Prognostic Factors and Radiographic Outcomes of Nontuberculous Mycobacterial Lung Disease in Rheumatoid Arthritis

Hideaki Yamakawa, Noboru Takayanagi, Yosuke Miyahara, Takashi Ishiguro, Tetsu Kanauchi, Toshiko Hoshi, Tsutomu Yanagisawa, and Yutaka Sugita

ABSTRACT. ***Objective.*** The aims of our study were to retrospectively review patients with rheumatoid arthritis (RA) with nontuberculous mycobacterial (NTM) lung disease, to assess the prognostic factors, and to analyze the time to disease deterioration according to the antirheumatic drugs received during the NTM lung disease followup period.

Methods. We retrospectively analyzed medical records of 98 HIV-negative RA patients with NTM lung disease treated at our institution, and investigated potential risk factors of mortality with Cox regression analysis. Time to radiologic deterioration was evaluated if antirheumatic drugs were not changed during observational periods and computed tomography was performed once each year.

Results. Mean patient age was 67.6 years, and median followup period was 4.4 years. NTM species included *Mycobacterium avium* complex (83.7%), *M. kansasii* (6.1%), *M. gordonae* (6.1%), and others (4.1%). Radiographic features included nodular/bronchiectatic (NB) disease (57.1%), fibrocavitary (FC) disease (14.3%), FC+NB disease (16.3%), and other types (12.2%). Initial management included observation in 74 (75.5%) patients. Negative prognostic factors of mortality were C-reactive protein (CRP) ≥ 1.0 mg/dl and radiographic features of FC, FC+NB, or other disease types. Median time to radiologic deterioration was 3.6 years. Erythrocyte sedimentation rate (ESR) > 50 mm/h was a negative prognostic factor of radiologic deterioration.

Conclusion. The most frequent NTM species was *M. avium* complex. CRP and radiographic features were prognostic factors for all-cause mortality, and ESR was a prognostic factor of radiologic deterioration. Further studies are warranted focusing on time to disease deterioration according to antirheumatic drug received during NTM followup. (First Release April 15 2013; J Rheumatol 2013;40:1307–15; doi:10.3899/jrheum.121347)

Key Indexing Terms:
RHEUMATOID ARTHRITIS NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE
DRUG TOXICITY PROGNOSTIC FACTORS RADIOLOGIC DETERIORATION

Rheumatoid arthritis (RA) is a destructive, systemic inflammatory disorder[1] with overall standardized mortality rates of 1.27 to 2.26[2,3]. Patients with RA have increased risk of infection compared with the general population[4]. Methotrexate (MTX), tumor necrosis factor (TNF) antagonists, and corticosteroid at doses > 10 mg daily are associated with increased risks of overall infection, and low-dose corticosteroid and TNF antagonists increase the risk of opportunistic infections[5]. Tuberculosis and nontuberculous mycobacteria (NTM) infections in association with concurrent administration of TNF antagonists have been reported[6,7]. Subsequently, much attention has been focused on prevention of tuberculosis in patients using TNF antagonists[8,9]. After such preventive efforts, cases of NTM diseases associated with anti-TNF therapy occurred twice as frequently as cases of tuberculosis associated with anti-TNF therapy in the United States[6]. In North America, crude incident rate per 100,000 patient-years of tuberculosis and NTM in the general population, RA patients unexposed to TNF antagonists, and RA patients using TNF antagonists were 2.8 and 4.1, 8.7 and 19.2, and 56 and 105, respectively[7]. NTM is of particular importance to patients with RA[7]. Thus, to elucidate the distinctive characteristics of NTM lung disease in RA patients receiving anti-TNF therapy, it might be necessary to compare these patients with those using other antirheumatic drugs.

NTM are ubiquitous organisms. *Mycobacterium avium* complex (MAC) includes at least 2 mycobacterial species, *M. avium* and *M. intracellulare*, the species most frequently associated with NTM lung disease in most of the world[10]. NTM lung disease comprises 5 clinical diseases: nodular/

From the Department of Respiratory Medicine and Department of Radiology, Saitama Cardiovascular and Respiratory Center, Saitama, Japan.

H. Yamakawa, MD; N. Takayanagi, MD, PhD; Y. Miyahara, MD; T. Ishiguro, MD, PhD; T. Yanagisawa, MD; Y. Sugita, MD, PhD, Department of Respiratory Medicine; T. Kanauchi, MD; T. Hoshi, MD, Department of Radiology, Saitama Cardiovascular and Respiratory Center.

Address correspondence to Dr. H. Yamakawa, Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, 1696 Itai, Kumagaya, Saitama 360-0105, Japan. E-mail: hide1144@jikei.ac.jp

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bronchiectatic (NB) disease, fibrocavitary (FC) disease, solitary pulmonary nodule, disseminated disease, and hypersensitivity-like disease[10]. We reported in Japanese that NTM lung disease was the most frequent pulmonary infection in 149 RA patients with pulmonary infections and that 59 (5.7%) of 1032 NTM lung disease patients in our institutions had RA[11]. However, those reports did not study features associated with outcome in RA patients with NTM.

The American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for NTM diseases state that patients with active NTM disease should receive TNF-α-blocking agents only if they are also receiving adequate therapy for the NTM disease[10]. Thus, is MTX or corticosteroid safe for RA patients with NTM lung disease? Assessment of clinical features, prognosis, and prognostic factors in RA patients with NTM lung disease may be increasingly useful because newer forms of biologic, immunosuppressive therapies are widely available for treatment of RA[12].

