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ORIGINAL RESEARCH

Safety of Tocilizumab on Rheumatoid Arthritis in Patients with Interstitial Lung Disease

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Purpose: The prognosis of rheumatoid arthritis (RA) with interstitial lung disease (ILD) is particularly poor. Although drugs that do not contribute to the progression of ILD should be used in RA treatment, none have been established. This study evaluated the safety of tocilizumab in terms of ILD activity.

Patients and Methods: This study prospectively enrolled all 55 patients with RA complicated by ILD who were treated with tocilizumab at Dokkyo Medical University Saitama Medical Center from April 2014 to June 2022. The outcome measures were MMP-3 and KL-6 as biomarkers of RA and ILD activity, respectively, and the relationship between them was analyzed.

Results: Both MMP-3 and KL-6 were significantly improved at 6 months of treatment ($P < 0.001$ and $P < 0.05$, respectively), and a weak correlation between MMP-3 and KL-6 was observed ($R^2 = 0.086$, $P = 0.087$). The group with increased MMP-3 due to RA progression had significantly higher KL-6 at 6 months compared with the group with RA improvement ($P < 0.05$). Also, the group with ILD progression on computed tomography had significantly higher MMP-3 compared with the groups with improvement or no change of ILD ($P < 0.05$ and $P < 0.01$, respectively). The mortality rate was 0% at 6 months, 2.0% at 1 year, 16.7% at 2 years, and 32.4% at 3 years, and mortality from acute exacerbation of ILD due to respiratory infection increased over time.

Conclusion: RA activity and ILD activity were found to be related at 6 months of treatment. Tocilizumab does not seem to affect the mechanism of ILD progression, as most patients showed improvement in both MMP-3 and KL-6 with tocilizumab within 6 months, when this drug would be expected to affect the lungs directly. However, respiratory infection exacerbated ILD from 1 year after the start of treatment. As immunosuppressive drugs, including tocilizumab, have a risk of respiratory infection, it is important to identify early signs of infection.

Keywords: interstitial lung disease, Krebs von den Lungen-6, KL-6, matrix metalloproteinase-3, MMP-3, rheumatoid arthritis, mortality, tocilizumab

Introduction

Around 10% of patients with rheumatoid arthritis (RA) have interstitial lung disease (ILD), which is an important and potentially fatal complication.[1–4]In RA with the usual interstitial pneumonia (UIP) pattern, which is a type of ILD, the reported 5-year mortality rate is over 50%.[5,6] Before RA treatment, a full screening to evaluate for ILD is required. When a patient with RA has ILD, drugs without risk of ILD progression should be used for RA treatment.

Methotrexate (MTX) is reported to have a risk of ILD development and progression.[7–9] Compared with other disease-modifying antirheumatic drugs (DMARDs), MTX therapy increases the risk of lung disease as it can cause lung damage due to cytokine release.[10,11] Respiratory side effects can be expected to occur within 4 weeks of starting MTX due to these idiosyncratic immunological responses.[12] However, in a systematic review of MTX, although 2.4% of patients had some type of lung toxicity, only 0.43% were definitive cases of pneumonitis attributable to MTX.[13] The response of the lungs to drug toxicity may be increased in patients who have RA with ILD compared with those without ILD. Although a treatment without lung toxicity should be used for RA patients with ILD, the relationship between RA treatment and

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lung toxicity has not been fully clarified. Some studies have reported that abatacept lowers the risk of ILD development and/or progression.[14–17] Non-MTX drugs or abatacept is therefore recommended for RA patients with UIP.[18] Also, anti-interleukin-6 (IL-6) treatments, such as tocilizumab and sarilumab, may not contribute to the development and/or progression of ILD,[16,17] given that IL-6 is a cytokine associated with progression of lung fibrosis.[19] However, in a systematic review, non-infectious pulmonary adverse effects were reported for which a causal relationship with tocilizumab could not be excluded.[20] Although anti-IL-6 therapy is theoretically expected to be safe, this has not been demonstrated clinically.

