Heart Association (NYHA) class III/IV HF. Swelling and tenderness were noted in most of his joints. Methotrexate (MTX) was initiated during his hospitalization and TCZ was introduced 6 months later. Our patient has been treated with MTX and TCZ for five years without any adverse events, and RA and HF have remained stable. Although it may be anecdotal, we suggest that TCZ may be used as a treatment option in patients with RA complicated by severe HF.

Key words——rheumatoid arthritis; heart failure; NYHA III/IV; treatment; tocilizumab
cm and 80 kg, respectively, and his body mass index was 29.4 cm/m². His body temperature was 38.4°C, blood pressure was 106/- mmHg, and heart rate was 117 beats per minutes. His oxygen saturation while breathing ambient air was 98%. A third heart sound was audible, while neither cardiac murmur nor pulmonary wheezing was detected. Leg edema was absent. Swelling and tenderness were found in almost all joints examined and swan neck deformities and ulnar deviations were noted in the bilateral hands. Biochemical tests showed a C-reactive protein (CRP) level of 24.4 mg/d and His RF and anti-CCP antibody levels were 161.8 IU/ml (normal < 10 IU/ml) and 69.8 U/ml (normal < 4.4 U/ml), respectively. His serum IgG, C3, C4, and matrix metaroproteinase-3 levels were 1310 mg/dl (normal 907−1950 mg/dl), 177 mg/dl (normal 65−135 mg/dl), 22.5 mg/dl (normal 10.9−39.7 mg/dl), and 258.7 ng/ml (normal 36.9−121.0 ng/ml), respectively, and his brain natriuretic peptide (BNP) concentration was 232.4 pg/ml (normal < 18.4 pg/ml). An X-P examination of the chest revealed cardiomegaly without pleural effusion (Fig. 2a) and cardiac ultrasonography showed severe diffuse hypokinesis (EF of 16.8%) and marked dilatation of the left ventricle (left ventricular diastolic diameter (7) of 77.9 mm) (Fig. 3). A granular ‘sparkling’ appearance with increased echogenicity characteristic to cardiac amyloidosis was not detected. An X-P of the bilateral hands and feet revealed the prominent erosion of bone, ankylosis, and joint space narrowing. The diagnosis of RA was confirmed according to the 1987 American College of Rheumatology classification criteria and NYHA class III/IV HF. He resumed taking 8 mg of MTX weekly and 10 mg of PSL daily, along with 1000 mg per day of sulfasalazine, and also restarted diuretics, angiotensin II blockers, anti-platelet therapy, and β-adrenergic receptor antagonists for HF. He was discharged from our hospital on hospital day 16.
In December 2009, 8 mg/kg of TCZ monthly was introduced because RA disease activity was not sufficiently under control. At the time of the induction of TCZ, his CRP level and ESR value were 0.78 mg/dl and 37 mm/hr, respectively and the disease activity score (DAS) 28-ESR was 6.87. His serum BNP value was 739.1 pg/ml and IL-6 level 26 pg/ml (normal 0−7 pg/ml). An X-P of the chest revealed cardiomegaly and an electrocardiogram indicated that there were no new ST-T segment changes. Follow-up cardiac ultrasonography showed that his LVEF was 16.6% and LVDd 79 mm. Six months after the induction of TCZ, DAS28-ESR improved to 1.93 and the dose of PSL administered was progressively tapered to 2.5 mg/day. Intravenous TCZ has been uneventfully repeated for five years and consecutive monitoring of cardiac function by ultrasonography has showed no evidence of deteriorations in HF. We have continued to administer TCZ intravenously, the patient has not been rehospitalized because an exacerbation in HF, and DAS 28-ESR remains within moderate disease activity (Fig. 4). An X-P of the chest had shown no further deterioration of heart failure (Fig. 2b). He is currently receiving 6 mg of MTX weekly and no PSL, and is using a mobility scooter.

Discussion

We herein described a RA patient with high disease activity, who had been compromised by NYHA class III/IV HF and successfully treated with TCZ for five years without adverse events. To the best of our knowledge, this is the first case report of the successful long-term treatment with TCZ of a patient with RA complicated by severe HF.