We hypothesized that host predisposition, NTM species, radiographic features, underlying respiratory disease, antirheumatic drugs at diagnosis, and initial management of NTM lung disease might influence all-cause mortality, and that antirheumatic drugs received during followup of NTM lung disease might influence time to radiologic deterioration of NTM lung disease. The aims of our study were thus to retrospectively review RA patients with NTM lung disease, assess the prognostic factors, and analyze time to disease deterioration according to the antirheumatic drugs received during the NTM lung disease followup period. Some results of this study were reported in the form of an abstract[13].

MATERIALS AND METHODS

Patients. We studied 98 RA patients with NTM lung disease over 18 years of age who fulfilled the 2007 ATS/IDSA NTM diagnostic criteria and were newly diagnosed from 1993 through June 2011. NTM lung disease diagnosis and therapy were conducted at Saitama Cardiovascular and Respiratory Center in Saitama, Japan. All patients fulfilled the revised criteria for RA of the American Rheumatism Association[14]. RA diagnosis and therapy were conducted by rheumatologists at other institutions.

Study design. This was a retrospective cohort study for which clinical data were collected from medical records. Baseline clinical measures were obtained within 1 month of the initial NTM diagnosis. Radiographic abnormalities were classified according to the following 6 disease patterns seen on chest high-resolution computed tomography (HRCT): NB, FC, FC+NB, several nodules with/without consolidation, disseminated, and unclassifiable[15]. We combined several nodules with/without consolidation and unclassifiable disease as other types. No patients had disseminated-type or hypersensitivity-like disease. Underlying respiratory diseases were classified as usual interstitial pneumonia (UIP), emphysema, previous pulmonary tuberculosis, bronchiolitis, and others. In patients with ≥ 2 underlying respiratory diseases, 1 dominant disease was chosen by consensus. Because bronchiectasis and NTM often coexist, making causality difficult to determine[10], bronchiectasis was not counted as an underlying respiratory disease[15]. Antirheumatic drugs administered at diagnosis and during followup of NTM lung disease were classified as follows: TNF antagonists/tocilizumab group if patients received either of these drugs; MTX group if patients received MTX but did not receive TNF antagonists/tocilizumab; corticosteroid group if patients received corticosteroid but did not receive TNF antagonists/tocilizumab or MTX; and other group. If drug administration for NTM lung disease was initiated within 6 months after diagnosis and continued for > 3 months, we considered this initial management[11]. If no treatment was initiated within 6 months after diagnosis, we considered initial management to be observation. Patients were followed through December 2011 or until death before December 2011. Survival status was obtained from medical records and/or telephone interviews. If the antirheumatic drug was not changed during the observational periods and HRCT was performed each year, assessment of radiologic change was independently performed by 2 radiologists and classified as improvement, no change, or deterioration. To quantify observer variation, κ coefficients of agreement were calculated for assessment of radiologic changes. Time to radiologic deterioration was evaluated for the period from the date of first HRCT to the date when deterioration was first observed. This study was approved by the institutional review board of Saitama Cardiovascular and Respiratory Center (no. 2011029).

Data analysis. Categorical baseline characteristics are summarized by frequency and percentage, and continuous characteristics are reported as mean ± SD. We compared baseline characteristics for each NTM species, each radiographic feature, each underlying respiratory disease, each antirheumatic drug received at diagnosis, initial management, and antirheumatic drugs during the NTM followup by Fisher's exact test or Kruskal-Wallis test in accord with nominal and continuous variables, respectively. We investigated potential risk factors of mortality with these variables chosen for entry into univariate Cox regression analysis: sex, age, smoking history, underlying pulmonary disease, systemic comorbidity, antirheumatic drugs received at diagnosis, NTM species, radiographic features, body mass index (BMI; we used the current World Health Organization BMI cutoff value for underweight of < 18.5 kg/m^2), hemoglobin, serum albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and initial management. We then performed multivariate Cox regression analysis with backward variable selection. Survival in each patient group was estimated by Kaplan-Meier analysis. All-cause mortality rates were compared with a log-rank test. For analysis of time to radiologic deterioration, data from patients without deterioration were censored at the last assessment. A value of $p < 0.05$ was considered statistically significant in all analyses. Missing data were categorized as "unknown" and were entered into each statistical analysis model. All data were analyzed with SAS version 9.1.3 (SAS Institute Inc.).

RESULTS

Patient characteristics, risk factors, and NTM species. Of the 98 patients, 65 were women (66.3%). Mean patient age was 67.6 years. No patients were infected with human immunodeficiency virus. NTM species included MAC in 82 patients (83.7%), *M. kansasii* in 6 (6.1%), and *M. gordonae* in 6 (6.1%). Others included *M. abscessus* in 2, *M. szulgai* in 1, and *M. chelonae* in 1 patient (Table 1).

Radiographic features. Radiographic features included NB disease in 56 patients (57.1%), FC disease in 14 (14.3%), FC+NB disease in 16 (16.3%), and other types, 12 (12.2%). Other types include several nodules with consolidation in 2 and unclassifiable in 10 patients (Table 2). In comparison with patients with FC or FC+NB disease, NB disease patients were significantly more frequently female, nonsmokers, received MTX at diagnosis, and underwent no treatment for NTM lung disease. Associated comorbidity, low BMI, hypoalbuminemia, and elevation of inflammatory markers occurred significantly more frequently in patients with FC or FC+NB disease than in those with NB disease.

Table 1. Baseline characteristics of the 98 study patients with nontuberculous mycobacteria lung disease classified by nontuberculous mycobacteria species. Data are no. (%) or ± SD.