In addition to ILD progression due to drugs, infection can also trigger exacerbation of ILD.[21] Immunity in patients with RA is reduced by both RA medication and RA itself. To reduce the risk of ILD exacerbation, respiratory infection, including pneumonia, should be diagnosed as early as possible by careful monitoring.

Immunological responses in RA may contribute to the development of ILD. It has been reported that anti-cyclic citrullinated peptide antibody (ACPA) is strongly expressed in lung tissue and bronchial alveolar lavage fluid in RA patients with ILD.[22] Therefore, if ILD is caused by immunological responses in RA, then ILD may be improved by RA treatment. However, there are multiple mechanisms of ILD in RA, given that some patients who are seropositive for ACPA do not show expression of ACPA in lung tissue.[22] Also, ILD occurs in RA patients who are ACPA negative. It is not clear why ILD manifests as a complication of RA.

The aim of this study was to clarify the effects of tocilizumab, which is theoretically safe for ILD, on rheumatoid ILD. Matrix metalloproteinase-3 (MMP-3) was evaluated as a biomarker for RA activity. MMP-3 reflects synovial inflammation and is correlated with histological synovitis in RA.[23] C-reactive protein (CRP) also reflects inflammation in RA but was not used as a biomarker because IL-6 induces the production of CRP, which shows a false negative when an anti-IL-6 antibody is used. Krebs von den Lungen-6 (KL-6) was evaluated as a measure of ILD activity. KL-6 is distributed mainly on the cell surface of type II alveolar epithelial cells and is a potential immunological biomarker reflecting the severity and progression of ILD.[24] This study also analyzed the relationship between MMP-3 and KL-6.

Materials and Methods

Study Design and Patients

This prospective study was conducted in the Division of Rheumatology at Dokkyo Medical University Saitama Medical Center, which was established in April 2014. This study enrolled and analyzed all 55 patients with RA complicated by ILD who were treated with tocilizumab at this facility from April 2014 to June 2022. Assuming a significance level of 0.05, power of 0.8, and an effect size of 0.8, the minimum sample size needed for parametric analysis is 25. We planned to enroll double the minimum sample size. After the number of patients surpassed 50, reaching 55, in June 2022, we stopped enrollment, completed data collection, and analyzed the data. After diagnosis of RA, all patients underwent chest computed tomography (CT) to screen for ILD. Treatment for ILD was not needed for all 55 patients because ILD activity was low or absent. All the patients required treatment with tocilizumab because of inadequate control of RA activity with conventional DMARDs. Clinical data of patients, excluding personal information, were extracted and analyzed. The outcome measure for RA was MMP-3, which reflects the activity of synovitis and is a biomarker of RA. The outcome measures for ILD were KL-6, which reflects the activity of lung fibrosis and is a biomarker of ILD, and chest CT. Individual percent changes in MMP-3 and KL-6 were calculated as (value after RA treatment – value before RA treatment)/(value before RA treatment) × 100 (%). The percent changes in MMP-3 and KL-6 from before RA treatment to 6 months after RA treatment and 1 year after RA treatment were analyzed. In addition, the percent changes between chest CT before and 1 year after the start of treatment were evaluated. Mortality was calculated at 6-month intervals from the diagnosis of ILD to the date of death. The Ethics Committee of Dokkyo Medical University (No. 20,132) approved this study. In accordance with the guidelines of the ethics committee, which included the Declaration of Helsinki, informed consent was via the opt-out method. Patients' clinical data, excluding personal information, were extracted from the medical records.

