Toyama,Yoshinari Takasaki (JuntendoUniversity); Naoichiro Yukawa, Tsuneyo Mimori (Kyoto University); Yukitaka Ueki (Sasebo Chuo Hospital), Shigeto Tohma (Sagamihara National Hospital), Kazuya Michishita, Kazuhiko Yamamoto (The University of Tokyo), Akira Hashiramoto, Syunichi Shiozawa (Kobe University); Akitomo Okada, Atsushi Kawakami (Nagasaki University); Tetsuji Sawada (Tokyo Medical University Hospital); Kazuhiko Ezawa (Kurashiki Kohsai Hospital); Sae Ochi (Tokyo Metropolitan Bokutoh Hospital); Hideto Kameda, Yuko Kaneko, Tsutomu Takeuchi (Keio University); Kenji Nagasaka (Ome Municipal General Hospital); Yoshinori Nonomura (Tokyo Kyosai Hospital); Kiyoshi Migita (National Hospital Organization Nagasaki Medical Center); Ayako Nakajima, Hisashi Yamanaka (Tokyo Women's Medical University). We appreciate Ms. Marie Yajima (Tokyo Medical and Dental University) for her contributions to data collection and the maintenance of the REAL database. Yokohama City Minato Red Cross Hospital is also a member of the REAL study group, but was not involved in this study. We sincerely thank all the rheumatologists and others caring for RA patients enrolled in the REAL.

References

1. Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B, Landewe RB, Smolen JS, Sokka T, van der Heijde DM (2010) Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 69(6):987–994. doi:10.1136/ard.2009.126748
2. Singh JA, Furst D, Saag KG (2012) 2012 update of the 2008 ACR recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of RA: reply to letter by Graudal et al. Arthritis Care Res (Hoboken). doi:10.1002/acr.21872
3. Koike R, Takeuchi T, Eguchi K, Miyasaka N (2007) Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. Mod Rheumatol 17(6):451–458. doi:10.1007/s10165-007-0626-3
4. Takeuchi T, Kameda H (2010) The Japanese experience with biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol 6(11):644–652. doi:10.1038/nrrheum.2010.154
5. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, Kamatani N, Harigai M, Ryu J, Inoue K, Kondo H, Inokuma S, Ochi T, Koike T (2008) Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis 67(2):189–194. doi:10.1136/ard.2007.072967
6. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, Takeuchi T, Tanaka Y, Yamanaka H, Fujii K, Freundlich B, Suzukawa M (2009) Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol 36(5):898–906. doi:10.3899/jrheum.080791
7. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, Yamanaka H, Tanaka Y (2012) Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol 22(4):498–508. doi:10.1007/s10165-011-0541-5
8. Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, Amano K, Nakajima A, Atsumi T, Koike T, Ihata A, Ishigatsubo Y, Saito K, Tanaka Y, Ito S, Sumida T, Tohma S, Tamura N, Fujii T, Sugihara T, Kawakami A, Hagino N, Ueki Y, Hashiramoto A, Nagasaka K, Miyasaka N, Harigai M (2012) Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 64(8):1125–1134. doi:10.1002/acr.21666
9. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP (2006) Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 54(8):2368–2376. doi:10.1002/art.21978
10. Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A, Listing J (2011) Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 70(11):1914–1920. doi:10.1136/ard.2011.151043
11. Lobo FS, Wagner S, Gross CR, Schommer JC (2006) Addressing the issue of channeling bias in observational studies with propensity scores analysis. Res Social Adm Pharm 2(1):143–151. doi:10.1016/j.sapharm.2005.12.001
12. Hetland ML, Lindegaard HM, Hansen A, Podenphant J, Unkerskov J, Ringsdal VS, Ostergaard M, Tarp U (2008) Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis 67(7):1023–1026. doi:10.1136/ard.2007.087262
13. ICH Steering Commitee. ICH harmonized tripartite guideline. Clinical safety data management: definitions and standards for expedited reporting (1995). URL: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf. Accessed 1 Nov 2013
14. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Gromnica-Ihle E, Antoni C, Herzer P, Kekow J, Schneider M, Zink A (2005) Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 52(11):3403–3412. doi:10.1002/art.21386
15. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Gorla R, Filippini M, Marchesoni A (2009) Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev 8(3):266–273. doi:10.1016/j.autrev.2008.11.002
16. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, Paulus HE, Mudano A, Pisu M, Elkins-Melton M, Outman R, Allison JJ, Suarez Almazor M, Bridges SL Jr, Chatham WW, Hochberg M, MacLean C, Mikuls T, Moreland LW, O'Dell J, Turkiewicz AM, Furst DE (2008) American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 59(6):762–784. doi:10.1002/art.23721
17. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, Aletaha D, Buch M, Gossec L, Huizinga T, Bijlsma JW, Burmester G, Combe B, Cutolo M, Gabay C, Gomez-Reino J, Kouloumas M, Kvien TK, Martin-Mola E, McInnes I, Pavelka K, van Riel P, Scholte M, Scott DL, Sokka T, Valesini G, van Vollenhoven R, Winthrop KL, Wong J, Zink A, van der Heijde D (2010) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying

antirheumatic drugs. Ann Rheum Dis 69(6):964–975. doi:10.1136/ard.2009.126532
18. Japan College of Rheumatology (2012) 2012 Update of Japanese guideline for use of TNF inhibitors http://www.ryumachi-jp.com/info/guideline_TNF_120704.pdf of subordinate document. Accessed 1 Nov 2013
19. Castro-Rueda H, Kavanaugh A (2008) Biologic therapy for early rheumatoid arthritis: the latest evidence. Curr Opin Rheumatol 20(3):314–319. doi:10.1097/BOR.0b013e3282f5fcf6
20. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, Furst DE (2011) High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 70(5):785–791. doi:10.1136/ard.2010.128637

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2014; Early Online: 1–6

DOI: 10.3109/14397595.2014.980384

informa
healthcare

ORIGINAL ARTICLE

Pulmonary infections following immunosuppressive treatments during hospitalization worsen the short-term vital prognosis for patients with connective tissue disease-associated interstitial pneumonia

Michi Tanaka[1,2], Ryuji Koike[1,2,3], Ryoko Sakai[1], Kazuyoshi Saito[4], Shintaro Hirata[4], Hayato Nagasawa[5], Hideto Kameda[6], Masako Hara[7], Yasushi Kawaguchi[7], Shigeto Tohma[8], Yoshinari Takasaki[9], Makoto Dohi[10], Yasuhiko Nishioka[11], Shinsuke Yasuda[12], Yasunari Miyazaki[13], Yuko Kaneko[14], Toshihiro Nanki[1,2], Kaori Watanabe[1,2], Hayato Yamazaki[1,2], Nobuyuki Miyasaka[2,15], and Masayoshi Harigai[1,2]

[1]*Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical Dental University, Bunkyo-ku, Tokyo, Japan,* [2]*Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical Dental University, Bunkyo-ku, Tokyo, Japan,* [3]*Clinical Research Center, Tokyo Medical Dental University Hospital, Bunkyo-ku, Tokyo, Japan,* [4]*First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Yahatanishi, Kitakyusyu, Japan,* [5]*Department of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe-shi, Saitama, Japan,* [6]*Division of Rheumatology, Department of Internal Medicine, School of Medicine, Toho University, Meguro-ku, Tokyo, Japan,* [7]*Institute of Rheumatology, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan,* [8]*Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Sagamihara-shi, Kanagawa, Japan,* [9]*Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Bunkyo-ku, Tokyo, Japan,* [10]*Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, Japan,* [11]*Department of Respiratory Medicine and Rheumatology, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima, Japan,* [12]*Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Kita-ku, Sapporo, Japan,* [13]*Department of Integrated Pulmonology, University Hospital of Medicine, Tokyo Medical & Dental University, Bunkyo-ku, Tokyo, Japan,* [14]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan, and* [15]*Global Center of Excellence (GCOE) Program; International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo, Japan*

Abstract

Objective. Connective tissue disease-associated interstitial pneumonia (CTD-IP) significantly affects the mortality of patients with CTD. The purpose of the present study is to identify causes and risk factors for death during hospitalization for immunosuppressive treatment of CTD-IP.

Methods. A multicenter, retrospective study was conducted that collected data from patients with CTD who had been hospitalized for commencing or intensifying immunosuppressive treatment of CTD-IP using a standardized case report form. Risk factors were identified using the Cox proportional hazard regression model.

Results. A total of 322 CTD-IP patients were enrolled with rheumatoid arthritis ($n = 84$), systemic lupus erythematosus ($n = 13$), polymyositis ($n = 33$), dermatomyositis ($n = 69$), systemic sclerosis ($n = 55$), mixed connective tissue disease ($n = 21$), microscopic polyangiitis ($n = 19$), and overlap syndrome ($n = 28$). Of the 42patients who died during hospitalization, 22 died from CTD-IP, 15 from CTD-IP and pulmonary infection, 2 from pulmonary infection, and 3 from other causes. Age ≥ 65 years and development of pulmonary infections after commencing or intensifying immunosuppressive treatments were identified as risk factors for death during hospitalization after adjusting for covariates.

Conclusion. Careful consideration of the benefit–risk balance of immunosuppressive treatment for CTD-IP is indispensable for improving the short-term vital prognosis of these patients.

Keywords

Connective tissue disease, Interstitial pneumonia, Immunosuppressive treatments, Pulmonary infections, Vital prognosis

History

Received 9 September 2014
Accepted 21 October 2014
Published online 10 December 2014

Introduction

Among the varieties of lung involvements in patients with connective tissue diseases (CTD), CTD-associated interstitial pneumonia (CTD-IP) is prevalent and has considerable influence on morbidity and mortality [1]. In clinical practice, CTD-IP is frequently observed in patients with rheumatoid arthritis (RA), polymyositis (PM)/dermatomyositis (DM), and systemic sclerosis (SSc). The prevalence of clinically definitive CTD-IP in RA, PM/DM, and SSc has been reported to be 7–14% [2], 5–46% [3], and 40–80% [1]; and 5-year survival rates were 40–90% [2,4–6], 50–87% [7,8], and 80–90% [9,10], respectively. Some studies even show that CTD-IP has a more unfavorable prognosis than idiopathic interstitial pneumonia when adjusted for age and gender [11,12].

Patients with active CTD-IP often receive treatments with corticosteroids with or without other immunosuppressants. The efficacy of immunosuppressive treatments depends on the type of CTD,

Correspondence to: Masayoshi Harigai MD, PhD, Department of Pharmacovigilance, Tokyo Medical and Dental University Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan. Tel: +81-3-5803-4677. Fax: +81-3-5803-4694. E-mail: mharigai.mpha@tmd.ac.jp

imaging pattern or pathological classification of CTD-IP, residual pulmonary function, and disease activity of CTD-IP [5,10,12–16]. Patients with CTD-IP sometimes develop life-threatening pulmonary complications, such as severe pulmonary infections [17–20] and mediastinal emphysema [21] during immunosuppressive treatment. To improve long-term survival of patients with CTD-IP, achieving better short-term survival is indispensable after the initial or remission induction treatment of CTD-IP. Few studies have reported short-term survival rates of patients with CTD-IP after commencing or intensifying immunosuppressive treatments [22–24], and little is known about the risk factors associated with death during treatment.

The present study reports the results of a multicenter, retrospective study of patients with CTD-IP who required hospitalization for immunosuppressive treatment. The purpose of this study was to identify causes and risk factors of death during hospitalization of CTD-IP patients with an emphasis on pulmonary infections occurring after commencing or intensifying immunosuppressive treatments.

Materials and methods

Patients

Ten university hospitals and one national hospital participated in this study. The retrospective cohort of this study consisted of patients with RA, systemic lupus erythematosus (SLE), PM, DM, SSc, mixed connective tissue disease (MCTD), microscopic polyangiitis (MPA), or overlap syndrome who required hospitalization for treatment of CTD-IP between April 2004 and March 2007. All participating hospitals searched their admission logs and enrolled virtually all patients eligible for this study. The diagnoses of CTDs were made by the attending rheumatologists with reference to the classification or diagnostic criteria of these diseases [25–30]. When one patient concurrently had two or more of the above-mentioned CTDs, the patient was classified as having overlap syndrome. The diagnosis of CTD-IP was determined by the attending physicians and investigators in the participating hospitals based on clinical manifestations, images on chest X-ray and thoracic computed tomography (CT), and laboratory tests, and confirmed by M.T. using medical records for each patient.