Characteristics	Total	Nontuberculous Mycobacteria Species				p†
		MAC	*M. kansasii*	*M. gordonae*	Others*	
No. patients	98 (100)	82 (100)	6 (100)	6 (100)	4 (100)	
Female	65 (66.3)	58 (70.7)	2 (33.3)	4 (66.7)	1 (25.0)	0.204
Age, mean yrs ± SD	67.6 ± 9.9	67.8 ± 10.3	64.2 ± 8.3	66.5 ± 7.2	72.0 ± 6.2	0.667
Smoker	32 (32.7)	24 (29.3)	4 (66.7)	3 (50.0)	1 (25.0)	0.083
Comorbidity	74 (75.5)	59 (72.0)	6 (100.0)	5 (83.3)	4 (100.0)	0.554
Respiratory disease	49 (50.0)	37 (45.1)	5 (83.3)	4 (66.7)	3 (75.0)	0.117
UIP	16 (16.3)	10 (12.2)	3 (50.0)	1 (16.7)	2 (50.0)	0.049
Pulmonary emphysema	9 (9.2)	8 (9.8)	0 (0.0)	0 (0.0)	1 (25.0)	1.000
Previous pulmonary tuberculosis	7 (7.1)	6 (7.3)	0 (0.0)	1 (16.7)	0 (0.0)	0.629
Bronchiolitis	7 (7.1)	5 (6.1)	1 (16.7)	1 (16.7)	0 (0.0)	0.218
Others	10 (10.2)	8 (9.8)	1 (16.7)	1 (16.7)	0 (0.0)	0.374
Systemic disease	47 (48.0)	39 (47.6)	3 (50.0)	3 (50.0)	2 (50.0)	1.000
Antirheumatic drugs						0.317
MTX	31 (31.6)	23 (28.0)	2 (33.3)	3 (50.0)	3 (75.0)	
Corticosteroid	27 (27.6)	22 (26.8)	3 (50.0)	1 (16.7)	1 (25.0)	
TNF antagonists/tocilizumab	6 (6.1)	4 (4.9)	0 (0.0)	2 (33.3)	0 (0.0)	
Others	34 (34.7)	33 (40.2)	1 (16.7)	0 (0.0)	0 (0.0)	
Body mass index, kg/m^2	19.6 ± 3.0	19.4 ± 2.8	18.4 ± 3.5	23.5 ± 3.7	19.8 ± 1.4	0.044
Hemoglobin, g/dl	12.2 ± 1.5	12.2 ± 1.4	12.0 ± 2.5	12.7 ± 1.4	13.0 ± 0.6	0.584
Albumin, g/dl	3.6 ± 0.6	3.6 ± 0.5	3.2 ± 0.7	3.3 ± 0.6	3.7 ± 0.5	0.117
ESR, mm/h	64.3 ± 35.5	61.7 ± 35.5	92.7 ± 31.8	67.0 ± 20.8	68.0 ± 47.3	0.160
CRP, mg/dl	4.50 ± 7.00	4.23 ± 6.12	8.67 ± 14.59	2.51 ± 4.11	6.73 ± 11.79	0.537
Radiographic features						0.143
NB	56 (57.1)	49 (59.8)	1 (16.7)	5 (83.3)	1 (25.0)	
FC	14 (14.3)	11 (13.4)	2 (33.3)	0 (0.0)	1 (25.0)	
FC+NB	16 (16.3)	15 (18.3)	1 (16.7)	0 (0.0)	0 (0.0)	
Others	12 (12.2)	7 (8.5)	2 (33.3)	1 (16.7)	2 (50.0)	
Initial management						0.208
Observation or 1 drug	76 (77.6)	66 (80.5)	3 (50.0)	5 (83.3)	2 (50.0)	
≥ 2 drugs	22 (22.4)	16 (19.5)	3 (50.0)	1 (16.7)	2 (50.0)	

* Includes *M. abscessus* (n = 2), *M. szulgai* (n = 1), and *M. chelonae* (n = 1). † In relation to all types of nontuberculous mycobacteria species except Others. MAC: *Mycobacterium avium* complex; UIP: usual interstitial pneumonia; MTX: methotrexate; TNF: tumor necrosis factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NB: nodular/bronchiectatic disease; FC: fibrocavitary disease.

Underlying respiratory diseases. At least 1 underlying respiratory disease was present in 49 patients and included UIP in 16 patients (16.3%), emphysema in 9 (9.2%), previous pulmonary tuberculosis in 7 (7.1%), bronchiolitis in 7 (7.1%), and others in 10 (10.2%). Smoking history and radiologic features were significantly different according to the underlying respiratory disease ($p < 0.001$). Unclassifiable disease was present in 10 of 16 patients with UIP, and 8 of 9 patients with emphysema had FC disease.

Antirheumatic drugs at diagnosis. Antirheumatic drugs received at diagnosis included MTX in 31 (31.6%) patients (12 patients concomitantly received corticosteroid), corticosteroids in 27 (27.6%), TNF antagonists/tocilizumab in 6 (6.1%; TNF antagonists in 5 patients and tocilizumab in 1 patient; 4 patients concomitantly received MTX, but none received corticosteroid), and others in 34 (34.7%). All 6 patients receiving TNF antagonist/tocilizumab underwent chest HRCT when starting these drugs, and 3 of the 6 patients already had radiologic findings compatible with NTM lung disease. The patients receiving TNF antagonists/tocilizumab were younger (mean age 58.8 yrs) than those receiving MTX (70.8 yrs) or corticosteroids (mean age 67.8 yrs; $p = 0.013$). NB disease was more frequent in the patients taking MTX (74.2%) or TNF antagonist/ tocilizumab (83.3%) than in those taking corticosteroids (29.6%; $p = 0.009$).