Assessment of MMP-3 and KL-6

MMP-3 and KL-6 were measured in blood samples. MMP-3 levels were measured by latex immunoassay (Panaclear MMP-3 "Latex"; Sekisui Medical Co., Ltd., Tokyo, Japan). The normal range of MMP-3 is 36.9–121.0 ng/mL for men and 17.3–59.7 ng/mL for women. KL-6 levels were measured by chemiluminescent enzyme immunoassay (Lumipulse G KL-6; FUJIREBIO Inc., Tokyo, Japan). The normal range of KL-6 is <500 U/mL.

Data Analysis

All statistical analyses were performed using Microsoft® Excel® 2019 MSO (Microsoft Corp., Redmond, WA) and JMP® Pro version 11.0.0 (SAS Institute, Cary, NC) statistical software. To minimize the effects of the sample size, a non-parametric analysis was performed. Paired samples were analyzed by the Wilcoxon signed-rank test. Unpaired samples were analyzed by the Mann–Whitney *U*-test. Relationships between two parameters were examined by correlation coefficients and linear regression analysis. Results are shown as the mean ± standard deviation, and a P value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

The patients' baseline characteristics are presented in Table 1. All patients had moderate or severe RA activity before treatment with tocilizumab and required biological therapy. Some patients were treated with corticosteroids for RA, and no patients were treated for ILD prior to ILD exacerbation.

MMP-3 and KL-6 After RA Treatment

To evaluate the effect of tocilizumab on RA and ILD, MMP-3 (Figure 1A) and KL-6 (Figure 1B) were examined before RA treatment and at 6 months and 1 year after RA treatment. The respective MMP-3 levels were 328 ± 346 ng/mL, 150 ± 195 ng/mL and 172 ± 215 ng/mL, and the respective KL-6 levels were 442 ± 315 U/mL, 437 ± 297 U/mL and 485 ± 376 U/mL. For both MMP-3 and KL-6, significant improvements were observed at 6 months ($P < 0.001$ and $P < 0.05$, respectively). Also, a significant improvement was observed for MMP-3 from before to 1 year after the start of treatment ($P < 0.001$). Neither MMP-3 nor KL-6 showed a significant improvement from 6 months to 1 year after RA treatment.

Table 1 Baseline Characteristics

Variable	Data
Age (median, range)	70, 21–83 years
Sex (n, male/female)	55, 22 / 33
Duration of RA (median, range)	1.4, 0.1–33.4 years
ACPA (positive/negative)	33 / 22
ACPA level (median, if positive)	241 U/mL
Type of ILD (UIP/NSIP)	14 / 41
Medication	
Methotrexate (n)	21
Salazosulfapyridine (n)	41
Corticosteroids (n)	16

Abbreviations: ACPA, anti-cyclic citrullinated peptide antibody; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

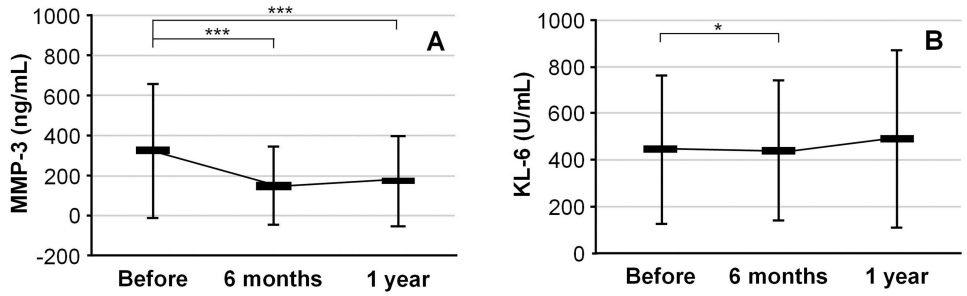

Figure 1 Changes over time in MMP-3 (**A**) and KL-6 (**B**) levels. *P<0.05, ***P<0.001 by the Wilcoxon signed-rank test for comparison of paired samples.

Relationship Between Percent Changes in MMP-3 and KL-6

To evaluate the relationship between percent changes in *MMP-3 and KL-6*, their correlations were assessed at 6 months (Figure 2A and 1) year after the start of RA treatment (Figure 2B). R^2 was 0.086 and 0.017, respectively. A weak positive correlation was observed at 6 months (P = 0.087).

