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Short Communication

Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients

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1. Introduction

Rheumatoid arthritis (RA) is a generally progressive, systemic autoimmune condition characterized by chronic erosive synovitis. Interstitial lung disease (ILD) is a common extra-articular manifestation of RA and is substantially more likely to cause morbidity and mortality [1]. Several disease-modifying anti-rheumatic drugs and numerous biological therapies for RA have been widely used. These treatments, targeted at alleviating symptoms and preventing joint destruction, represent an important advancement in RA treatment [2,3]. However, these agents pose a potential risk to RA patients, with ILD having been reported [4,5]. Furthermore, the optimal treatment of RA-ILD has not been determined.

We previously conducted a retrospective study of RA patients and assessed the risk of ILD exacerbation after the administration of biological therapy [5]. In this study, we indicated that tumor necrosis factor (TNF) inhibitors could potentially exacerbate ILD. Additionally, we identified KL-6 as a valuable surrogate marker for the early detection of ILD. These data suggested that non-TNF inhibitors were a more suitable treatment option for RA patients with ILD [5].

Abatacept is a soluble fusion protein, comprising cytotoxic T-lymphocyte-associated protein 4 and an Fc portion of immunoglobulin G1. Clinical studies have demonstrated its efficacy and safety in patients with RA [6,7]. In Japan, abatacept has been available since September 2010, and recently, it has been used as an alternative to TNF inhibitors. However, it remains unclear whether it also has the potential risk of worsening pre-existing ILD. In the present study, we

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investigated the effectiveness and safety of abatacept as a treatment for RA-ILD in comparison with those of TNF-inhibitors [5].

2. Methods

2.1. Patient population and study design

Records of 16 RA-ILD patients for whom abatacept treatment was initiated before March 2013 at the Department of Rheumatology, Kameda Medical Center, were initially reviewed for this study. All patients had been treated with abatacept for more than one year, and their serial data were available for this retrospective analysis. To determine the effect of abatacept on ILD progression, we retrospectively reviewed the patients' clinical findings, which were documented in their medical records, and analyzed the changes in chest computed tomography (CT) findings. We also compared the serum levels of KL-6 and matrix metalloproteinase 3 (MMP-3) before and one year after the initiation of treatment with abatacept. This retrospective and observational study was approved by the ethics committee of our institution (15 February 2013).

RA was diagnosed in the patients of the current study by rheumatologists on the basis of clinical symptoms, physical histories, and laboratory findings. The presence of ILD was confirmed by two pulmonologists. We visually assessed the severity of ILD using chest CT images as previously reported [5,8]. ILD severity was classified based on its vertical extent: grade 0, ILD not determined; grade 1, extended less than one-third; grade 2, extended more than one-third but less than two-thirds; and grade 3, extended more than two-thirds. The clinical activity of RA was evaluated using the Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS28-ESR) and Simplified Disease Activity Index (SDAI) values.

2.2. Statistical analyses

We used the Wilcoxon signed-rank test to analyze the changes in clinical parameters. This analysis was performed using SPSS Version 21. Data were expressed as mean values with standard deviations. For all statistical analyses, a p value of less than 0.05 was considered to be significant.

3. Results

3.1. Baseline characteristics

The mean age of the 16 patients was 71.1±8.8 years, and 63% patients were female (Table 1). The mean stage, class of RA, DAS28-ESR, and SDAI were 2.5±0.9, 2.2±0.8, 4.47±1.40, and 16.9±11.3, respectively. Of the 16 patients, 7 (44%) were previously administered TNF inhibitors (5 received etanercept [ETN] and 2 received infliximab), and 2 (13%) were administered the anti-interleukin-6 (IL-6) receptor antibody, tocilizumab. Analysis of patient CT scans confirmed that 9 (56%) patients had grade 1 ILD, 4 (25%) and 3 (10%) patients had grade 2 and grade 3 ILD, respectively.

Table 1 – Baseline characteristics of patients who initiated abatacept and TNF-inhibitors

	Abatacept[a] (n=16)	TNF-inhibitors[a] (n=46)	p-value
Age – yr	71.1±8.8	66.3±9.0	0.062
Gender–Male / Female – n.	6/10	20 / 24	0.769
State of rheumatoid arthritis			
stage	2.5±0.9	2.4±1.1	0.693
class	2.2±0.8	2.3±0.6	0.439
Levels of serum KL-6	575.6±544.9	371.1±292.9	0.127
Prednisolone – n (%)	14 (88)	42 (91)	0.643
-mg/day	6.6±2.4	7.7±3.2	0.631
ILD grade – n (%)			
1	9 (56)	24 (52)	1.0
2	4 (25)	16 (35)	0.549
3	3 (10)	6 (13)	0.683
ILD events[b] – n (%)	0	14 (30)	0.013
mild	–	10 (22)	–
moderate	–	3 (7)	–
severe	–	1 (2)	–

Plus-minus values are means ± SD.

[a] Seven patients switched the use of TNF inhibitors to abatacept for the increase of KL-6 levels or exacerbation of ILD; then, those data were duplicated in this analysis.

[b] To categorize the gravity of ILD events, we defined them as: "mild," ILD worsened but persisting in the same grade; "moderate," ILD increased 1 grade, e.g., from level 0 to 1; "severe," ILD grade increased by 2 levels [5].

3.2. Effect of abatacept on RA-ILD

After the initiation of abatacept, none of the patients experienced a worsening of ILD severity at one year (p=0.157). Moreover, two patients with grade 1 ILD showed complete resolution (Fig. 1A). The differences in the mean levels of KL-6 in 16 patients were not statistically significant between baseline and one-year post-abatacept initiation (575.6±544.9 vs. 530.7±468.5 U/mL, p=0.642). Additionally, in agreement with previous studies, MMP-3, DAS28-ESR, and SDAI values significantly decreased following abatacept treatment [6,7], and we were subsequently able to reduce the mean doses of prednisolone (PSL).

3.3. Comparison with the data in our previous study

To compare the effects of abatacept on RA-ILD with those of TNF-inhibitors, we surveyed all patients with RA who had been receiving biologic therapy up to March 2013 and selected 46 RA-ILD patients undergoing treatment with TNF-inhibitors (Table 1). The data replicated the data of our previous study [5], and seven patients switched their use of TNF inhibitors to abatacept owing to an increase in KL-6 levels or exacerbation of ILD. As shown in Table 1, the baseline characteristics of