Initial management. In 74 patients (75.5%), the initial management was observation. Patients receiving 0–1 drug more frequently had NB disease and higher BMI than did patients receiving 2–4 drugs.

Mortality. Death from any cause occurred in 38 patients (38.8%) over a median 4.4-year followup period (range 0.02–26.4 yrs), and overall cumulative 5- and 10-year mortality rates were 33.9% and 52.6%, respectively, whereas those of patients with MAC lung disease were 32.8% and 47.3%, respectively. Patients died from pneumonia (23.7%), progression of NTM lung disease (15.8%), UIP (10.5%), other respiratory diseases (13.2%), nonrespiratory diseases (15.8%), and unknown causes (21.1%).

Table 2. Baseline characteristics of the 98 study patients with nontuberculous mycobacteria lung disease classified by radiographic features. Data are no. (%) or ± SD.

Characteristic	Radiographic Features				
	NB	FC	FC+NB	Others*	p†
No. patients	56 (100)	14 (100)	16 (100)	12 (100)	
Female	48 (85.7)	2 (14.3)	9 (56.3)	6 (50.0)	< 0.001
Age, mean yrs ± SD	66.6 ± 11.0	71.4 ± 6.9	67.8 ± 9.0	68.2 ± 8.4	0.248
Smoker	10 (17.9)	11 (78.6)	7 (43.8)	4 (33.3)	< 0.001
Comorbidity	34 (60.7)	14 (100.0)	14 (87.5)	12 (100.0)	0.002
Respiratory disease	15 (26.8)	13 (92.9)	10 (62.5)	11 (91.7)	< 0.001
UIP	1 (1.8)	0 (0.0)	5 (31.3)	10 (83.3)	0.002
Pulmonary emphysema	1 (1.8)	8 (57.1)	0 (0.0)	0 (0.0)	< 0.001
Previous pulmonary tuberculosis	5 (8.9)	0 (0.0)	2 (12.5)	0 (0.0)	0.530
Bronchiolitis	6 (10.7)	1 (7.1)	0 (0.0)	0 (0.0)	0.444
Others	2 (3.6)	4 (28.6)	3 (18.8)	1 (8.3)	0.08
Systemic disease	23 (41.1)	9 (64.3)	8 (50.0)	7 (58.3)	0.244
Antirheumatic drugs					0.009
MTX	23 (41.1)	3 (21.4)	2 (12.5)	3 (25.0)	
Corticosteroid	8 (14.3)	6 (42.9)	8 (50.0)	5 (41.7)	
TNF antagonists/tocilizumab	5 (8.9)	0 (0.0)	1 (6.3)	0 (0.0)	
Others	20 (35.7)	5 (35.7)	5 (31.3)	4 (33.3)	
Body mass index, kg/m^2	20.1 ± 2.7	18.2 ± 2.3	17.8 ± 3.0	20.8 ± 3.5	0.011
Hemoglobin, g/dl	12.2 ± 1.5	12.2 ± 1.4	12.2 ± 1.7	12.5 ± 1.5	0.972
Albumin, g/dl	3.7 ± 0.6	3.2 ± 0.4	3.4 ± 0.5	3.7 ± 0.4	0.011
ESR, mm/h	55.5 ± 32.2	77.9 ± 40.9	80.8 ± 39.2	67.7 ± 30.4	0.041
CRP, mg/dl	2.41 ± 3.71	6.66 ± 8.07	10.48 ± 10.68	3.71 ± 7.08	0.001
Nontuberculous mycobacteria species					0.143
MAC	49 (87.5)	11 (78.6)	15 (93.8)	7 (58.3)	
M. kansasii	1 (1.8)	2 (14.3)	1 (6.3)	2 (16.7)	
M. gordonae	5 (8.9)	0 (0.0)	0 (0.0)	1 (8.3)	
Others	1 (1.8)	1 (7.1)	0 (0.0)	2 (16.7)	
Initial management					< 0.001
Observation or 1 drug	51 (91.1)	10 (71.4)	8 (50.0)	7 (58.3)	
≥ 2 drugs	5 (8.9)	4 (28.6)	8 (50.0)	5 (41.7)	

* Others includes several nodules with consolidation (n = 2) and unclassifiable (n = 10) cases. † In relation to all types of radiographic features except Others. NB: nodular/bronchiectatic; FC: fibrocavitary; UIP: usual interstitial pneumonia; MTX: methotrexate; TNF: tumor necrosis factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MAC: *Mycobacterium avium* complex.

Prognostic factors of all-cause mortality. Log-rank testing showed the following findings. There was a significant difference between survival curves in patients with MAC and *M. kansasii* (p = 0.024; Figure 1A). Because 3 patients with *M. kansasii* infection and UIP died early as a result of acute exacerbation of UIP (2 patients) and pneumothorax (1 patient), and 1 patient died of respiratory failure owing to bronchiolitis, outcomes of patients infected with *M. kansasii* were extremely poor. Survival curves for patients with NB disease were significantly different from those for patients with FC, FC+NB, or other disease types (p < 0.001; Figure 1B). Survival curves were also significantly different between patients with no underlying respiratory disease and those with UIP (p < 0.001), emphysema (p < 0.001), or other disease (p = 0.023; Figure 1C). Survival curves for patients receiving MTX were significantly different from those for patients receiving corticosteroid (p = 0.022) or other drugs (p = 0.024) at diagnosis (Figure 1D). Finally, there was no significant difference between survival curves in patients whose initial management included 0–1 drug and those in patients receiving 2–4 drugs (p = 0.151). A multivariate Cox proportional hazard model showed CRP level ≥ 1.0 mg/dl and radiographic features of FC, FC+NB, or other disease types to be negative prognostic factors of mortality (Table 3).