Relationship Between KL-6 and RA Activity

To evaluate the relationship between KL-6 and RA activity, patients were divided into four groups according to RA activity. With MMP-3 before RA treatment taken as reference, patients with an MMP-3 decrease of ≥50% after 6 months or 1 year were defined as the complete remission (CR) group. Patients with an MMP-3 decrease of ≥10% to <50% were defined as the partial remission (PR) group. Patients with a percent change in MMP-3 of ≥-10% to <10% were defined as the no change (NC) group. Patients with an increase in MMP-3 by ≥10% were defined as the progressive disease (PD) group. Figure 3A and B show the relationship between percent change in KL-6 and RA activity group at 6 months and

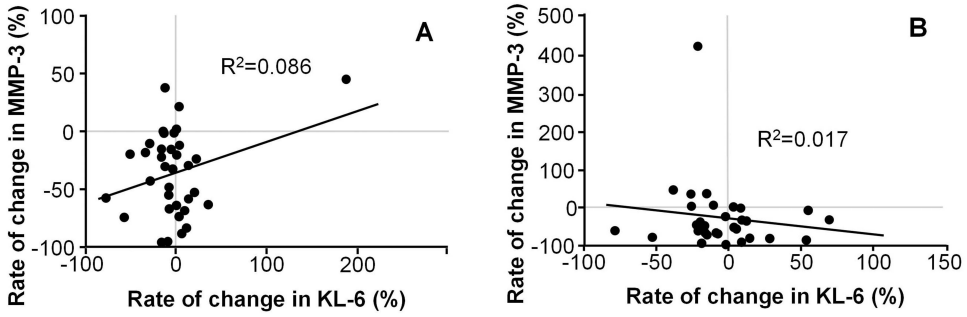

Figure 2 Results of linear regression analysis of the relationship between percent changes in MMP-3 and KL-6 at 6 months (**A**) and 1 year (**B**) after the start of treatment. The coefficients of determination (R^2) are shown.

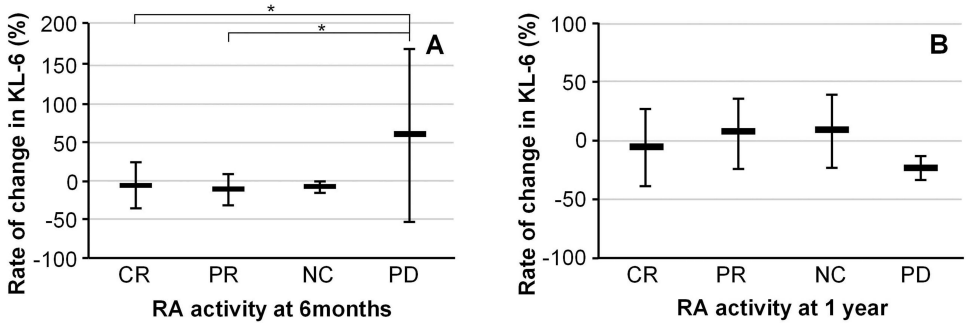

Figure 3 Relationship between percent change in KL-6 and RA activity group at 6 months (**A**) and 1 year (**B**) after the start of treatment. The PD group with RA progression also showed an increase in KL-6 at 6 months after RA treatment. *P<0.05 by the Tukey-Kramer HSD test.

1 year after RA treatment, respectively. The percent change in KL-6 at 6 months after RA treatment was −5.4 ± 29.4%, −11.5 ± 19.4%, −7.3 ± 7.6% and 59.4 ± 110.1% in the CR, PR, NC and PD groups, respectively. The respective values at 1 year were −7.4 ± 32.3%, 4.7 ± 29.6%, 6.6 ± 30.1% and −24.8 ± 9.8%. At 6 months, the mean percent change in KL-6 showed a significant increase in the PD group compared with the CR and PR groups (both $P < 0.05$). However, no significant differences were observed at 1 year.