Collection of clinical data

Clinical data were systematically extracted for each patient using a standardized case report form and included age, gender, disease duration in months for each CTD, clinical characteristics of CTD-IP (i.e., new-onset or recurrent and presence or absence of mediastinal emphysema), details of treatment for CTD-IP after admission [i.e., maximum prednisolone (PSL)-equivalent daily dosage of oral corticosteroid, use of methylprednisolone pulse (mPSL pulse) therapy, and use of immunosuppressants], pulmonary infections after commencing or intensifying immunosuppressive therapy for CTD-IP, and the status of the patient with CTD-IP at discharge by the attending physician's global assessment (improved, unchanged, deteriorated, or death). These data were based on medical records obtained during hospitalization and outpatient visits after discharge. Causes of death were determined by two board-certified rheumatologists (M.T. and M.H.) and a board-certified specialist of infectious diseases (R.K.) based on medical records during hospitalization and the outpatient clinic. The start date of the observation period was the date immunosuppressive treatment for CTD-IP was commenced or intensified after hospitalization. Observation was stopped either on the date of death, loss-to-follow-up, or on March 30, 2007, whichever came first.

Statistical analysis

For group comparisons involving categorical variables, the chi-square or Fisher's exact test was used. Continuous variables were compared using the Mann–Whitney U test. To identify risk factors for death during hospitalization, the multivariate Cox proportional hazards regression model was used with the forced entry procedure. In addition, we used Benjamini and Hochberg (BH) method [31] to correct for multiple comparisons. BH method is one of the approaches to multiple comparison problems by controlling the false discovery rate (FDR). All analyses were performed using SPSS software, version 17.0 (SPSS Japan, Tokyo, Japan).

Ethics

This study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and other participating hospitals. The guidelines of the Helsinki Declaration and the ethics guidelines for epidemiologic research in Japan were followed. The ethics guideline for epidemiological research in Japan requires notifying eligible patients of the study and allows implementation of that study without obtaining individual written informed consent. This study was publicized by leaflets or posters in outpatient clinics of each participating hospital. Patients were excluded from the study if they expressed unwillingness to participate.

Results

Clinical characteristics of patients with CTD-IP

We enrolled 322 patients who were hospitalized for treatment of CTD-IP between April 2004 and March 2007. The numbers of cases with each CTD were 84 RA (26.1%), 13 SLE (4%), 33 PM (10.2%), 69 DM (21.4%), 55 SSc (17.1%), 21 MCTD (6.5%), 19 MPA (5.9%), and 28 overlap syndrome (8.7%). The median (range) observation and hospitalization periods of the patients were 1.1 (0–3.2) years and 1.8 (0–32.1) months, respectively. Demographic and clinical features of the patients at admission for each CTD-IP are summarized in Table 1. The mean age of patients with MPA was highest and that of patients with SLE lowest. The proportion of female patients with MPA was significantly lower than those for other diseases ($p = 0.001$, chi-square test). Patients with PM, DM, and MPA tended to have shorter disease duration. The rate of newly developed CTD-IP in patients with SLE and DM was significantly higher ($p = 0.002$, chi-square test) and that in RA patients was significantly lower ($p = 0.002$, chi-square test) compared with those with other diseases.

Treatment of CTD-IP

Following admission, immunosuppressive treatments for CTD-IP were commenced or intensified in all patients, using oral corticosteroids, mPSL pulse therapy, intravenous cyclophosphamide therapy (IVCY), and/or other immunosuppressants (Table 1). Patients with RA were more frequently treated with mPSL pulse therapy ($p = 0.001$, chi-square test) and less frequently with IVCY ($p < 0.001$, chi-square test). Patients with SSc were treated less frequently with mPSL pulse therapy ($p < 0.001$, chi-square test) and oral corticosteroids ($p = 0.008$, chi-square test) and more frequently with IVCY ($p < 0.001$, chi-square test). Patients with MCTD were treated less frequently with mPSL pulse therapy ($p < 0.001$, chi-square test). In addition to IVCY, the main immunosuppressants used for CTD-IP were cyclosporine (68/133; 51.1%), tacrolimus (48/133; 36.1%), and azathioprine (10/133; 7.5%).

Prognosis and causes of death of CTD-IP patients

At discharge, 223 cases (69.3%) showed improvement, 54 cases (16.8%) had no change, 3 cases (0.9%) deteriorated according to the

Table 1. Clinical characteristic of patients with CTD-IP.

	Age (years)	Gender (Female)	Disease duration (months)	Newly developed	Treatments for CTD-IP during hospitalization			
					mPSL pulse	CS	IS	IVCY
RA ($n=84$)	65.4 ± 9.1	57.1%	123.7 ± 128.7	42.9%‡	49.3%§	93.3%	37.8%	6.8%‖
SLE ($n=13$)	43.9 ± 16	92.3%	73.6 ± 128.9	84.6%†	23.1%	100%	25%	23.1%
PM ($n=33$)	56 ± 10	81.8%	26.7 ± 59.7	69.7%	35.5%	96.8%	51.6%	16.1%
DM ($n=69$)	54.8 ± 12	65.2%	23.6 ± 42.3	72.1%†	35.9%	98.4%	59.4%	22.2%
SSc ($n=55$)	56 ± 16	58.2%	71.5 ± 98.6	46.3%	14%‖	80.4%¶	43.1%	56.9%**
MCTD ($n=21$)	54.8 ± 13.4	61.9%	55.7 ± 74.3	57.1%	10%‖	95%	60%	15%
MPA ($n=19$)	73.2 ± 8.1	42.1%*	18.9 ± 21.3	52.6%	21%	100%	36.8%	15.8%
Overlap ($n=28$)	52.6 ± 11.7	92.9%	49.9 ± 76.5	64.3%	23.1%	88.5%	42.3%	42.3%

mPSL pulse methylprednisolone pulse therapy, *CS* corticosteroid, *IS* immunosuppressants other than IVCY, *IVCY* intravenous cyclophosphamide, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *PM* polymyositis, *DM* dermatomyositis, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *MPA* microscopic polyangiitis, *Overlap* overlap syndrome.
Statistical significance was defined as $p<0.05$ and adjusted residual as absolute value more than 2.00.
*Significantly lower percentage of female ($p=0.001$; chi-square test).
†Significantly higher percentage of newly developed CTD-IP ($p=0.002$; chi-square test).
‡Significantly lower percentage of newly developed CTD-IP ($p=0.002$; chi-square test).
§Significantly higher percentage of concomitant use ($p=0.001$; chi-square test).
‖Significantly lower percentage of concomitant use ($p=0.001$; chi-square test).
¶Significantly lower percentage of concomitant use ($p=0.008$; chi-square test).
**Significantly higher percentage of concomitant use ($p<0.001$; chi-square test).

attending physicians' global assessment, and 42 cases (13%) died during hospitalization (Table 2). In-hospital mortality rates were significantly higher for RA (20.2%) and DM (21.7%) and lower for SSc and overlap syndrome, compared with those for other diseases ($p<0.001$, chi-square test). Of the 42 deaths during hospitalization, the causes of death were CTD-IP for 22 cases, CTD-IP and pulmonary infection for 15, pulmonary infection for 2, CTD-IP and pulmonary hypertension for 1, pulmonary hypertension for 1, and pulmonary hemorrhage for 1. Six patients died after discharge from the hospital and before the end of the observation period. The cause of death was unknown in 5 of these cases and was heart failure in 1 case.

Because 17 deaths during hospitalization were totally or partially attributed to pulmonary infection after immunosuppressive treatment for CTD-IP was initiated, according to the attending physician, we examined the prognosis for the 43 cases that developed pulmonary infections. Of these 43 cases, 17 died before discharge, including 7 with DM; 4 with RA; and 2 each for PM, SSc, and MPA. The mortality rate for each CTD-IP ranged from 40 to 67% (Table 2). The types of the pulmonary infection in these 43 cases were mixed pulmonary infection for 13 cases, bacterial pneumonia for 12 cases, *Pneumocystis jirovecii* pneumonia for 6 cases, bronchitis for 3 cases, *P. jirovecii* pneumonia and *Cytomegalovirus* pneumonia for 2 cases, *Cytomegalovirus* pneumonia for 1 case, fungal pneumonia for 1 case, non-tuberculous mycobacterial infection for 1 case, influenza for 1 case, and unknown for 3 cases. Because we did not collect information about prophylaxis, we were unable to examine its association with development of pulmonary infection.

Risk factors for death during hospitalization

The 42 patients who died during hospitalization accounted for 87.5% of all 48 deaths during the observation period of this study,

Table 2. Status of patients with CTD-IP at discharge.

	Status of CTD-IP patients at discharge				Development of pulmonary infections‡
	Improved	Unchanged	Deteriorated	Deceased	
RA ($n=84$)	61	6	0	17*	10 (4)
SLE ($n=13$)	11	1	0	1	2
PM ($n=33$)	24	4	0	5	3 (2)
DM ($n=69$)	49	5	0	15*	15 (7)
SSc ($n=55$)	27	25*	1	2†	4 (2)
MCTD ($n=21$)	18	1	2	0	3
MPA ($n=19$)	18	2	0	2	5 (2)
Overlap ($n=28$)	18	10	0	0†	1
All	223	54	3	42	43 (17)

The status of CTD-IP patients at discharge is summarized according to the attending physicians' global assessment as improved, unchanged, deteriorated, or deceased.
RA rheumatoid arthritis, *SLE* systemic lupus erythematosus, *PM* polymyositis, *DM* dermatomyositis, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *MPA* microscopic polyangiitis, *Overlap* overlap syndrome.
Statistical significance was defined as $p<0.05$, and adjusted residual as absolute value more than 2.00.
Numbers in parentheses are numbers of deaths during hospitalization.
*Significantly higher percentage ($p<0.001$; chi-square test).
†Significantly lower percentage ($p<0.001$; chi-square test).
‡Development of pulmonary infections after new or additional immunosuppressive treatments for CTD-IP.

Table 3. Univariate analyses for death during hospitalization of patients with connective tissue disease-associated interstitial pneumonia.

	Survived cases ($n=263$)	Deceased cases ($n=31$)	p value
Characteristics of the patients			
Age (years)*	57 ± 13.8	66.2 ± 11.9	<0.001†
Age (= or > 65 y/o)	31.9%	64.5%	<0.001‡
Gender (female)	65%	67.7%	0.76‡
Disease duration of each CTD (months)*	62.7 ± 96.2	66.5 ± 106.3	<0.81†
Newly developed CTD-IP	58.4%	40%	0.054‡
Development of mediastinal emphysema during hospitalization	5%	10.1%	0.016‡
Development of pulmonary infections during hospitalization	10%	50.0%	<0.001 =
New or additional treatments for CTD-IP after admission			
Concomitant use of mPSL pulse therapy	26%	80.6%	<0.001‡
Concomitant use of CS	94.3%	83.9%	0.029‡
Maximum dosage of CS (mg/day of PSL equivalent)*	38.7 ± 18.2	58 ± 43.4	0.008†
Concomitant use of immunosuppressant other than IVCY	48.3%	35.5%	0.17‡
Concomitant use of IVCY	24.1%	22.6%	0.85‡

CTD connective tissue disease, *CTD-IP* connective tissue disease associated interstitial pneumonia, *CS* corticosteroid, *PSL* prednisolone, *IVCY* intravenous cyclophosphamide.
*Mean ± SD, p values were calculated using the Mann–Whitney test (†) or chi-square test (‡).

indicating that clinical management during hospitalization is important to improve short-term vital prognosis of patients with CTD-IP. We, therefore, examined risk factors for death during hospitalization in 294 patients who had detailed information about immunosuppressive treatment for CTD-IP. We compared surviving and deceased cases using univariate analyses (Table 3) and selected variables for the multivariate Cox regression hazard analysis to evaluate the risk factors for death during hospitalization.

Based on the results of univariate analyses (Table 3), we applied age (≥ 65 years old), development of mediastinal emphysema, development of pulmonary infection after commencing or intensifying immunosuppressive treatments, concomitant use of mPSL pulse therapy, and the maximum daily dosage of oral corticosteroids into multivariate Cox proportional hazards regression models by the forced entry procedure. Age (≥ 65 years old; $p=0.001$), development of pulmonary infection ($p=0.004$), and concomitant use of mPSL pulse therapy ($p=0.032$) were identified as significant risk factors for death during hospitalization (Table 4). After corrections for multiple comparisons using FDR and BH methods [31], age (≥ 65 years old) and development of pulmonary infection remained significant. Because we observed a significant association between use of mPSL pulse therapy and maximum daily dosage of oral corticosteroids, we used'mPSL pulse therapy or maximum daily dosage of oral corticosteroids ≥ 40 mg/day" with the other three factors in Table 3 as independent variables and performed a multivariate Cox proportional hazards regression analysis. This second model also identified age (≥ 65 years old) and development of pulmonary infection as significant risk factors (data not shown).

Discussion

This multicenter, large-scale, retrospective analysis of CTD-IP patients in Japan was implemented to determine the short-term vital prognosis and to identify risk factors for death after commencing or intensifying immunosuppressive treatments for CTD-IP. There are three major findings from our study. First, the overall mortality rate of patients with CTD-IP during hospitalization for immunosuppressive treatment for IP was 13% (42/322). Second, CTD-IP patients with RA and DM had higher in-hospital mortality rates following immunosuppressive treatments. Third, advanced age (≥ 65 years old) and development of pulmonary infection were significant risk factors for death during hospitalization after corrections for multiple comparisons.