Antirheumatic drugs during NTM followup. Antirheumatic drugs received during NTM followup included MTX in 17 patients (35.4%), corticosteroids in 12 (25.0%), and TNF antagonists/tocilizumab in 9 (18.8%; TNF antagonists in 7 patients, tocilizumab in 2 patients). Of the 9 patients receiving TNF antagonists/tocilizumab, 6 were started on these drugs after a confirmed negative study of 3 sputum specimens for acid-fast bacilli smears, but nontuberculous mycobacteria were cultured after starting treatment. However, therapy was continued because these drugs were so effective against the RA. The other 3 patients were diagnosed as having NTM lung disease at the start of TNF

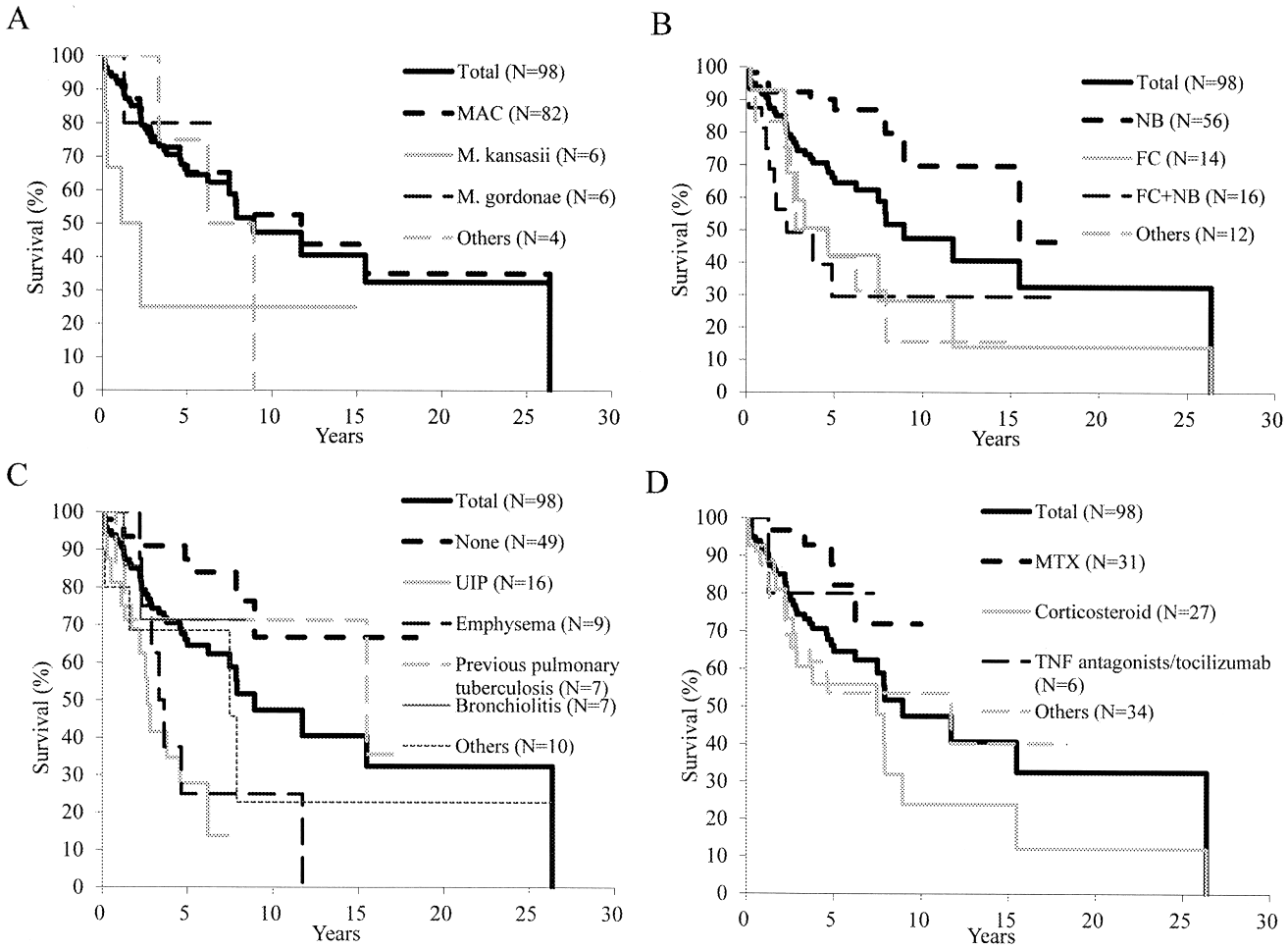

Figure 1. Kaplan-Meier survival curves of all-cause mortality stratified by nontuberculous mycobacterial (NTM) species (A), radiographic features (B), underlying respiratory disease (C), and antirheumatic drugs received at diagnosis (D) in patients with NTM and rheumatoid arthritis. Overall cumulative 5- and 10-year mortality rates were 33.9% and 52.6%, respectively. Log-rank testing indicated a significant difference between survival curves in the following: (A) patients with *M. avium* complex (MAC) or *M. kansasii* (MST 11.7 vs 1.7 yrs, respectively; $p = 0.024$); (B) patients with nodular/bronchiectatic (NB) disease (MST 15.48 yrs) or fibrocavitary (FC) disease (MST 4.65 yrs; $p < 0.001$), FC+NB disease (MST 2.30 yrs; $p < 0.001$), or other types (MST 3.71 yrs; $p < 0.001$); (C) patients with no underlying respiratory disease (MST not reached) or underlying respiratory disease of usual interstitial pneumonia (UIP; MST 2.68 yrs; $p < 0.001$), emphysema (MST 3.49 yrs; $p < 0.001$), or other disease (MST 7.48 yrs; $p = 0.023$); and (D) patients who received methotrexate (MTX) at NTM diagnosis (MST not reached) or who received corticosteroid (MST 7.48 yrs; $p = 0.022$) or other drugs (MST 11.70 yrs; $p = 0.024$). MST: median survival time; TNF: tumor necrosis factor.