Relationship Between MMP-3 and ILD Activity

To evaluate the relationship between MMP-3 and ILD activity, patients were divided into three groups according to ILD activity. Chest CT scans before RA treatment were taken as reference, differences in chest CT at 1 year after RA treatment were evaluated and patients were divided into the following groups: improvement, no change and progression. The percent change in MMP-3 at 1 year after RA treatment was −23.2 ± 98.8%, −34.7 ± 44.8% and 196.5 ± 318.8% in the respective groups (Figure 4). Significant differences were observed between the improvement and progression groups ($P < 0.05$) and between the no change and progression groups ($P < 0.01$).

The percent changes in MMP-3 and KL-6 according to type of ILD are shown in Table 2. A significant difference in the percent change in KL-6 was observed between UIP and nonspecific interstitial pneumonia (NSIP) at 6 months, but no significant difference was observed at 1 year. Also, in the relationship between the percent change in MMP-3 and the type of ILD, no significant difference was observed between UIP and NSIP at 6 months or 1 year.

Mortality in RA with ILD

Among the RA patients with ILD in this study, all were alive at 6 months after the start of treatment, and there were 12 deaths at 36 months. Table 3 shows mortality in these patients in 6-month intervals up to 36 months. All of these deaths were due to acute exacerbation of ILD induced by respiratory infection, and mortality increased as time elapsed.

Discussion

Most patients in this study showed decreases in both MMP-3 and KL-6 at 6 months after the start of RA treatment with tocilizumab, and a weak correlation was observed between MMP-3 and KL-6. Although some patients showed increasing KL-6 or MMP-3, patients with RA progression had increased KL-6, and patients with ILD progression on chest CT also had increased MMP-3. Thus, ILD activity was related to RA activity. Considering that no patients experienced acute exacerbation of ILD in the initial 6 months, tocilizumab did not affect the pathway of ILD in these patients. However, acute exacerbation of ILD occurred due to respiratory infection from 1 year after the start of treatment, and mortality increased as time elapsed.

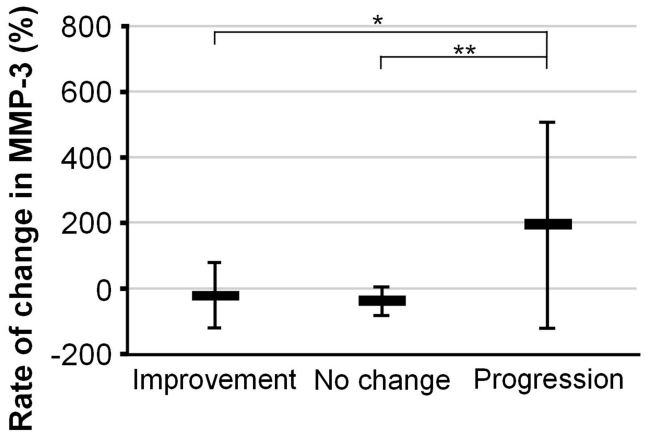

Figure 4 Relationship between MMP-3 and ILD activity evaluated by chest CT at 1 year after RA treatment. The group with ILD progression on chest CT also showed increased MMP-3. *P<0.05, **P<0.01 by the Tukey-Kramer HSD test.

Table 2 % Change in MMP-3 and KL-6 According to Type of ILD

	6 months			12 months		
	UIP	NSIP		UIP	NSIP	
MMP-3	−35.6 ± 34.9%	−41.6 ± 43.3%	N.S.	21.2 ± 157.0%	−36.6 ± 62.2%	N.S.
KL-6	−16.5 ± 17.9%	3.3 ± 44.4%	P<0.05	−8.1 ± 27.1%	−2.7 ± 31.3%	N.S.