In clinical practice, patients with CTD-IP often develop a pulmonary infection and sometimes die from this complication. To the best of our knowledge, this is the first study that demonstrates an association with statistical significance between development of pulmonary infections after commencing or intensifying immunosuppressive treatment and death during hospitalization. Several investigators have reported IP as a risk factor for infection or serious infection in patients with CTD [19,32–35]. These data strongly indicate the importance of prophylaxis, monitoring, and early diagnosis of pulmonary infection during immunosuppressive treatment of CTD-IP.

Our study identified older age (≥ 65 years old) as a significant risk factor for death during hospitalization for immunosuppressive treatment of CTD-IP. Kocheril et al. [12] performed a case–control study of patients with CTD-ILD (interstitial lung disease)

Table 4. Multivariate Cox proportional hazards regression analysis for death during hospitalization of patients with CTD-IP.

Risk factors	Hazard ratio	95% CI	p value
Age (≥ 65 years old)	3.98	1.70–9.32	0.001*
Development of pulmonary infections after new or additional immunosuppressive treatments for CTD-IP	3.40	1.49–7.72	0.004*
Concomitant use of mPSL pulse therapy	2.86	1.09–7.50	0.032
Maximum dosage of CS (mg/day of PSL equivalent)†	1.01	0.996–1.02	0.16
Development of mediastinal emphysema	1.35	0.45–4.06	0.60

95% CI 95% confidence interval, *CTD-IP* connective tissue disease-associated interstitial pneumonia, *CS* corticosteroid, *PSL* prednisolone.
Significant risk factors for death during hospitalization for immunosuppressive treatment of CTD-IP were identified using Cox proportional hazards regression models.
*These p values were statistically significant after corrections for multiple comparisons using FDR and BH methods [31].

and idiopathic interstitial pneumonia and found that the hazard of death increased by 4% per 1-year increment in age at the diagnosis of CTD-ILD. Other studies, however, have failed to find a significant association between age and prognosis of collagen vascular disease-IP (CVD-IP) in patients with PM/DM [36,37] or SSc [38] following treatment for CVD-IP. The association of age with vital prognosis may be altered by other factors, such as types of CTD and treatment provided.

Several studies have investigated the long-term vital prognosis for patients with CTD-IP. Su et al. [9] estimated the survival of patients with CTD-ILD using the Stanford ILD database and reported that 1-year, 3-year, and 5-year survival rates at the last follow-up from diagnosis of ILD were 88%, 61%, and 53%, respectively. This and other studies showed that the probability of survival of patients with CTD-IP greatly decreased during the first and second years after diagnosis and tended to plateau after that [4,11,12]. A study of patients with acute exacerbation of CTD-IP (6 with RA, 6 with DM, and 3 with SSc) found that the 90-day survival rate after hospital treatment for acute exacerbation of CTD-IP was only 33% [39]. These data indicate that patients with CTD-IP have an unfavorable short-term vital prognosis especially after initiation of therapy for CTD-IP. Altogether, these results are compatible with the results of our study.

A number of studies have found that RA patients with CTD-IP have a poor vital prognosis [1,2,4–6]. Hakala [40] analyzed the clinical course of 49 RA patients admitted to their hospital with interstitial lung fibrosis, and reported a poor prognosis, with a median survival of 3.5 years and a 5-year survival rate of 39%. Rajasekaran et al. [5] reported a similarly poor prognosis for 18 patients with RA-ILD, with a 5-year survival rate of 44%. Park et al. [4] reported that the survival of RA patients with CVD-IP was lower than that for patients with other CVD-IPs. The high in-hospital mortality rate of RA patients with CTD-IP in our study is in agreement with these previous reports of long-term vital prognosis.

The presence of ILD in patients with PM/DM resulted in increased mortality [7,8,13]. Marie et al. [13] reported that survival of PM/DM patients with ILD (PM/DM-ILD) was 94.4%, 90.4%, and 86.5% at years 1, 3, and 5, respectively. Fujisawa et al. [7] compared the prognosis of ILD between patients with PM and DM. They reported that DM patients with ILD had significantly shorter survival rates than PM patients with ILD (5-year survival, 55.6% vs. 87.1%, respectively), and that most of the deaths in patients with DM-ILD were from respiratory failure due to deterioration of ILD. In our study, 15 of 69 DM patients (21.7%) and 5 of 33 PM patients (15.2%) died during hospitalization. The cause of death in patients with DM was CTD-IP for 8 cases, CTD-IP and pulmonary infection for 6, and pulmonary infection for 1. These results support a shorter vital prognosis for CTD-IP in DM compared with that in PM and other CTDs.

There are certain limitations in our study. First, the patients with CTD-IP enrolled in this study were limited to hospitalized patients, who might have a more severe or treatment-resistant CTD-IP than non-hospitalized patients. Those patients with less severe CTD-IP not requiring immunosuppressive treatments with hospitalization were excluded from our study. Second, the observation period of our study was shorter than those of previous reports. However, the probability of survival after treatment with any immunosuppressants in PM/DM [22,37] or SSc [23,24] patients tended to plateau after two years of follow-up. Therefore, careful clinical management during hospitalization would be important not only for short-term, but also for mid- to long-term vital prognosis of patients with CTD-IP. Third, we could not collect previously reported risk factors for an unfavorable prognosis [5,10,12–16], such as chest X-ray, thoracic CT images, and results of pulmonary function tests. Additional risk factors might have been identified if we had collected and applied these data to this study.

In conclusion, proper management of patients with CTD-IP with careful consideration of benefit–risk balance for immunosuppressive treatments is necessary to improve the short-term prognosis of these patients. Because the development of pulmonary infections after the initiation of immunosupression has a substantial influence on the mortality rate of patients with CTD-IP, physicians should pay special attention to evaluation of the risk for the pulmonary infections and consider initiating preventive measures before starting immunosuppressive treatment for CTD-IP.

Acknowledgements

This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare, Japan (H23-meneki-sitei-016 and H19-meneki-ippan-009 to N. Miyasaka, H22-meneki-ippann-001 to M. Harigai) and by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science (#20390158 to M. Harigai, #19590530 to R. Koike, and #50277141 to M. Tanaka). This work was also supported by the grant from the Japanese Ministry of Education, Global Center of Excellence (GCOE) Program, "International Research Center for Molecular Science in Tooth and Bone Diseases" (to N. Miyasaka).

Other members of the investigators group of this study were as follows: Yoshiya Tanaka, M.D. Ph.D. (The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan), Kazuhiko Yamamoto, M.D., Ph.D. (Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo), Hirofumi Amano, M.D., Ph.D. (Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine), Koichi Amano, M.D., Ph.D. (Department of Rheumatology & Clinical Immunology, Saitama Medical Center, Saitama Medical University), Naohiko Inase, M.D., Ph.D. (Department of Respiratory Medicine, University Hospital of Medicine, Tokyo Medical & Dental University), Yuichiro Fujieda, M.D., Ph.D., Takashi Kurita, M.D., Ph.D., and Hiromi Hagiwara, M.D. (Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine).

Conflict of interest

Nishioka Y has received research grants from Chugai Pharmaceutical Co. Ltd. and Mitsubishi Tanabe Pharmaceutical Co. Ltd., *Miyasaka N* has received research grants from Abbott Japan Co. Ltd., Astellas Pharma Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Dainihon-Sumitomo Pharma Co. Ltd., Daiichi-Sankyo Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K. Ltd., Takeda Pharmaceutical Co. Ltd., Teijin Pharma Ltd., and received Consulting fee or honorarium from Abbott Japan Co. Ltd., Bristol Myers Squibb, Janssen Pharmaceutical KK, and Otsuka Pharmaceutical Co. Ltd. *Harigai M* has received research grants from Abbvie Japan Co. Ltd., Astellas Pharma Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., and UCB Japan.

References

1. de Lauretis A, Veeraraghavan S, Renzoni E. Review series: aspects of interstitial lung disease: connective tissue disease-associated interstitial lung disease: how does it differ from IPF? How should the clinical approach differ? Chron Respir Dis. 2011;8(1):53–82.
2. Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc. 2007;4(5):443–8.
3. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis. 2004;63(3):297–301.
4. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen

vascular disease-related subtypes. Am J Respir Crit Care Med. 2007;175(7):705–11.
5. Rajasekaran A, Shovlin D, Saravanan V, Lord P, Kelly C. Interstitial lung disease in patients with rheumatoid arthritis: comparison with cryptogenic fibrosing alveolitis over 5 years. J Rheumatol. 2006;33(7):1250–3.
6. Tsuchiya Y, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, Sugita Y. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. Eur Respir J. 2011;37(6):1411–7.
7. Fujisawa T, Suda T, Nakamura Y, Enomoto N, Ide K, Toyoshima M, et al. Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. J Rheumatol. 2005;32(1):58–64.
8. Chen IJ, Jan Wu YJ, Lin CW, Fan KW, Luo SF, Ho HH, et al. Interstitial lung disease in polymyositis and dermatomyositis. Clin Rheumatol. 2009;28(6):639–46.
9. Su R, Bennett M, Jacobs S, Hunter T, Bailey C, Krishnan E, et al. An analysis of connective tissue disease-associated interstitial lung disease at a US Tertiary Care Center: better survival in patients with systemic sclerosis. J Rheumatol. 2011;38(4):693–701.
10. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med. 2002;165(12):1581–6.
11. Hubbard R, Venn A. The impact of coexisting connective tissue disease on survival in patients with fibrosing alveolitis. Rheumatology (Oxford). 2002;41(6):676–9.
12. Kocheril SV, Appleton BE, Somers EC, Kazerooni EA, Flaherty KR, Martinez FJ, et al. Comparison of disease progression and mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia. Arthritis Rheum. 2005;53(4):549–57.
13. Marie I, Hachulla E, Cherin P, Dominique S, Hatron PY, Hellot MF, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum. 2002;47(6):614–22.
14. Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV. Interstitial lung disease in polymyositis and dermatomyositis. Clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis. 1990;141(3):727–33.
15. Ito M, Kaise S, Suzuki S, Kazuta Y, Sato Y, Miyata M, et al. Clinico-laboratory characteristics of patients with dermatomyositis accompanied by rapidly progressive interstitial lung disease. Clin Rheumatol. 1999;18(6):462–7.
16. Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. Curr Opin Rheumatol. 2005;17(6):701–6.
17. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol. 2010;39(5):360–7.
18. Teh CL, Ling GR. Causes and predictors of mortality in hospitalized lupus patient in Sarawak General Hospital, Malaysia. Lupus. 2013;22(1):106–11.
19. Bligny D, Mahr A, Toumelin PL, Mouthon L, Guillevin L. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum. 2004;51(1):83–91.
20. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol. 2007;26(5):663–70.
21. Le Goff B, Cherin P, Cantagrel A, Gayraud M, Hachulla E, Laborde F, et al. Pneumomediastinum in interstitial lung disease associated with dermatomyositis and polymyositis. Arthritis Rheum. 2009;61(1):108–18.
22. Takada K, Kishi J, Miyasaka N. Step-up versus primary intensive approach to the treatment of interstitial pneumonia associated with dermatomyositis/polymyositis: a retrospective study. Mod Rheumatol. 2007;17(2):123–30.
23. White B, Moore WC, Wigley FM, Xiao HQ, Wise RA. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. Ann Intern Med. 2000;132(12):947–54.
24. Domiciano DS, Bonfa E, Borges CT, Kairalla RA, Capelozzi VL, Parra E, et al. A long-term prospective randomized controlled study of non-specific interstitial pneumonia (NSIP) treatment in scleroderma. Clin Rheumatol. 2011;30(2):223–9.
25. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007;66(2):222–7.
26. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187–92.
27. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344–7.
28. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23(5):581–90.
29. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271–7.
30. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31(3):315–24.
31. Benjamini Y, Hochberg Y. Controlling the false discovery rate - a practical and powerful approach to multiple testing. J Roy Stat Soc B Met. 1995;57(1):289–300.
32. Komano Y, Tanaka M, Nanki T, Koike R, Sakai R, Kameda H, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol. 2011;38(7):1258–64.
33. Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(8):1125–34.
34. Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martinez-Berriotxoa A, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther. 2009;11(4):R109.
35. Marie I, Menard JF, Hachulla E, Cherin P, Benveniste O, Tiev K, et al. Infectious complications in polymyositis and dermatomyositis: a series of 279 patients. Semin Arthritis Rheum. 2011;41(1):48–60.
36. Fathi M, Vikgren J, Boijsen M, Tylen U, Jorfeldt L, Tornling G, et al. Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. Arthritis Rheum. 2008;59(5):677–85.
37. Kang EH, Lee EB, Shin KC, Im CH, Chung DH, Han SK, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology (Oxford). 2005;44(10):1282–6.
38. Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S, et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford). 2007;46(1):124–30.
39. Tachikawa R, Tomii K, Ueda H, Nagata K, Nanjo S, Sakurai A, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. Respiration. 2012;83(1):20–7.
40. Hakala M. Poor prognosis in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis. Chest. 1988;93(1):114–8.

Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2014; Early Online: 1–7

DOI: 10.3109/14397595.2014.970740

informa
healthcare

ORIGINAL ARTICLE

Sonographic measurements of low-echoic synovial area in the dorsal aspect of metatarsophalangeal joints in healthy subjects

Masao Hiraga[1], Kei Ikeda[2], Koichiro Shigeta[1], Akito Sato[3], Tamami Yoshitama[4], Ryota Hara[5], and Yasuhito Tanaka[5]

[1]*Kirishima Medical Center, Kirishima, Kagoshima, Japan,* [2]*Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan,* [3]*Sato Clinic, Kirishima, Kagoshima, Japan,* [4]*Yoshitama Rheumatoid Arthritis and Internal Medicine Clinic, Kirishima, Kagoshima, Japan, and* [5]*Department of Orthopaedic Surgery, The Center for Rheumatic Diseases, Nara Medical University, Kashihara, Nara, Japan*

Abstract

Introduction. Assessment of synovitis in the metatarsophalangeal (MTP) joints with ultrasound has been shown to improve the accuracy of assessment of rheumatoid arthritis (RA). However, the presence of intraarticular low-echoic synovial area (LESA) in the MTP joints in healthy subjects complicates the sonographic assessment of these joints.

Method. Healthy subjects with no arthritic symptoms in their MTP joints were recruited. All subjects completed a questionnaire and underwent physical examination and sonographic assessment. LESAs in the dorsal aspect of all MTP joints were measured in the longitudinal view.

Results. One thousand non-arthritic MTP joints in 100 healthy subjects (female 73, mean age 41.0 years old) were evaluated. Measurable LESAs were identified in all joints assessed. Mean length of LESA in each of the 1st–5th MTP joints was 17.8, 13.9, 11.9, 10.6, and 9.2 mm, respectively, whereas mean thickness was 2.4, 2.4, 1.8, 1.2, and 0.8 mm, respectively. Multivariate linear regression models identified the difference between 1st and 5th MTP joints as the most independently influential factor on the measurement of LESA.

Conclusions. Our data provide the normal reference values for the measurements of LESA in Japanese, which should be taken into consideration when the synovitis in MTP joints is evaluated with ultrasound.

Keywords

Metatarsophalangeal joint, Measurement, Rheumatoid arthritis, Synovitis, Ultrasound

History

Received 3 September 2014
Accepted 25 September 2014
Published online 3 November 2014

Introduction

The metatarsophalangeal (MTP) joints are frequently involved in patients with rheumatoid arthritis (RA) and their involvement has adverse consequences on the radiographic and functional outcomes [1–5]. Therefore, the assessment of MTP joints has been included in the 2010 American College of Rheumatology (ACR)/European Colleague Against Rheumatism (EULAR) classification criteria [6,7], ACR core set [8], Disease Activity Score (DAS) [9], and modified Sharp scores [10,11]. A number of studies have reported that the widely used 28-joint count [12], which does not include MTP joints, can underestimate the disease activity of RA [5,13–17], suggesting that the assessment of these joints is important in the management of RA. However, the clinical assessment of MTP joints can be unreliable [18], which partially explains the inconsistent results on the association between MTP joints involvement and radiographic progression [5,17].

Musculoskeletal ultrasound directly visualizes the inflammation in synovial tissues and enables more reliable assessment than clinical examination does [18–20]. Ultrasound has also been shown to improve the accuracy of diagnosis [21–25] and the assessment of disease activity of RA [26–31]. Since MTP joints are the joints where discordance between ultrasound and clinical examination frequently occurs [19,32,33], they have been included in many global sonographic assessment systems for RA [34–38].

However, accurate assessment of mild synovitis in the MTP joints is more difficult even with ultrasound as compared to that in the finger joints due to the presence of intraarticular low-echoic synovial area (LESA) in the non-arthritic MTP joints in healthy subjects, possibly causing overestimation. In order to distinguish between normally identified LESA and pathologic synovial hypertrophy, standard reference values for the measurement of LESA are needed. Although Schmidt et al. reported the standard reference values for the thickness of capsular distension in the 1st and 2nd MTP joints [39], those in the lesser toes, where RA-specific pathologies are frequently identified [4,34,35], remain to be determined.

In this study, we measured the LESA of 1,000 non-arthritic MTP joints in 100 healthy subjects to provide standard reference values for each MTP joint and to determine the factors which independently influence the measurements.

Methods

Study subjects

One hundred volunteers who reported neither any current/previous diseases, any previous injuries, nor any current arthritic symptoms were recruited from the staff members working at the Kirishima Medical Center. The study design and procedures were approved by the Ethics Committee of Chiba University and subjects' written informed consent was obtained according to the Declaration of Helsinki.

Correspondence to: Kei Ikeda, Department of Allergy and Clinical Immunology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan. Tel: +81-43-226-2198. Fax: +81-43-226-2199. E-mail: K.Ikeda@faculty.chiba-u.jp

Background survey and physical assessment

All subjects completed a questionnaire form for background information including sex, age, height, weight, dominant foot, and sporting activities. Dominant foot was defined as the foot with which the subject usually kicks a ball. Subjects also underwent physical assessment for the presence of hallux valgus, which was determined whether the angle between two lines tangential to the medial aspects of 1st metatarsal and 1st proximal phalanx was $>15°$.

Ultrasound examination

A gray-scale (GS) ultrasound was performed in a temperature-controlled room by a single sonographer (MH), who was experienced in musculoskeletal ultrasound, using a HI VISION Ascendus with a linear array multi-frequency transducer (5–18 MHz for GS) (Hitachi Medical Corporation, Tokyo, Japan). Machine settings were not changed throughout the study period with a B mode gain at 17 dB and a dynamic range of 70 dB.

Dorsal aspect of the 1st to 5th MTP joints were assessed bilaterally. Patients lay on a couch in the supine position, keeping the sole flat on the couch with the ankle and toes relaxed. The knee was flexed to a right angle. Each joint was thoroughly scanned and a longitudinal imaging plane which was perpendicular to the bone surface at midline of the toe was determined. The footprint of transducer was placed approximately parallel to the skin surface above the joint space, where the anisotropy of joint capsule was minimal. LESA was defined as an intraarticular region continuous from joint space, which is recognized on ultrasound as a low-echoic area relative to the surrounding tissues. The length of LESA was defined as the maximum distance between two parallel lines which were tangential to the proximal and distal rims of LESA (Figure 1A), whereas the thickness of LESA was defined as the maximum distance between two parallel lines, one was tangential to the surface of metatarsal covered by LESA and the other was tangential to the superficial rim of LESA (Figure 1B). Measurements were performed on images with a clearly visible layer of gel, which ensured that minimal pressure was applied to the skin surface.

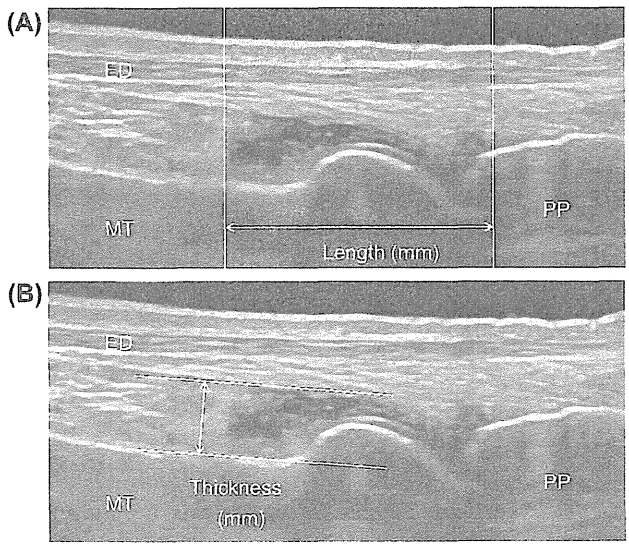

Figure 1. Ultrasonographic measurement of length and thickness of intraarticular low-echoic synovial area in metatarsophalangeal joint. (A) Measurement of length. (B) Measurement of thickness. ED, extensor digitorum; MT, metatarsal; PP, proximal phalanx.

Statistical analysis

Categorical data were summarized with numbers and proportions. Normally distributed continuous data were summarized with means and standard deviations (SDs) and were analyzed using parametric tests (two-sample *t*-test, paired *t*-test, or repeated measures ANOVA). Bonferroni's correction was applied for multiple testing. Multivariate analyses were performed using linear regression models with a stepwise method. Statistical analysis was performed using SPSS version 21.0 (IBM Japan, Tokyo, Japan). Two-sided *P* values less than 0.05 were considered statistically significant.

Results

Study subjects

One hundred healthy subjects free of arthritic symptoms were studied. As shown in Table 1, 73 subjects (73%) were female and mean ± SD age was 41.0 ± 10.2 years old. Mean ± SD height was 159.8 ± 8.5 cm, whereas mean ± SD weight was 55.2 ± 9.4 kg. Ninety-five subjects (95%) reported that their dominant foot was the right one. Seventeen subjects (17%) reported to be currently engaging in some sporting activities. On physical examination, three subjects (3%) had hallux valgus (all female).

Sonographic measurement of intraarticular low-echoic synovial area in 1st–5th MTP joint

A total of 1,000 MTP joints were measured. Measurable LESA was identified in all joints assessed. Mean ± SD length and thickness of LESA in all MTP joints were 12.7 ± 3.6 mm and 1.7 ± 1.0 mm, respectively.

Mean ± SD length of LESA in each of the 1st–5th MTP joints (200 joints each) was 17.8 ± 3.1, 13.9 ± 2.0, 11.9 ± 1.8, 10.6 ± 1.5, and 9.2 ± 1.3 mm, respectively (Figure 2A). There was a statistically significant difference in the length of LESA among 1st–5th MTP joints ($P<0.001$, repeated measures ANOVA) and the differences between any adjacent MTP joints were statistically significant (all $P<0.001$, paired *t*-test with Bonferroni's correction) (Figure 2A). On the other hand, mean ± SD thickness of LESA in each of the 1st–5th MTP joints was 2.4 ± 1.0, 2.4 ± 0.9, 1.8 ± 0.9, 1.2 ± 0.5, and 0.8 ± 0.2 mm, respectively (Figure 2B). There was a statistically significant difference in the length of LESA among 1st–5th MTP joints ($P<0.001$, repeated measures ANOVA) and the differences between 2nd and 3rd, 3rd and 4th, and 4th and 5th MTP joints were statistically significant (all $P<0.001$, paired *t*-test with Bonferroni's correction) (Figure 2B).

Comparisons of measurements of low-echoic synovial area between dominant and non-dominant feet

The length and thickness of LESA in all MTP joints were significantly larger in dominant foot (500 joints) than in non-dominant foot (500 joints) (mean ± SD length 12.9 ± 3.8 mm vs. 12.5 ± 3.4 mm, $P<0.001$; mean ± SD thickness 1.8 ± 1.0 mm vs. 1.7 ± 1.0 mm, $P=0.005$; paired *t*-test).

Table 1. Demographics and characteristics of study subjects.

	Sex		
	Female	Male	Total
Number, *n*	73	27	100
Age, mean ± SD (year-old)	41.0 ± 10.2	37.7 ± 12.1	42.2 ± 9.3
Height (cm)	156.0 ± 4.9	170.0 ± 7.6	159.8 ± 8.5
Weight (kg)	51.6 ± 6.4	65.0 ± 9.4	55.2 ± 9.4
Sporting activity, present, *n* (%)	9 (12)	8 (30)	17 (17)
Hallux valgus, present, *n* (%)	3 (4)	0 (0)	3 (3)

SD standard deviation.