antagonist/tocilizumab therapy, which was administered after we received informed consent from these patients because their RA disease activity was so high. Baseline patient characteristics according to these antirheumatic drugs were not statistically different (Table 4).

Risk factors of radiologic deterioration of NTM lung disease. Interobserver agreement regarding radiologic changes was good ($\kappa = 0.862$, 95% CI 0.733–0.990). Radiologic deterioration occurred in 20 patients (41.7%) over a 1.4-year median followup period (range 0.12–9.1 yrs). Median time to radiologic deterioration was 3.6 years, and the 5-year deterioration rate was 53.4%. Log-rank test showed no difference between Kaplan-Meier curves for each time to radiologic deterioration stratified by antirheumatic drug therapy (Figure 2). A multivariate Cox proportional hazard model showed that ESR > 50 mm/h was a negative prognostic factor of radiologic deterioration.

DISCUSSION

We investigated patients with RA with NTM lung disease to assess prognostic factors of all-cause mortality and to determine which antirheumatic drugs can be safely administered during followup of NTM lung disease. Survival rate was longest in patients with an HRCT pattern of NB disease versus that of patients with FC/FC+NB disease or other disease types. A CRP level ≥ 1.0 mg/dl was also found to be a negative prognostic factor of mortality. ESR > 50 mm/h was found to be a negative prognostic factor of radiologic deterioration.

Of the NTM species, *M. xenopi* is associated with a worse prognosis than MAC[16,17]. No patients in our study

Table 3. Factors associated with risk of all-cause mortality in the study patients.

Variable	Univariate Cox Regression Crude HR (95% CI)	p	Multivariate Cox Regression, Final Model Adjusted HR (95% CI)	p
Sex				
Female	Reference	—		
Male	1.975 (1.032–3.780)	0.040		
Age				
< 70 yrs	Reference	—		
≥ 70 yrs	2.561 (1.302–5.040)	0.006		
Smoking status				
Never smoker	Reference	—		
Ex/current smoker	1.501 (0.775–2.907)	0.229		
Respiratory comorbidity				
None	Reference	< 0.001††		
UIP	8.013 (3.176–20.216)	< 0.001		
Pulmonary emphysema	5.812 (2.091–16.154)	< 0.001		
Previous pulmonary tuberculosis	1.960 (0.506–7.602)	0.330		
Bronchiolitis	2.090 (0.441–9.911)	0.353		
Others	3.372 (1.096–10.380)	0.034		
Systemic comorbidity				
None	Reference	—		
Some	1.192 (0.624–2.279)	0.595		
Antirheumatic drugs				
MTX	Reference	0.090††		
Corticosteroid	3.597 (1.303–9.926)	0.013		
TNF antagonists/ tocilizumab	1.383 (0.161–11.859)	0.767		
Others	2.700 (0.965–7.551)	0.058		
BMI				
≥ 18.5 kg/m^2	Reference	0.379††		
< 18.5 kg/m^2	0.799 (0.399–1.602)	0.527		
Unknown	2.174 (0.488–9.684)	0.308		
Hemoglobin				
≥ 10.0 g/dl	Reference	—		
< 10.0 g/dl	0.450 (0.173–1.167)	0.101		
Albumin				
≥ 3.5 g/dl	Reference	0.023††		
< 3.5 g/dl	0.370 (0.182–0.752)	0.006		
Unknown	0.534 (0.191–1.496)	0.233		
ESR				
< 50 mm/h	Reference	0.058††		
≥ 50 mm/h	2.570 (1.155–5.719)	0.021		
Unknown	2.877 (0.845–9.798)	0.091		
CRP				
< 1.0 mg/dl	Reference	—	Reference	—
≥ 1.0 mg/dl	2.686 (1.296–5.565)	0.008	2.348 (1.097–5.024)	0.028
Radiographic features				
NB	Reference	< 0.001††	Reference	[< 0.001]††
FC/FC+NB	5.235 (2.355–11.638)	< 0.001	4.291 (1.903–9.678)	< 0.001
Others	5.384 (2.131–13.601)	< 0.001	5.902 (2.327–14.972)	< 0.001
Initial management				
Observation or 1 drug	Reference	—		
≥ 2 drugs	1.652 (0.827–3.298)	0.155		
NTM species				
MAC	Reference	—		
Others†	1.614 (0.735–3.545)	0.233		

† Others includes patients with *M. kansasii* (n = 6), *M. gordonae* (n = 6), *M. abscessus* (n = 2), *M. szulgai* (n = 1), and *M. chelonae* (n = 1). Factors determined by a multivariate Cox proportional model with backward selection. †† Indicates p value for the variable. UIP: usual interstitial pneumonia; MTX: methotrexate; TNF: tumor necrosis factor; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NB: nodular/bronchiectatic disease; FC: fibrocavitary disease; NTM: nontuberculous mycobacteria; MAC: *Mycobacterium avium* complex.