Abbreviations: ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MMP-3, matrix metalloproteinase-3; N.S., not significant; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Table 3 Mortality (%) in RA Patients with ILD

	6 months	12 months	18 months	24 months	30 months	36 months
Mortality (%)	0	2.0	10.4	16.7	25.6	32.4

In this study, the median age was 70 years and the male to female ratio was 1:1.5. The mean age at RA onset in Japan has increased significantly, from 55.8 years in the period 2002–2003 to 59.9 years in the period 2012–2013.[25] Thus, the number of patients over 60 years of age has been rising. Also, the male to female ratio was 1:2.6 in the period 2010–2011,[26] and elderly-onset RA shows a male predilection.[27] Considering the current trend in age of onset and the male to female ratio, the patients in this study seem to reflect the RA population in Japan.

ILD induced by tocilizumab was evaluated at 6-month intervals after the start of RA treatment. In anti-TNF therapy, 70% of deaths due to ILD occurred in the first 5 weeks after starting biological therapy.[22] Similar to anti-TNF agents, tocilizumab is a biological drug, but it simply inhibits IL-6 and does not show accumulation of toxicity. However, the longer immunosuppressive drugs like tocilizumab are used, the greater the risk of respiratory infection. The evaluation interval of 6 months was appropriate for detecting early drug-induced exacerbation of ILD as well as later exacerbation due to respiratory infection as a result of immunosuppression.

IL-6 is one of the important cytokines involved in lung fibrosis. Soluble IL-6Rα (sIL-6Rα) binds IL-6, and the IL-6/sIL-6Rα complex can then activate various cells in the lung. Stimulation of IL-6 trans-signaling in fibroblasts increases extracellular matrix protein production and the proliferation of fibroblasts.[28] Therefore, anti-IL-6 treatment will inhibit lung fibrosis by suppressing IL-6 trans signaling. In addition, sIL-6Rα is released by M_2 macrophages. Abatacept is reported to inhibit migration of M_2 macrophages into the lungs.[29] Theoretically, this suggests that both tocilizumab and abatacept will inhibit lung fibrosis by suppressing IL-6 trans signaling. Our results support this theory.

In terms of type of ILD, UIP accounted for 25.5% of cases in our study. By contrast, UIP was reported to account for 78.8% in a study at the Saitama Cardiovascular and Respiratory Center (below, the Saitama study), which is a Japanese institution similar to Dokkyo Medical University Saitama Medical Center.[5] We cannot explain the reasons for this difference, except for the possible impact of the different study periods. The patients in the Saitama study were enrolled from 1996 to 2006, about 10 to 20 years before our study. The mortality rate at 3 years was 50.0% for UIP in our study, which was almost the same as in the Saitama study. UIP has a poor prognosis now, the same as in the past. For NSIP, the mortality at 3 years was 25.6% in our study, compared with 6.3% in the Saitama study. Differences in RA treatment may explain this difference in mortality. In 2003, infliximab came to market as the first biological drug approved in Japan, and it was followed by etanercept as the second in 2005. Given that biological drugs were sold only at the end of the study period, few patients in the Saitama study would have received these drugs. The reason for the increased mortality among patients with NSIP in our study might be that immunosuppression due to treatment of RA with tocilizumab increased the risk of infection compared with RA treatment without biologic drugs.[21]

Mortality increased from 1 year after RA treatment over the course of the study period. Respiratory infection is a risk factor for mortality even in RA without ILD because most RA drugs have immunosuppressive effects and an increased risk of opportunistic infection.[30] Although there is a low likelihood that tocilizumab directly contributed to progression of ILD, exacerbation of ILD may have occurred due to infection associated with tocilizumab.[21] The risk of infection

increased over time as the period of RA treatment became longer. It is important to diagnose infection earlier by monitoring, regardless of whether ILD is present.