The development of HF is known to be more common in RA patients than in the general population. Patients with RA have an approximately 2-fold higher risk of heart failure, and this comorbidity has a profound impact on mortality in these patients1−2). The higher frequency of myocardial infarction and increased prevalence of left ventricular diastolic dysfunction have previously been reported in patients with RA3), and these pathophysiology are the main contributors to the development of HF. The disease duration of RA is an important predictor...
of both cardiovascular events and diastolic dysfunction. Anti-CCP antibody and RF positivity as well as severe disease conditions such as extra-articular manifestations are also well-known risk factors for cardiovascular events\(^2\text{-}^8\), all of which are poor RA prognostic factors and, thus, the main considerations for introducing biological agents\(^9\). However, TNF-\(\alpha\) inhibitor therapy is contraindicated in patients with class III/IV HF\(^5\text{-}^6\). Our patient first presented to a different hospital in 2007 and was diagnosed with 3-vessel coronary artery disease and severe HF with diffuse hypokinesia in the left ventricle at the age of 41. Although our patient appeared to be younger than the peak age of onset, his anti-CCP antibody level, RF positivity, and long disease duration as well as obesity, a long-standing history of cigarette smoking, and hypertension all contributed to increasing the risk of developing cardiovascular events and diffuse hypokinesia.

Our patient was almost bedridden and RA disease activity was high at the time of admission. An X-ray of the hands revealed advanced joint deformity. Therefore, we were compelled to introduce TCZ even in the presence of severe HF after he failed to reach the optimal level of disease activity in spite of receiving MTX monotherapy for several months. His RA disease activity has subsequently improved without any marked deteriorations. Moreover, regular ultrasonography demonstrated that LVEF had remained stable and his serum BNP value had not worsened over the five years. He has not been readmitted to our hospital due to deteriorated HF and has been able to move around in a mobility scooter.

Several studies have reported elevated levels of inflammatory cytokines, such as TNF-\(\alpha\) and IL-6, and circulating leukocytes in the plasma of HF patients, as well as in the failing myocardium itself\(^9\). The magnitude of the increase of TNF-\(\alpha\) was reported to be directly correlated with the severity of disease, hence the hypothesis that TNF-\(\alpha\) might play a role in the pathophysiology of HF\(^7\). Nevertheless, clinical trials using TNF-\(\alpha\) inhibitors in patients with moderate to severe HF mainly owing to ischemic etiology (> 60% for each study), with reduced ejection fraction of ≤ 30−35%, failed to demonstrate their efficacy and affected the clinical outcome\(^2\text{-}^12\).

A recent study showed that compared to controls, plasma levels of TNF-\(\alpha\) were only significantly elevated in HF with preserved EF (≥ 50%) (HFPEF), while levels of TNF receptor 1 and TNF receptor 2 were significantly elevated in both HFPEF and HF with reduced EF (≤ 50%) (HEREF). Furthermore, TNF receptor 2 was significantly elevated in HFPEF relative to HFREF, while IL-6 was not significantly different between controls and the HF groups. Interestingly, the primary etiology of HF was found to be much less likely to be ischemic in the HFPEF group and conversely, ischemic event was the main reason for HF in the HEREF group\(^13\). Another study also demonstrated that elevated plasma TNF receptor 1 was associated with a higher risk for HFPEF versus HEREF\(^14\). Taken together, HFPEF develops mainly after non-ischemic comorbidity and TNF-\(\alpha\)-mediated inflammation might be a point of pathophysiological difference between HF phenotypes. If anti-TNF-\(\alpha\) inhibitor therapy was given to patients with HEPEF, a clinically relevant benefit would be obtained compared to previous studies.

IL-6 is a proximal inflammatory mediator produced mainly by T cells, macrophages, and adipocytes, and promotes inflammatory responses via membrane-bound or circulating soluble IL-6 receptor (IL-6R) on monocytes, hepatocytes, and endothelial cells\(^15\). Soluble IL-6 activates the membrane-bound IL-6R, thereby initiating downstream proinflammatory cascades that increase hepatic production of C-reactive protein, fibrinogen, and other acute-phase reactants\(^16\). On the basis of recent genetic evidence in human beings, IL-6R signaling seems to have a causal role in development of coronary heart disease. In 25,458 coronary heart disease cases and 100,740 controls, the IL-6R rs7529229 single nucleotide polymorphism (SNP) marking a non-synonymous variant previously reported to be associated with increased proteolytic cleavage of the soluble IL-6R from its membrane-bound form, was associated with decreased odds of coronary heart disease events\(^17\). Another study dealing with the Asp358Ala variant in IL-6R, which impairs classic IL-6R signaling, also demonstrated a high association between IL-6R signaling and coronary artery disease\(^18\). Thus, IL-6 blockade could provide a novel therapeutic approach to prevention of coronary heart disease. Our patient was diagnosed with 3-vessel coronary artery disease and severe HFREF at the age of 41 and has been successfully and uneventfully treated by IL-6 blockade TCZ for five years. There is a possibility that...
TCZ has prevented the further deterioration of HFREF secondary to coronary artery disease for a long period of time. TCZ may be an efficacious treatment option in patients with active RA complicated by severe HF. We need to ascertain the safety and efficacy of TCZ in a larger number of patients with RA accompanied by ischemic heart disease-associated HF.

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References