Table 4. Baseline characteristics of the 48 study patients with nontuberculous mycobacterial lung disease according to antirheumatic drugs received during disease followup. Data are no. (%) patients unless otherwise indicated.

Characteristics	Total	Antirheumatic Drugs Post-NTM Diagnosis				p*
		MTX	Corticosteroid	TNF Antagonists/ Tocilizumab	Others	
No. patients	48 (100)	17 (100)	12 (100)	9 (100)	10 (100)	
Female	35 (72.9)	14 (82.4)	7 (58.3)	6 (66.7)	8 (80.0)	0.354
Age, mean yrs ± SD	67.0 ± 8.9	66.5 ± 8.4	65.7 ± 9.2	67.0 ± 8.5	69.5 ± 10.3	0.996
Smoker	15 (31.3)	5 (29.4)	5 (41.7)	3 (33.3)	2 (20.0)	0.905
Comorbidity						
Respiratory disease	23 (47.9)	8 (47.1)	5 (41.7)	5 (55.6)	5 (50.0)	0.916
Systemic disease	24 (50.0)	7 (41.2)	8 (66.7)	4 (44.4)	5 (50.0)	0.416
Body mass index, kg/m^2	19.9 ± 2.8	20.4 ± 2.6	20.0 ± 2.8	20.0 ± 4.2	19.0 ± 2.0	0.710
Hemoglobin, g/dl	12.4 ± 1.4	12.1 ± 1.3	12.2 ± 1.9	12.7 ± 1.5	12.7 ± 0.8	0.597
Albumin, g/dl	3.7 ± 0.5	3.6 ± 0.5	3.5 ± 0.5	3.7 ± 0.3	4.1 ± 0.3	0.469
ESR, mm/h	58.8 ± 33.5	64.9 ± 33.9	67.7 ± 33.6	45.8 ± 39.7	43.9 ± 24.5	0.475
CRP, mg/dl	2.74 ± 3.85	3.26 ± 4.22	4.80 ± 5.01	1.39 ± 1.16	0.59 ± 0.92	0.423
NTM species						0.884
MAC	39 (81.3)	12 (70.6)	10 (83.3)	7 (77.8)	10 (100.0)	
Others†	9 (18.8)	5 (29.4)	2 (16.7)	2 (22.2)	0 (0.0)	
Radiographic features						0.952
NB	32 (62.7)	11 (64.7)	7 (58.3)	6 (66.7)	8 (80.0)	
FC	5 (10.4)	2 (11.8)	1 (8.3)	1 (11.1)	1 (10.0)	
FC+NB	7 (14.6)	2 (11.8)	3 (25.0)	2 (22.2)	0 (0.0)	
Others	4 (8.3)	2 (11.8)	1 (8.3)	0 (0.0)	1 (10.0)	
Antirheumatic drugs at NTM diagnosis						< 0.001
MTX	19 (39.6)	15 (88.2)	0 (0.0)	3 (33.3)	1 (10.0)	
Corticosteroid	10 (20.8)	0 (0.0)	10 (83.3)	0 (0.0)	0 (0.0)	
TNF antagonists/tocilizumab	6 (12.5)	2 (11.8)	1 (8.3)	3 (33.3)	0 (0.0)	
Others	13 (27.1)	0 (0.0)	1 (8.3)	3 (33.3)	9 (90.0)	
Initial management						0.519
Observation or 1 drug	36 (75.0)	12 (70.6)	8 (66.7)	8 (88.9)	8 (80.0)	
≥ 2 drugs	12 (25.0)	5 (29.4)	4 (33.3)	1 (11.1)	2 (20.0)	

† Includes patients with *M. gordonae* (n = 5), *M. kansasii* (n = 2), *M. abscessus* (n = 2). * In relation to all types of antirheumatic drugs except Others. NTM: nontuberculous mycobacteria; MTX: methotrexate; TNF: tumor necrosis factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MAC: *Mycobacterium avium* complex; NB: nodular/bronchiectatic disease; FC: fibrocavitary disease.

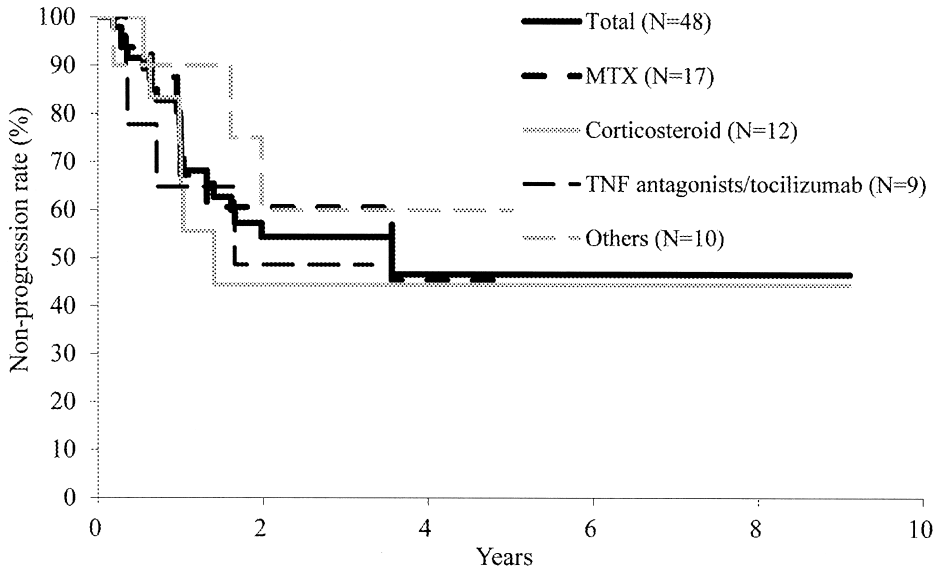

Figure 2. Kaplan-Meier survival curves for time to radiologic progression stratified by antirheumatic drugs. There were no significant differences in time to radiologic progression according to the antirheumatic drugs received during the nontuberculous mycobacteriosis followup period; median times to progression were 3.56, 1.40, and 1.66 years in the methotrexate (MTX), corticosteroid, and tumor necrosis factor (TNF) antagonists/tocilizumab groups, respectively.