It has not been clarified which factors cause ILD in patients with RA. As evidence that ILD is caused by RA, it has been reported that ACPA is strongly expressed in lung tissue and bronchial alveolar lavage fluid in RA patients with ILD.[22] Those results suggest that the target of ACPA is present in the lungs in addition to the joints and that ILD may develop as a result of RA with ACPA. In our results, a trend was observed that ILD activity was correlated with RA activity (eg, Figures 3A and 4). It has been hypothesized that in the lungs of patients with a genetic predisposition to RA, exposure to environmental stimuli such as smoke promotes citrullination of peptides in the lungs, thereby triggering the production of ACPA.[31] However, there are thought to be multiple mechanism of ILD in RA, given that some RA patients with ILD who are seropositive for ACPA do not show expression of ACPA in lung tissue.[22] In addition, ILD occurs in RA patients who are negative for ACPA. Thus, ILD may also develop through a pathway without ACPA. One possibility is that RA and idiopathic interstitial pneumonia develop as independent diseases at the same time, because some studies have reported that ILD caused after the start of tocilizumab.[20] Whatever the cause, it is not currently possible to categorize rheumatoid ILD because the mechanism of ILD has not been clarified.

A limitation of our study was that there was no control group, such as a non-treatment group or non-tocilizumab group. However, this study was not a clinical trial, and setting up a control group would raise ethical issues. If patients who need to be treated with biological antirheumatic drugs were allocated to the control group and not adequately treated for 1 year, articular destruction would occur. Also, anti-TNF alpha antibody could not be set as a control group, because of the possible risk of ILD exacerbation.[16] We provided the best treatment for each patient, and patients who required tocilizumab were enrolled and analyzed. We believe that this study provides useful results for RA and ILD, even if there was no control group. In our study, 16 patients received corticosteroids as RA treatment. Fifteen of these patients started using corticosteroids before the introduction of tocilizumab, and 1 started taking corticosteroids 10 months after the introduction of tocilizumab. No significant differences in KL-6 were observed according to corticosteroid use at 6 month (with vs without corticosteroids, 584 ± 411 vs 395 ± 249 U/mL) or at 1 year (723 ± 494 vs 439 ± 343 U/mL). Therefore, use of corticosteroids would not have affected the results of our study. MMP-3 is also increased by renal dysfunction. KL-6 is also increased by carcinomas or hypersensitivity pneumonitis. No patients had these diseases. In studies of RA, Disease Activity Score 28 (DAS28) is often used to evaluate RA activity. DAS-28 is calculated using the erythrocyte sedimentation rate or C-reactive protein and joint scores for the number of tender and swollen joints. DAS28 is used only in rheumatology because its calculation is complicated and the evaluation of joints is difficult. Because the results of this study have potential implications for physicians in both rheumatology and pulmonary medicine, and because MMP-3 can be easily measured, we used MMP-3 rather than DAS28 to evaluate RA activity. A weak positive correlation was observed between the percent changes in MMP-3 and KL-6 at 6 months. The reason why the correlation was weak might be that the fluctuations in KL-6 were small compared with those in MMP-3. Even if the fluctuations are small, a larger sample size might enable the detection of a significant correlation. We are planning to continue this study.

Conclusion

This study showed a trend in which ILD activity was correlated with RA activity. In most RA patients with ILD, both RA and ILD were improved by RA treatment with tocilizumab at 6 months. Those results show that tocilizumab did not affect the mechanism of ILD directly. Tocilizumab is an option for RA patients with ILD, considering that tocilizumab appears to be safe for ILD. However, mortality in RA patients with ILD increased over time because of respiratory infection. Respiratory infection was caused by the immunosuppressive effect of tocilizumab, and thus tocilizumab contributed indirectly to exacerbation of ILD. Although tocilizumab does not affect the mechanism of ILD directly, to reduce mortality, it is important to detect signs of infection and start treatment as early as possible.

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Disclosure

The authors report no conflicts of interest in this work.

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