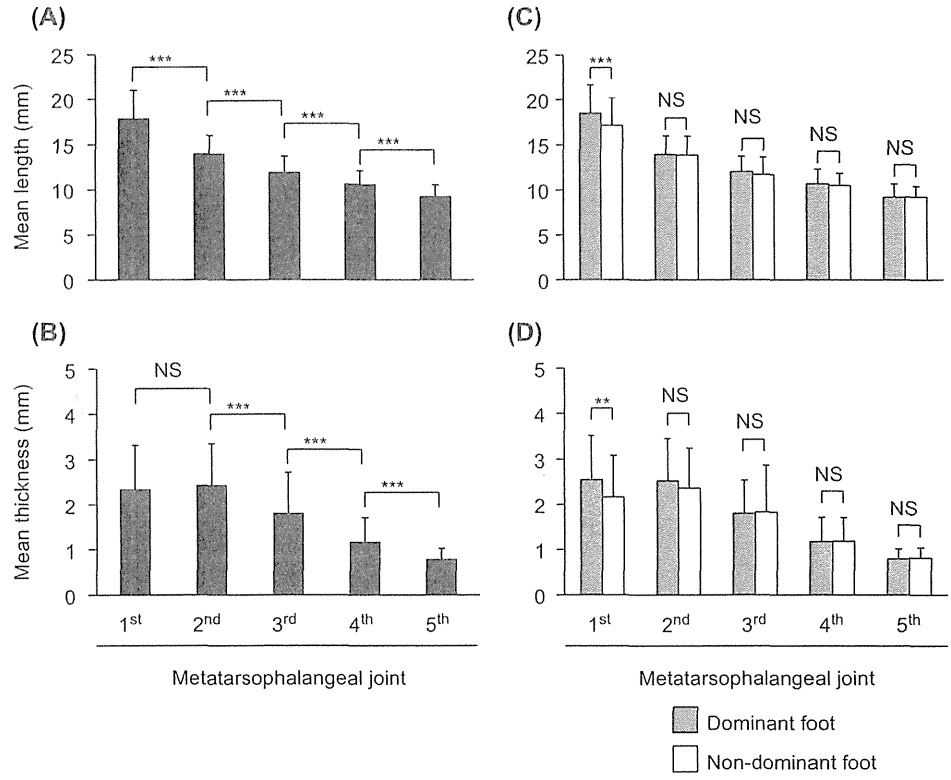

Figure 2. Comparisons of measurements of low-echoic synovial area between 1st and 5th metatarsophalangeal joints and between dominant and non-dominant feet. Presented in bar charts are mean length (A and C) and mean thickness (B and D). Error bars represent standard deviations (SDs). (A and B) Comparisons between different metatarsophalangeal joints. Statistically significant difference was present among 1st–5th metatarsophalangeal joints ($P < 0.001$, repeated measures ANOVA). (C and D) Comparisons between dominant (gray bar) and non-dominant (blank bar) feet. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, post-hoc test (A and B) or paired t-test (C and D) with Bonferroni's correction. NS, not significant.

When compared in each MTP joint, however, these statistically significant differences were only present in the 1st MTP joint (mean ± SD length 18.5 ± 3.1 vs. 17.2 ± 3.0 mm, $P < 0.001$; mean ± SD thickness 2.5 ± 1.0 vs. 2.2 ± 0.9 mm, $P = 0.002$) but not in the other MTP joints (paired t-test with Bonferroni's correction) (Figure 2C and D).

Comparisons of measurements of low-echoic synovial area between sexes

The length and thickness of LESA in all MTP joints were significantly larger in male subjects (270 joints) than in female ones (730 joints) (mean ± SD length 13.1 ± 3.6 vs. 12.6 ± 3.6 mm, $P = 0.049$; mean ± SD thickness 1.9 ± 1.2 vs. 1.7 ± 0.9 mm, $P < 0.001$; two-sample t-test).

When compared in each MTP joint, however, these statistically significant differences were absent except for the length of LESA in the 4th MTP joint (mean ± SD length 11.2 ± 1.5 vs. 10.4 ± 1.4 mm, $P = 0.002$, two-sample t-test with Bonferroni's correction) (Figure 3A and B).

Influence of sporting activities on measurements of low-echoic synovial area

The length and thickness of LESA in all MTP joints were significantly larger in subjects who were engaging in sporting activities (170 joints) than in those who were not (830 joints) (mean ± SD length 13.4 ± 3.7 vs. 12.6 vs. 3.6 mm, $P = 0.007$; mean ± SD thickness 1.9 ± 1.2 vs. 1.7 ± 0.9 mm, $P < 0.001$; two-sample t-test).

When compared in each MTP joint, these statistically significant differences were present in the 1st MTP joint (mean ± SD thickness 2.9 ± 1.2 vs. 2.2 ± 0.9 mm, $P = 0.001$), the 2nd MTP joint (mean ± SD length 14.9 ± 2.3 vs. 13.7 ± 1.9 mm, $P = 0.017$; mean ± SD thickness 3.0 ± 1.2 vs. 2.3 ± 0.8 mm, $P < 0.001$), and the 4th MTP joint (mean ± SD length 11.3 ± 1.6 vs. 10.5 ± 1.4 mm, $P = 0.008$; mean ± SD thickness 1.4 ± 0.7 vs. 1.1 ± 0.5 mm, $P = 0.032$) (two-sample t-test with Bonferroni's correction) (Figure 3C and D).

Influence of hallux valgus on measurements of low-echoic synovial area

As the proportion of subjects who had hallux valgus was very small, there were no statistically significant differences in the length and thickness of LESA in all MTP joints between subjects who had hallux valgus (30 joints) and those who did not (970 joints) (mean ± SD length 12.7 ± 4.0 vs. 12.7 ± 3.6 mm, $P = 0.995$; mean ± SD thickness 1.7 ± 1.0 vs. 1.7 ± 1.0 mm, $P = 0.797$; two-sample t-test). The differences were also not statistically significant in the 1st MTP joint or the other MTP joints (two-sample t-test with Bonferroni's correction).

Correlations between age and measurements of low-echoic synovial area

There were no statistically significant correlations between subject's age and the length or thickness of LESA in all MTP joints (length, $r = -0.01$, $P = 0.919$; thickness, $r = -0.03$, $P = 0.321$; Pearson's correlation coefficient).

When analyzed in each MTP joint, however, weak but statistically significant inverse correlation was present between age and the thickness of LESA in the 5th MTP joint ($r = -0.21$, $P = 0.014$, Pearson's correlation coefficient with Bonferroni's correction) (Figure 4).

Correlations between physical frame and measurements of low-echoic synovial area

As expected, weak but statistically significant correlations were present between subject's height and length of LESA ($r = 0.10$, $P = 0.002$), between height and thickness ($r = 0.15$, $P < 0.001$), between weight and length ($r = 0.08$, $P = 0.014$), and between weight and thickness ($r = 0.18$, $P < 0.001$) (Pearson's correlation coefficient).

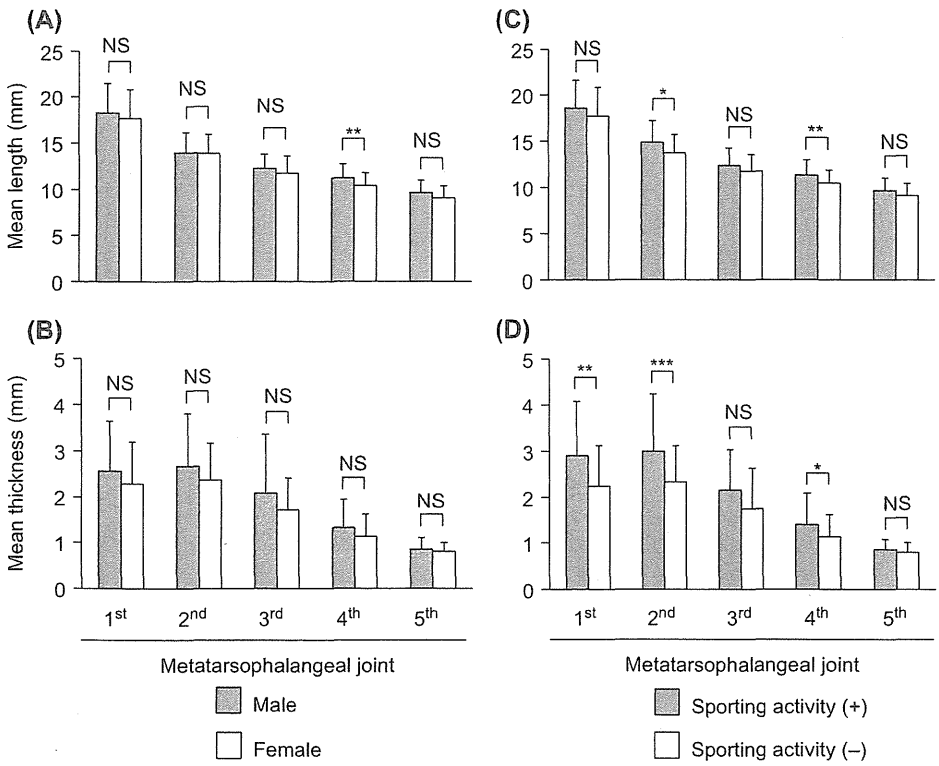

Figure 3. Comparisons of measurements of low-echoic synovial area between sexes and between presence and absence of sporting activities. Presented in bar charts are mean length (A and C) and mean thickness (B and D). Error bars represent standard deviations (SDs). (A and B) Comparisons between male (gray bar) and female (blank bar). (C and D) Comparisons between presence (gray bar) and absence (blank bar) of sporting activities. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, two-sample t-test with Bonferroni's correction. NS, not significant.

When analyzed in each MTP joint, statistically significant correlations were present between height and length in the 2nd MTP joint ($r=0.19$, $P=0.043$), the 3rd MTP joint ($r=0.22$, $P=0.008$), the 4th MTP joint ($r=0.29$, $P<0.001$), and the 5th MTP joint ($r=0.27$, $P<0.001$) (Figure 5A); between height and thickness in the 2nd MTP joint ($r=0.26$, $P<0.001$), the 3rd MTP joint ($r=0.26$, $P=0.001$), and the 4th MTP joint ($r=0.27$, $P<0.001$) (Figure 5B); between weight and length in the 4th MTP joint ($r=0.20$, $P=0.019$) and the 5th MTP joint ($r=0.28$, $P<0.001$) (Figure 5C); and between weight and thickness in the 1st MTP joint ($r=0.24$, $P=0.024$), the 2nd MTP joint ($r=0.32$, $P<0.001$), the 3rd MTP joint ($r=0.25$, $P=0.002$), and the 4th MTP joint ($r=0.27$, $P<0.001$) (Figure 5D).

Multivariate linear regression models

Multivariate linear regression analyses were performed to identify the factors which independently influenced the length and thickness of LESA in all MTP joints ($n=1{,}000$). As shown in Table 2, how close to the 1st MTP joint was the single dominant

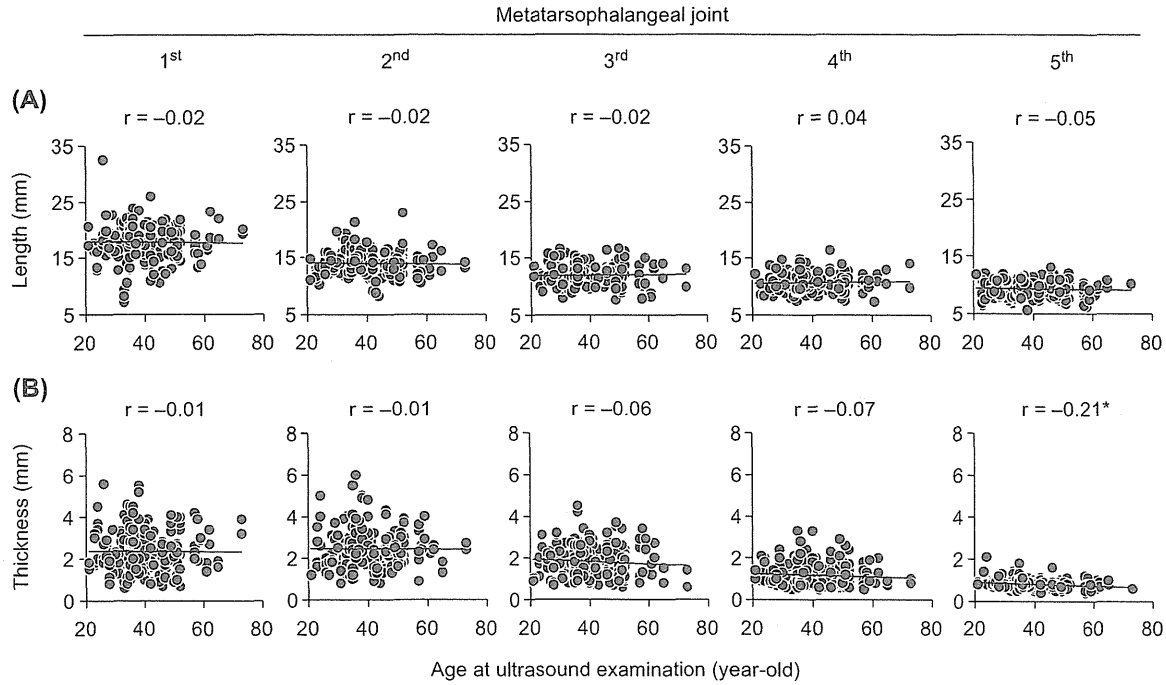

Figure 4. Correlations between age and measurements of low-echoic synovial area. (A) Correlations between age and length. (B) Correlations between age and thickness. Presented above each scatter plot is Pearson's correlation coefficient (r). $^{*}P<0.05$.