had *M. xenopi* infection. Log-rank testing showed a significant difference between survival curves in patients with MAC and *M. kansasii*. However, because *M. kansasii*-infected patients died of underlying respiratory diseases, it might be misleading to highlight the difference in survival percentages.

In our study, FC, FC+NB disease, or other disease types were negative prognostic factors for all-cause mortality. Other radiographic features included 10 unclassifiable cases. Because all patients with unclassifiable disease had UIP, outcome associated with other radiographic features was poorer than that of NB disease.

We previously reported that 243 (38.2%) of 634 patients with MAC lung disease had underlying pulmonary diseases, and overall cumulative 5- and 10-year mortality rates of those 634 patients were 23.9% and 46.5%, respectively[15]. In the present study limited to patients with RA, 50.0% of patients presented with at least 1 underlying pulmonary disease, and overall cumulative 5- and 10-year mortality rates of the patients with RA with MAC lung disease were 32.8% and 47.3%, respectively. Because the review periods of this study cohort and the previous cohort were not the same, we could not compare them statistically. However, differences in the rates of underlying pulmonary disease between the 2 studies might be one reason for the difference in 5-year mortality rates.

Roles of antirheumatic drugs in the development of infections have been discussed previously[4,5,6,7,8,11,18,19,21,22,23,24,25], and NTM lung disease during therapy with TNF antagonists and tocilizumab has been reported[6,7,11,20,21,22,24,25,26,27]. In our study, antirheumatic drugs received at diagnosis included MTX, corticosteroid, TNF antagonists/tocilizumab, and others. The difference in survival curves between patients receiving MTX and corticosteroid was significant and may be because patients receiving MTX had NB disease more frequently than did patients receiving corticosteroids.

Kitada and coworkers reported that more than half of patients with NB MAC lung disease had radiologic deterioration at 5 years[27]. The 5-year deterioration rate in our present study was 53.4%. Although we hypothesized that antirheumatic drugs administered during followup of NTM lung disease might influence time to radiologic deterioration, we found no such difference for each antirheumatic drug. Mori and coworkers reported favorable therapeutic outcomes of NTM lung diseases in the setting of biological therapy[28]. However, the Japanese guidelines for use of infliximab and etanercept in RA recommend that TNF antagonists be avoided in patients with a history of NTM infection[29]. Griffith and Aksamit stated that TNF-α blockers confer an important predisposition for potentially serious, even fatal, NTM infection and must be used with extreme caution in patients with NTM disease[30]. Moreover, Winthrop and coworkers stated that 39% of patients with RA NTM exposed to TNF antagonists died, with a median time between infection and death of 569 days[7]. Our study was underpowered statistically to show a difference; thus, further studies are needed to determine which RA drug is safest in RA patients with NTM lung disease.

One of the most important and unresolved questions in MAC lung disease concerns immediate versus delayed start of treatment. In this study, initial management of three-quarters of the patients was by observation only, and initial management was not associated with all-cause mortality. One reason for this might be that patients whose initial management included treatment with 0–1 drug more frequently had NB disease than did patients treated with 2–4 drugs. Further accumulation of data is required to assess the relation between initial management and outcome.

A limitation of this study is that it was retrospective, so some clinical and laboratory findings were not available. Also, because of the way we classified antirheumatic drugs at diagnosis and during followup of NTM lung disease, the risk of combination therapy, e.g., TNF antagonists and MTX, contributing to infection was not assessed. However, Greenberg and coworkers reported no synergistic risks of infection for MTX and TNF antagonist combination therapy[5]. Further, we could not evaluate the effect on all-cause mortality of the antirheumatic drugs taken during the NTM lung disease followup period.

Finally, we evaluated time to radiologic deterioration only if antirheumatic drugs were not changed during the observational periods and CT was performed each year. Thus, this variable was evaluated in only 48 patients. Analysis was hampered by statistical power because of the small number of patients in the subgroups within the study. Further, because these 48 patients were not a random sampling of the 98 patients in the study, there is the possibility of sample bias.

We conclude that despite these limitations, our study clarified the following points. CRP level ≥ 1.0 mg/dl and radiographic features of FC, FC+NB, or other disease types were negative prognostic factors for all-cause mortality. Survival curves were significantly different between patients with no underlying respiratory disease and those with UIP, emphysema, or other disease and in patients receiving MTX and corticosteroids or other drugs at diagnosis. In this nonrandomized setting, conclusions that can be made about the association between NTM treatment and mortality are extremely limited. The complex courses of RA treatment prevented adequate assessment of whether specific antirheumatic drugs were associated with outcomes. Further studies are needed to clarify both the relation of underlying respiratory disease, antirheumatic drugs administered at diagnosis, or initial management and outcome; and the safety of antirheumatic drugs in RA patients with NTM lung disease.

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