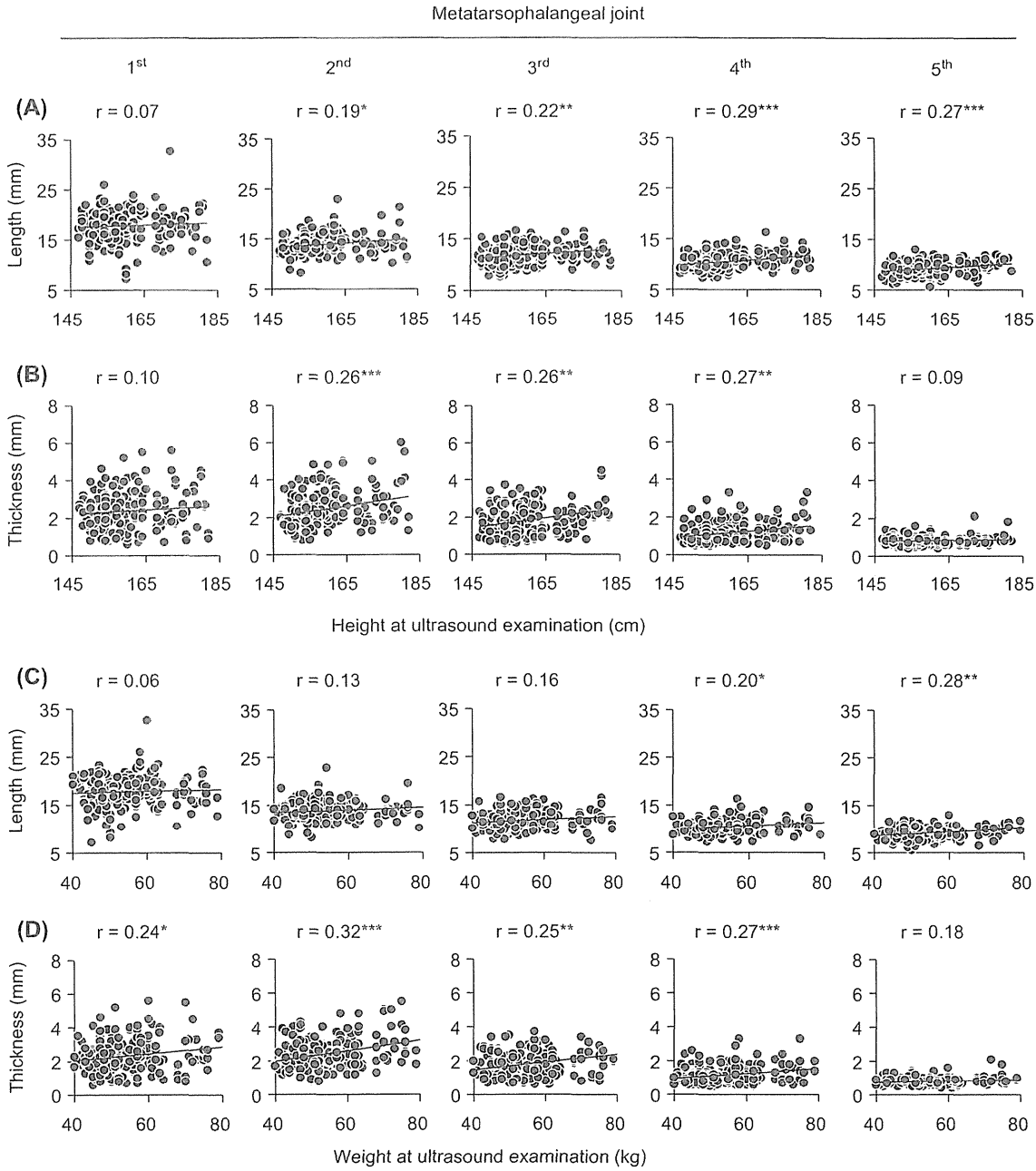

Figure 5. Correlations between physical frame and measurements of low-echoic synovial area (A) Correlations between height and length. (B) Correlations between height and thickness. (C) Correlations between weight and length. (D) Correlations between weight and thickness. Presented above each scatter plot is Pearson's correlation coefficient (r). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

factor for both the length (β coefficient −0.798, $P<0.001$) and the thickness (β coefficient −0.622, $P<0.001$) of LESA. Whether engaging in sporting activities or not and whether in the dominant foot or not were a slightly but significantly influential factor on both the length (sporting activity, β coefficient 0.065, $P=0.001$; dominant foot, β coefficient 0.051, $P=0.006$) and the thickness (sporting activity, β coefficient 0.121, $P<0.001$; dominant foot, β coefficient 0.047, $P=0.048$) of LESA. Interestingly, patient's height significantly influenced only the length (β coefficient 0.082, $P<0.001$), while patient's weight significantly influenced only the thickness (β coefficient 0.155, $P<0.001$).

Discussion

In this study, measurable LESA was identified in all MTP joints assessed, confirming that a normal, non-arthritic MTP joint usually exhibits intraarticular low-echoic area on ultrasound in the dorsal aspect. This finding has a considerable implication on the assessment of synovitis in these joints. Synovial fluid and hypertrophy are defined as "*abnormal* hypoechoic or anechoic-intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal" and "*abnormal* hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal", respectively [40]. Thus, *normal* LESA should be subtracted from the sonographic finding when the presence and the severity of gray-scale synovitis in the MTP joint are assessed, particularly using a certain grading system [41]. Moreover, our data demonstrate that LESA in the 1st and 2nd MTP joints are significantly longer and thicker as compared to those in the lesser MTP joints and the measurements decrease towards the 5th MTP joint. These data indicate that the severity of gray-scale synovitis should not be overestimated in

Table 2. Linear regression models for measurement of low-echoic synovial area in metatarsophalangeal joints of healthy subjects.

Dependent variable	Explanatory variable	β coefficient	*P* value
Length	MTP joint number (1st–5th)	−0.798	<0.001
	Height	0.082	<0.001
	Sporting activity	0.065	0.001
	Dominant foot	0.051	0.006
Thickness	MTP joint number (1st–5th)	−0.622	<0.001
	Weight	0.155	<0.001
	Sporting activity	0.121	<0.001
	Dominant foot	0.047	0.048

MTP metatarsophalangeal.

the 1st and 2nd MTP joints, while the severity should not be underestimated in the MTP joint in lesser toes.

Exact histopathology of LESA in the MTP joints remains unknown. Anechoic fluid that was displaceable and compressible was present in the vast majority of LESAs in the MTP joints. However, hypoechoic intraarticular tissue that was nondisplaceable and poorly compressible was also frequently identified in LESAs (Figure 1) although separately measuring these different sonographic features was technically difficult. Because LESA in normal MTP joints does not usually accompany Doppler signals [42], the non-fluid part of LESA can represent either thickened synovial lining, edematous subintimal tissue, or cellular infiltration without significant vascularization, probably due to the constant mechanical stress in the fore foot.

As compared with the differences between 1st and 5th MTP joints, other factors showed much smaller independent influence on the measurements of LESA in multivariate analyses (Table 2). Nevertheless, it is interesting to note that the subject's height only influenced the length of LESA, whereas the subject's weight only influenced the thickness. The models also retained sporting activity and dominant foot as a significantly influential factor, suggesting that repeated mechanical stress or overuse can result in the subclinical enlargement of LESA in MTP joints.

We had hypothesized that the LESA in MTP joints would be larger in older subjects because previous studies had reported the high prevalence of synovitis in the joints with degenerative changes in the foot [42,43] and the other joints [44–47]; however, age did not significantly influence the measurements of LESA in the multivariate analyses in our study (Table 2) and it inversely correlated with the thickness of LESA in the 5th MTP joints in the univariate analysis (Figure 4B). We assume that the occurrence of degenerative changes that accompany synovial inflammation is infrequent in non-arthritic, relatively young subjects. We also speculate that the inverse correlation between age and the thickness of LESA in the 5th MTP joints in our study was due both to the lighter weight in older subjects ($r = -0.10$, $P = 0.001$, Pearson's correlation coefficient) and to the younger age of subjects who were engaging in sporting activities (mean age 36.9 vs. 41.8 years old, $P = 0.068$, two-sample *t*-test).

This study has several limitations. First, all subjects in our study were Japanese and our data may not be globally generalizable. In fact, mean values for the thickness of synovial area in the 1st and 2nd MTP joints in our study were larger than those in the report by Schmidt et al. [39] even though our study subjects were significantly shorter and lighter. Multinational studies are needed to elucidate whether this is due to differences in the methods of measurements, the machines used, or subjects' life style and genetic background.

Second, synovial Doppler signal was not evaluated in our study. The absence of synovial Doppler signal in the normal MTP joints, which Keen et al. had already reported [42], could have also been confirmed in our study. In addition, comparison with other imaging modalities such as MRI would have added construct validity to our measurements.

Third, the associations between various factors and the measurements of LESA demonstrated in this study can only be applied to the subjects without arthritic symptoms. Technically, whether these associations can also be applied to synovial hypertrophy (i.e. *abnormal* LESA) in symptomatic subjects needs further confirmation.

In conclusion, our data confirm that intraarticular low-echoic synovial area is identified with ultrasound in non-arthritic MTP joints in healthy subjects and also provide the normal reference values in Japanese subjects. Our data also demonstrate that the low-echoic area is larger in the 1st and 2nd MTP joints as compared with that in the lesser MTP joints, which should be taken into consideration when the synovitis in MTP joints is evaluated with ultrasound.

Conflict of interests

None.

References

1. Budiman-Mak E, Conrad KJ, Roach KE. The foot function index: a measure of foot pain and disability. J Clin Epidemiol. 1991;44(6):561–70.
2. van der Leeden M, Steultjens M, Dekker JH, Prins AP, Dekker J. The relationship of disease duration to foot function, pain and disability in rheumatoid arthritis patients with foot complaints. Clin Exp Rheumatol. 2007;25(2):275–80.
3. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum. 2000;43(9):1927–40.
4. Landewe RB, Strand V, Conaghan PG, van der Heijde D. Damage and progression on radiographs in individual joints: data from pivotal randomized controlled trials. J Rheumatol. 2011;38(9):2018–22.
5. Bakker MF, Jacobs JW, Kruize AA, van der Veen MJ, van Booma-Frankfort C, Vreugdenhil SA, et al. Misclassification of disease activity when assessing individual patients with early rheumatoid arthritis using disease activity indices that do not include joints of feet. Ann Rheum Dis. 2012;71(6):830–5.
6. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–8.
8. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993;36(6):729–40.
9. van der Heijde DM, van't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990;49(11):916–20.
10. van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van't Hof MA, van Rijswijk MH, van de Putte LB. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992;35(1):26–34.
11. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865–76.
12. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44–8.
13. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum. 1994;37(4):470–5.

14. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995;38(1):38–43.
15. Landewe R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006;65(5):637–41.
16. Kapral T, Dernoschnig F, Machold KP, Stamm T, Schoels M, Smolen JS, Aletaha D. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? Arthritis Res Ther. 2007;9(4):R72.
17. van Tuyl LH, Britsemmer K, Wells GA, Smolen JS, Zhang B, Funovits J, et al. Remission in early rheumatoid arthritis defined by 28 joint counts: limited consequences of residual disease activity in the forefeet on outcome. Ann Rheum Dis. 2012;71(1):33–7.
18. Marhadour T, Jousse-Joulin S, Chales G, Grange L, Hacquard C, Loeuille D, et al. Reproducibility of joint swelling assessments in long-lasting rheumatoid arthritis: influence on Disease Activity Score-28 values (SEA-Repro study part I). J Rheumatol. 2010;37(5):932–7.
19. Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. Ann Rheum Dis. 2005;64(3):375–81.
20. Salaffi F, Filippucci E, Carotti M, Naredo E, Meenagh G, Ciapetti A, et al. Inter-observer agreement of standard joint counts in early rheumatoid arthritis: a comparison with grey scale ultrasonography–a preliminary study. Rheumatology (Oxford). 2008;47(1):54–8.
21. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis. 2010;69(2):417–9.
22. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis. 2011;70(3):500–7.
23. Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Sanayama Y, Takahashi K, et al. Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League against rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. Arthritis Rheum. 2013;65(4):890–8.
24. Fukae J, Shimizu M, Kon Y, Tanimura K, Matsuhashi M, Kamishima T, et al. Screening for rheumatoid arthritis with finger joint power Doppler ultrasonography: quantification of conventional power Doppler ultrasonographic scoring. Mod Rheumatol. 2009;19(5):502–6.
25. Kawashiri SY, Suzuki T, Okada A, Yamasaki S, Tamai M, Nakamura H, et al. Musculoskeletal ultrasonography assists the diagnostic performance of the 2010 classification criteria for rheumatoid arthritis. Mod Rheumatol. 2013;23(1):36–43.
26. Naredo E, Moller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum. 2008;58(8):2248–56.
27. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958–67.
28. Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Ann Rheum Dis. 2012;71(6):799–803.
29. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. J Rheumatol. 2013;40(12):1967–76.
30. Ogishima H, Tsuboi H, Umeda N, Horikoshi M, Kondo Y, Sugihara M, et al. Analysis of subclinical synovitis detected by ultrasonography and low-field magnetic resonance imaging in patients with rheumatoid arthritis. Mod Rheumatol. 2013.
31. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol. 2013;23(3):456–65.
32. Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Ann Rheum Dis. 2004;63(4):382–5.
33. Le Boedec M, Jousse-Joulin S, Ferlet JF, Marhadour T, Chales G, Grange L, et al. Factors influencing concordance between clinical and ultrasound findings in rheumatoid arthritis. J Rheumatol. 2013;40(3):244–52.
34. Sheane BJ, Beddy P, O'Connor M, Miller S, Cunnane G. Targeted ultrasound of the fifth metatarsophalangeal joint in an early inflammatory arthritis cohort. Arthritis Rheum. 2009;61(7):1004–8.
35. Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009;61(9):1194–201.
36. Dougados M, Jousse-Joulin S, Mistretta F, d'Agostino MA, Backhaus M, Bentin J, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. Ann Rheum Dis. 2010;69(5):828–33.
37. Dougados M, Devauchelle-Pensec V, Ferlet JF, Jousse-Joulin S, D'Agostino MA, Backhaus M, et al. The ability of synovitis to predict structural damage in rheumatoid arthritis: a comparative study between clinical examination and ultrasound. Ann Rheum Dis. 2013;72(5):665–71.
38. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka M, Norimoto A, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission. Arthritis Care Res. 2014. doi: 10.1002/acr.22303. [Epub ahead of print].
39. Schmidt WA, Schmidt H, Schicke B, Gromnica-Ihle E. Standard reference values for musculoskeletal ultrasonography. Ann Rheum Dis. 2004;63(8):988 94.
40. Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005;32(12):2485–7.
41. Szkudlarek M, Court-Payen M, Jacobsen S, Klarlund M, Thomsen HS, Ostergaard M. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955–62.
42. Keen HI, Redmond A, Wakefield RJ, Freeston J, Grainger AJ, Hensor EM, et al. An ultrasonographic study of metatarsophalangeal joint pain: synovitis, structural pathology and their relationship to symptoms and function. Ann Rheum Dis. 2011;70(12):2140–3.
43. Iagnocco A, Filippucci E, Riente L, Meenagh G, Delle Sedie A, Sakellariou G, et al. Ultrasound imaging for the rheumatologist XXXV. Sonographic assessment of the foot in patients with osteoarthritis. Clin Exp Rheumatol. 2011;29(5):757–62.
44. Hayashi D, Roemer FW, Katur A, Felson DT, Yang SO, Alomran F, et al. Imaging of synovitis in osteoarthritis: current status and outlook. Semin Arthritis Rheum. 2011;41(2):116–30.
45. Krasnokutsky S, Belitskaya-Levy I, Bencardino J, Samuels J, Attur M, Regatte R, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. Arthritis Rheum. 2011;63(10):2983–91.
46. Wittoek R, Jans L, Lambrecht V, Carron P, Verstraete K, Verbruggen G. Reliability and construct validity of ultrasonography of soft tissue and destructive changes in erosive osteoarthritis of the interphalangeal finger joints: a comparison with MRI. Ann Rheum Dis. 2011;70(2):278–83.
47. Kortekaas MC, Kwok WY, Reijnierse M, Huizinga TW, Kloppenburg M. In erosive hand osteoarthritis more inflammatory signs on ultrasound are found than in the rest of hand osteoarthritis. Ann Rheum Dis. 2013;72(6):930–4.

Arthritis Care & Research
Vol. 66, No. 10, October 2014, pp 1576–1581
DOI 10.1002/acr.22303

BRIEF REPORT

Prediction of Relapse After Discontinuation of Biologic Agents by Ultrasonographic Assessment in Patients With Rheumatoid Arthritis in Clinical Remission: High Predictive Values of Total Gray-Scale and Power Doppler Scores That Represent Residual Synovial Inflammation Before Discontinuation

TARO IWAMOTO,[1] KEI IKEDA,[2] JUNICHI HOSOKAWA,[2] MIEKO YAMAGATA,[2] SHIGERU TANAKA,[2] AYAKO NORIMOTO,[2] YOSHIE SANAYAMA,[2] DAIKI NAKAGOMI,[2] KENTARO TAKAHASHI,[2] KOICHI HIROSE,[2] TAKAO SUGIYAMA,[3] MAKOTO SUEISHI,[3] AND HIROSHI NAKAJIMA[2]

Objective. This prospective study aimed to determine whether the comprehensive ultrasonographic assessment of synovial inflammation predicts relapse after discontinuation of treatment with a biologic agent in patients with rheumatoid arthritis (RA) in clinical remission.

Methods. RA patients in clinical remission (Disease Activity Score in 28 joints [DAS28] <2.6) receiving treatment with a biologic agent who agreed to discontinue the treatment were recruited. Patients underwent a comprehensive ultrasound scan on 134 synovial sites in 40 joints and were prospectively followed up for 6 months. Physicians who evaluated the patients during the study period were blinded to the baseline ultrasound findings.

Results. Forty-two patients receiving either a tumor necrosis factor antagonist or tocilizumab were enrolled. Using the optimal cutoff values determined by receiver operating characteristic curve analysis, relapse rates were significantly higher in patients whose total ultrasound scores at discontinuation were high than in those whose total ultrasound scores were low ($P < 0.001$ for both total gray-scale and power Doppler scores), whereas the difference between high and low DAS28 was not statistically significant ($P = 0.158$ by log rank test). Positive and negative predictive values were 80.0% and 73.3% for the total gray-scale score and 88.9% and 74.2% for the total power Doppler score, respectively.

Conclusion. In RA patients in clinical remission receiving treatment with a biologic agent, residual synovial inflammation determined by comprehensive ultrasound assessment predicted relapse within a short term after discontinuation of the treatment. Our data provide a rationale and groundwork to conduct a large-scale study for establishment of ultrasound-based strategies to optimize the period of treatment with a biologic agent.

Introduction

Clinical, structural, and functional outcomes of rheumatoid arthritis (RA) have substantially improved due to the availability of therapy with a biologic agent (1). However, since biologic agents are expensive and increase the risk of infection, these agents should be given to the right patients for the right period of time. One possible strategy to optimize the treatment period is to discontinue the treatment

[1]Taro Iwamoto, MD: Chiba University Hospital and National Hospital Organization Shimoshizu Hospital, Yotsukaido, Chiba, Japan; [2]Kei Ikeda, MD, PhD, Junichi Hosokawa, MD, Mieko Yamagata, MD, Shigeru Tanaka, MD, Ayako Norimoto, MD, Yoshie Sanayama, MD, Daiki Nakagomi, MD, PhD, Kentaro Takahashi, MD, PhD, Koichi Hirose, MD, PhD, Hiroshi Nakajima, MD, PhD: Chiba University Hospital, Chiba, Japan; [3]Takao Sugiyama, MD, PhD, Makoto Sueishi, MD, PhD: National Hospital Organization Shimoshizu Hospital, Yotsukaido, Chiba, Japan.

Dr. Ikeda has received consulting fees, speaking fees, honoraria, and/or research grant support (less than $10,000 each) from AbbVie and Mitsubishi-Tanabe. Dr. Nakajima has received consulting fees, speaking fees, honoraria, and/or research grant support (less than $10,000 each) from Astellas, Chugai, and Mitsubishi-Tanabe.

Significance & Innovations

- Patients with rheumatoid arthritis in clinical remission receiving treatment with a biologic agent still have residual synovial inflammation detected by ultrasonography.
- Residual synovial inflammation determined by ultrasonographic assessment predicts relapse after discontinuation of treatment with a biologic agent.

with a biologic agent once the disease becomes clinically quiescent (2–4). Tanaka et al reported that 55% of the patients who discontinued infliximab sustained a low disease activity state (Disease Activity Score in 28 joints [DAS28] ≤3.2) after 1 year and that "a deep remission" (DAS28 <2.225) at discontinuation predicted the sustained low disease activity (4). However, the prediction of a good clinical course based on baseline DAS28 was not very accurate (positive predictive value [PPV] 71.4%, negative predictive value 67.4%), which might be due to the limited accuracy of clinical measures to reflect the true residual inflammation in synovial tissues (5).

Musculoskeletal ultrasound, conversely, directly visualizes the inflammation in synovial tissues and has been shown to improve the accuracy of diagnosis (6–8) and the assessment of disease activity of RA (5,9–11). Ultrasound also has been shown to predict relapse in RA patients who achieved clinical remission (12,13). However, Saleem et al reported that ultrasonographic findings of the metacarpophalangeal (MCP) joints and the wrist joints in the dominant hand were not identified as significant predictors of relapse in 40 patients with RA who discontinued tumor necrosis factor (TNF) blockade therapy (14), and no other published studies to our knowledge have investigated the role of ultrasound in predicting relapse after discontinuation of treatment with a biologic agent. We hypothesized that the ultrasonographic assessment of the unilateral hand may not accurately represent the total residual inflammation in the entire body and may have not provided the study with sufficient statistical power.

In this prospective study, we comprehensively evaluated inflammation in 134 synovial sites in 40 joints in order to revaluate the role of musculoskeletal ultrasound in predicting relapse after discontinuation of treatment with a biologic agent in patients with RA.

Patients and methods

Patients. Patients with RA in remission (DAS28 <2.6) receiving treatment with a biologic agent who agreed to discontinue the treatment were recruited. Patients underwent clinical, laboratory, and ultrasonographic assessment at baseline and also underwent clinical and laboratory assessments every month after discontinuation of the treatment with a biologic agent for 6 months. The study design was approved by the Ethics Committee of Chiba University, and subjects' written informed consent was obtained according to the Declaration of Helsinki.

Address correspondence to Kei Ikeda, MD, PhD, Department of Allergy and Clinical Immunology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan. E-mail: K.Ikeda@faculty.chiba-u.jp.
Submitted for publication October 23, 2013; accepted in revised form February 4, 2014.

Clinical and laboratory assessments at baseline. Clinical and laboratory assessments at baseline included 28 swollen and tender joint counts, visual analog scale for physician and patient global assessment, Health Assessment Questionnaire disability index, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and anti–cyclic citrullinated peptide antibody.

Ultrasound examination. Ultrasound was performed at baseline by rheumatologists trained for musculoskeletal ultrasound (TI, KI, AN, YS, DN, or KT) who were blinded to clinical information and laboratory data. A systematic multiplanar gray-scale (GS) and power Doppler (PD) ultrasound examination of 134 synovial sites in 40 joints (DAS28 joints + ankles + metatarsophalangeal joints; see Supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract) was performed using either Aplio XG, Viamo (Toshiba Medical Systems), HI VISION Avius, or HI VISION Ascendus (Hitachi Medical), depending on availability. The machine setting for PD ultrasound was optimized as previously described (8).

Ultrasound findings of GS synovitis and PD positivity were defined according to the consensus definitions (15). Severity of ultrasound findings was graded semiquantitatively on a scale of 0–3 as previously described (8,9). These GS and PD scores graded by the same sonographers showed good intra- and interobserver reliabilities in the previous study (8). Each patient's total GS and PD scores were calculated by summing the corresponding scores of 40 joints.

Followup assessment after discontinuation of treatment with a biologic agent and definition of relapse. Patients were assessed monthly by rheumatologists who were blinded to the baseline ultrasound findings (TI, KI, JH, MY, ST, YS, KH, MS, or HN) and received routine clinical management after discontinuation of treatment with a biologic agent. Patients were considered as having a relapse when the DAS28 was >3.2 and antirheumatic treatment was escalated.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics, version 21. Normally distributed continuous data were analyzed using parametric tests (Student's *t*-test). Non–normally distributed data were analyzed using nonparametric tests (Mann-Whitney U test or Spearman's rank correlation coefficient). Categorical data were analyzed using the chi-square test or Fisher's exact test. Relapse-free survival data were analyzed using the log rank test. Multivariate analyses were performed using lo-

Table 1. Baseline variables of rheumatoid arthritis patients who relapsed within 6 months and those who did not after discontinuation of treatment with a biologic agent*

	Total (n = 42)†	Relapse within 6 months		P‡
		No (n = 24)	Yes (n = 16)	
Women, no. (%)	33 (79)	18 (75)	14 (88)	0.439
Age, mean ± SD years	59.6 ± 12.8	58.0 ± 14.4	62.3 ± 10.4	0.334
Disease duration, mean ± SD years	8.2 ± 6.7	7.9 ± 6.1	7.0 ± 4.9	0.811
Duration of remission, mean ± SD months§	22.8 ± 15.5	22.3 ± 15.3	24.9 ± 16.6	0.580
DAS28, median (IQR)	1.9 (1.2–2.5)	2.0 (1.2–2.5)	1.9 (1.5–2.5)	0.609
DAS28-CRP, median (IQR)	1.5 (1.3–1.9)	1.5 (1.3–1.9)	1.6 (1.5–1.9)	0.389
SDAI, median (IQR)	3.3 (2.0–5.1)	2.9 (1.3–4.9)	3.6 (2.4–5.9)	0.180
CDAI, median (IQR)	3.2 (2.0–4.6)	2.7 (1.2–4.8)	3.5 (2.1–5.1)	0.275
HAQ DI, median (IQR)	0.2 (0.0–0.5)	0.1 (0.0–0.5)	0.3 (0.0–0.7)	0.721
RF positive, no. (%)	35 (83)	19 (79)	14 (88)	0.681
Anti-CCP positive, no. (%)	31 (74)	17 (71)	12 (75)	1.000
Discontinued biologic agent, no.				0.174
Infliximab	17	12	5	
Etanercept	3	0	3	
Adalimumab	6	3	2	
Golimumab	5	4	1	
Certolizumab pegol	1	0	1	
Tocilizumab	10	5	4	
Dosage of methotrexate, mg/week¶				0.553
Median (IQR)	8.0 (6.0–12.0)	8.0 (6.0–10.5)	8.0 (6.0–12.0)	
No.	38	22	15	
Dosage of prednisolone, mg/day¶				0.667
Median (IQR)	3.0 (2.0–5.0)	2.5 (2.0–4.5)	3.3 (2.52–4.0)	
No.	7	4	2	
Total GS score, median (IQR)	6.0 (2.0–15.3)	3.0 (1.0–8.0)	13.0 (5.3–16.8)	0.005
Total PD score, median (IQR)	0.0 (0.0–2.3)	0.0 (0.0–0.0)	2.0 (0.0–4.8)	0.002

* DAS28 = Disease Activity Score in 28 joints; IQR = interquartile range; CRP = C-reactive protein; SDAI = Simplified Disease Activity Index; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; DI = disability index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide antibody; GS = gray-scale; PD = power Doppler.
† Two patients were excluded during the followup period.
‡ By chi-square test (Fisher's exact test), 2-sample *t*-test, or Mann-Whitney U test.
§ Retrospectively determined by reviewing the medical record.
¶ Dosages of methotrexate/prednisolone in patients who were receiving the medication are shown.

gistic regression models into which all possible explanatory variables were forcedly entered. *P* values less than 0.05 were considered significant.

Results

Patient characteristics. Forty-two patients (33 women, 9 men) were enrolled in this study. All patients fulfilled both the American College of Rheumatology (ACR) 1987 classification criteria for RA (16) and the 2010 ACR/European League Against Rheumatism classification criteria for RA (17). As shown in Table 1, the mean ± SD age and disease duration were 59.6 ± 12.8 years and 8.2 ± 6.7 years, respectively. The mean duration of remission was 22.8 months (range 3–73 months). Thirty-two patients were receiving TNF antagonists, whereas 10 were receiving tocilizumab. Seven patients were receiving corticosteroids (prednisolone ≤9 mg daily).

Ultrasound findings. Ultrasound showed minimal synovial inflammation in the majority of patients (Table 1). GS synovitis was detected most frequently in the wrist (51.2%), knee (28.9%), and MCP joints (21.4%), whereas PD synovitis was detected most frequently in the wrist (16.7%), elbow (3.6%), and MCP joints (3.1%; see Supplementary Figure 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract). Representative ultrasound images are shown in Supplementary Figure 2 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract).

Clinical course and treatment escalation. During the study period, 1 patient with diabetes mellitus who developed cellulitis in the lower legs was excluded from further analyses. Another patient who developed acute exacerbation of interstitial lung disease and received methylprednisolone pulse therapy was also excluded. In the remaining 40 patients, antirheumatic treatment was escalated in 16 (40.0%), with either the discontinued biologic agent (n = 14), tacrolimus (n = 1), or an increased dose of methotrexate (n = 1). All of these patients had a DAS28 >3.2 when the antirheumatic medication was escalated. The mean ± SD period until relapse was 14.8 ± 6.3 weeks. Conversely, 23 patients remained at a DAS28 ≤3.2 without

Table 2. Receiver operating characteristic curve analysis and predictive values of baseline variables for relapse within 6 months after discontinuation of treatment with a biologic agent*

	AUC (95% CI)	Optimal cut point	Relapse, no. No (n = 24)	Relapse, no. Yes (n = 16)	P†	Predictive values, % Sensitivity	Specificity	PPV	NPV
DAS28	0.55 (0.37–0.73)	≥1.5	15	13	0.297	81	38	46	75
Total GS score	0.76 (0.60–0.91)	≥14	2	8	0.007	50	92	80	73
Total PD score	0.73 (0.56–0.91)	≥3	1	8	0.001	50	96	89	74

* AUC = area under the receiver operating characteristic curve; 95% CI = 95% confidence interval; PPV = positive predictive value; NPV = negative predictive value; DAS28 = Disease Activity Score in 28 joints; GS = gray-scale; PD = power Doppler.
† By chi-square test or Fisher's exact test.

treatment escalation. One patient had a transient increase of a DAS28 >3.2, but antirheumatic treatment was not escalated. No patients received intraarticular or intramuscular injection of corticosteroid during the study period. Antirheumatic treatment was deescalated only in the abovementioned patient with diabetes mellitus, who was excluded from the analyses.

Difference in baseline variables between patients who had a relapse and those who did not. As shown in Table 1, no clinical variables, including composite measures at discontinuation, were significantly different between patients who had a relapse and those who did not. Conversely, total GS and PD scores were significantly greater in patients who had a relapse than those who did not (median 13.0 versus 3.0; $P = 0.005$ for total GS score and median 2.0 versus 0.0; $P = 0.002$ for total PD score by Mann-Whitney U test). As expected, we found a significant correlation between total GS and PD scores ($\rho = 0.586$, $P < 0.001$ by Spearman's rank correlation coefficient).

Receiver operating characteristic (ROC) curve analysis. We next performed ROC curve analyses for the total GS and PD scores to predict relapse within 6 months after discontinuation of treatment with a biologic agent. Areas under the ROC curve for total GS and PD scores were larger (0.76 and 0.73, respectively) than that for the DAS28 (0.55) (Table 2).

Predictive values and relapse-free survival. When the cut points determined by ROC curve analysis were applied, patients with a greater total GS (≥14) or PD (≥3) score at discontinuation of treatment with a biologic agent had significantly greater chances to have a relapse than those with smaller scores (PPVs 80.0% versus 26.7%; $P = 0.007$ for total GS score and 88.9% versus 25.8%; $P = 0.001$ for total PD score by Fisher's exact test), whereas the difference between a high and low DAS28 was not statistically significant (PPV 46.4% versus 25.0%; $P = 0.297$ by chi-square test) (Table 2). Furthermore, the relapse-free period was significantly shorter in patients with a greater total GS or PD score ($P < 0.001$ for both), while the difference between a high and low DAS28 was not statistically significant ($P = 0.158$ by log rank test) (Figure 1).

Multivariate regression analysis. Finally, we performed multivariate logistic regression analyses to determine the independent predictive values of total GS and PD scores for relapse after discontinuation of treatment with a biologic agent. However, the models that included various combinations of variables did not retain any variables due to the small sample size.

Discussion

In this study, total ultrasound scores for synovial inflammation were identified as statistically significant predictors of relapse after discontinuation of treatment with a

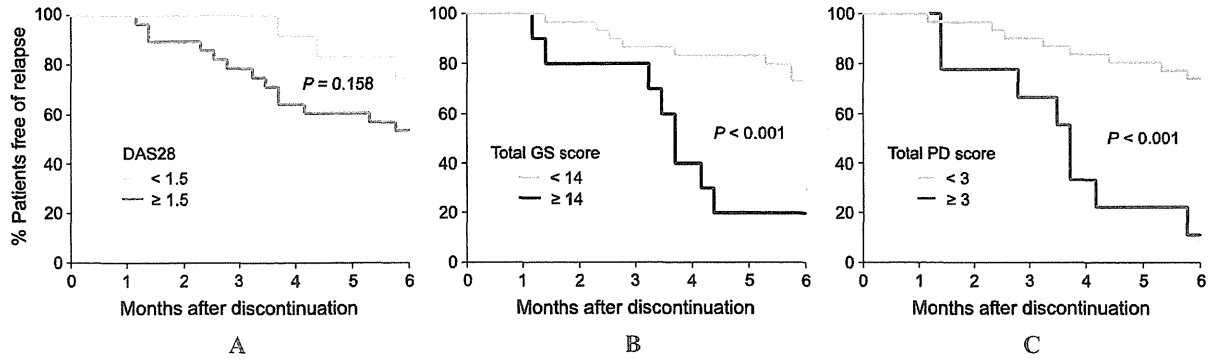

Figure 1. Differences in relapse-free periods between high and low Disease Activity Scores in 28 joints (DAS28) or between high and low ultrasound scores at discontinuation of treatment with a biologic agent. **A**, DAS28, **B**, total gray-scale (GS) score, and **C**, total power Doppler (PD) score. *P* values were calculated by the log rank test.

biologic agent in RA patients, whereas other baseline clinical measures, including the DAS28, were not. Given that the relapse was defined by the DAS28 and treatment escalation, both of which were determined by rheumatologists who were blinded to ultrasound findings, the superiority of ultrasound scores over the DAS28 in predicting relapse in this study is significant. Most of the patients whose total PD score was ≥3 had a relapse within 6 months, suggesting that minimal PD activity represents "a true deep remission" and is a prerequisite for successful cessation of treatment with a biologic agent.

Unexpectedly, total GS score was also identified as a significant predictor of relapse. It remains unclear whether this only reflects the correlation between GS and PD scores or truly represents an independent value of GS synovitis in predicting relapse after discontinuation of treatment with a biologic agent, since the small sample size of our study did not withstand the multivariate analysis. Because 3 of 4 patients who had a total GS score ≥14 but a total PD score <3 experienced a relapse (data not shown), we speculate that residual synovial hypertrophy without abnormally increased blood flow may serve as a scaffold for active inflammation to recur when potent therapy is discontinued (see Supplementary Figures 2E and F, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract). Nevertheless, the independent predictive value of GS synovitis and the possible value of a model that combines GS and PD synovitis need further investigation.

We successfully revaluated the utility of musculoskeletal ultrasound, which was not apparent in the previous study (14), by increasing the number of joints scanned. However, comprehensive ultrasonographic assessment is not feasible to be performed in daily practice; therefore, the next step should be the identification of a proper joint set to be scanned. However, the wide distribution of residual GS and PD synovitis in our cohort seems to reflect the heterogeneous nature of RA (see Supplementary Figure 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22303/abstract) and indicates the difficulty in reducing the number of joints to be scanned without compromising the accuracy. We speculate that scanning the currently or recently symptomatic joints could efficiently identify the insidiously active joints, although this hypothesis needs further evaluation.

The short length of the study period also raises a question as to how long the predictive capability of ultrasound findings would last after discontinuation of treatment with a biologic agent. In addition, the limited sample size in our study also does not allow for subanalyses on the difference between biologic agents of different modes of action. Taken together, a study with a larger number of patients and a longer followup period is needed to establish optimal ultrasound-based strategies to reduce the unnecessarily long-term use of biologic agents. The potent capability of total ultrasound scores to predict relapse within a short term after discontinuation of treatment with a biologic agent shown in our study provides a rationale to conduct such a large-scale study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ikeda had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ikeda.

Acquisition of data. Iwamoto, Ikeda, Hosokawa, Yamagata, Tanaka, Norimoto, Sanayama, Nakagomi, Takahashi, Hirose, Sugiyama, Sueishi.

Analysis and interpretation of data. Iwamoto, Ikeda, Nakajima.

REFERENCES

1. Ikeda K, Cox S, Emery P. Aspects of early arthritis. Biological therapy in early arthritis: overtreatment or the way to go? Arthritis Res Ther 2007;9:211.
2. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:27–35.
3. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2008;58 Suppl: S126–35.
4. Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. Ann Rheum Dis 2010;69:1286–91.
5. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58: 2958–67.
6. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Ann Rheum Dis 2010;69:417–9.
7. Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of rheumatoid arthritis in patients with very early synovitis. Ann Rheum Dis 2011;70:500–7.
8. Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Sanayama Y, Takahashi K, et al. Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. Arthritis Rheum 2013;65:890–8.
9. Naredo E, Moller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti–tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum 2008;58:2248–56.
10. Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Ann Rheum Dis 2012;71:799–803.
11. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. J Rheumatol 2013;40:1967–76.
12. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B,