active phase of CTD when immunosuppressive treatment starts or intensifies. Our study is the first to satisfy these methodological conditions.

Our study has several limitations. First, the different approval status of medications from Western countries should be considered when generalizing. Because of the lack of approval by the Japanese regulatory agency, few patients used mycophenolate mofetil and rituximab in our cohort. Second, we enrolled patients with "articular RA" who used less PSL and more biologics. As a sensitivity analysis, we conducted an additional multivariate analysis excluding patients with articular RA and found essentially the same risk factors (Supplementary Table 5, available online at jrheum.org).

We have shown the prevalence and types of PI during immunosuppressive treatment among patients with CTD. Significant risk factors age ≥ 65 years, ≥ 20 pack-years of smoking, and elevated serum creatinine at baseline and maximum PSL doses, both at baseline and when PI developed. To reduce the risk of PI in patients with these irreversible risk factors, investigations for novel treatment strategies with lower doses of corticosteroid are warranted. The results of our study mean that all physicians should take appropriate measures to prevent PI.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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APPENDIX 1.

List of study collaborators. Investigators of the Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for connective tissue disease (PREVENT) study group, and their affiliations: Hiromi Hagiwara, Yuichiro Fujieda (Hokkaido University); Tsutomu Takeuchi, Michito Hirakata (Keio University); Shintaro Hirata, Kazuyoshi Saito (University of Occupational and Environmental Health); Jun Kishi, Yuko Toyoda (Tokushima University); Hirofumi Amano, Naoto Tamura (Juntendo University); Kenchi Takenaka (Ome Municipal General Hospital); Koichi Amano (Saitama Medical Center); Futoshi Hagiwara (Sagamihara National Hospital); Tadashi Hosoya (Tokyo Metropolitan Geriatric Hospital); Yasuhiro Katsumata (Tokyo Women's Medical University).

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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

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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.

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Conflict of interest

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ORIGINAL ARTICLE

Postoperative complications in patients with rheumatoid arthritis using a biological agent—A systematic review and meta-analysis

Hiromu Ito[1], Masayo Kojima[2], Keiichiro Nishida[3], Isao Matsushita[4], Toshihisa Kojima[5], Takeo Nakayama[6], Hirahito Endo[7], Shintaro Hirata[8], Yuko Kaneko[9], Yutaka Kawahito[10], Mitsumasa Kishimoto[11], Yohei Seto[12], Naoyuki Kamatani[12], Kiichiro Tsutani[13], Ataru Igarashi[13], Mieko Hasegawa[14], Nobuyuki Miyasaka[15], and Hisashi Yamanaka[12]

[1]*Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan,* [2]*Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan,* [3]*Department of Human Morphology, Okayama University Graduate School of Medicine, Okayama, Japan,* [4]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama, Toyama, Japan,* [5]*Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan,* [6]*Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan,* [7]*Division of Rheumatology, Department of Internal Medicine, School of Medicine, Toho University, Tokyo, Japan,* [8]*The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan,* [9]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan,* [10]*Department of Inflammation and Immunology, Graduate school of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan,* [11]*Immuno-Rheumatology Center, St Luke's International Hospital, Tokyo, Japan,* [12]*Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan,* [13]*Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan,* [14]*The Japan Rheumatism Friendship Association, Tokyo, Japan, and* [15]*Tokyo Medical and Dental University, Tokyo, Japan*

Abstract

Objectives. To evaluate, through a systematic review of the literature, the association between the use of biological disease-modifying antirheumatic drugs (bDMARDs) and surgical site infection (SSI) or wound healing delay after orthopedic surgery in patients with rheumatoid arthritis (RA).
Methods. A systematic review of articles indexed in the Cochrane Library, PubMed, and Web of Science from 1992 to 2012 was performed. The search aimed to identify studies describing SSI or wound healing delay in patients with RA treated with or without bDMARDs. Articles fulfilling the predefined inclusion criteria were reviewed systematically and their quality was appraised.
Results. There was no Cochrane review on this subject. We found 75 articles through specific searches of PubMed and Web of Science, and hand searching. After inclusion and exclusion by full-text review, 10 articles were found for SSI, and 5 articles for delayed wound healing. The use of bDMARDs appeared to increase the rate of SSI slightly, especially in large joint-replacement surgery. Delayed wound healing was not increased by the use of bDMARDs. However, the definitions of SSI and delayed wound healing varied between the reviewed articles. Most of the articles focused on tumor necrosis factor-α inhibitors.
Conclusion. bDMARDs slightly increase the relative risk of SSI but not that of delayed wound healing after orthopedic surgery and should be used with appropriate caution.

Keywords

Biological agent, Delayed wound healing, Perioperative complication, Rheumatoid arthritis, Surgical site infection, Systematic review

History

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Introduction

Recent advances in medication have brought about a substantial paradigm shift in the treatment of rheumatoid arthritis (RA). Biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the management of RA and have markedly changed the functional status of patients with RA.

Despite treatment with such agents, structural damage can accumulate over time and a certain percentage of patients inevitably require surgical intervention [1]. Over the years, serious concern has been raised by rheumatologists, orthopedic surgeons, and patients regarding the perioperative complications after orthopedic surgery in patients receiving bDMARDs. The adverse consequences of the inhibition of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), or T-cell function may include serious complications such as surgical site infection (SSI) and/or delayed wound healing, especially in patients undergoing total joint replacement. Several articles on this topic have been published in the past decade, although the findings of these articles are conflicting. Considering the huge benefit patients receive from an appropriate surgical intervention, patients, rheumatologists, and orthopedic surgeons should consider the risk–benefit balance based on the evidence of the risks associated with surgical intervention, especially when used with the new medications. Since more evidence recently became available on this topic, we thought that a new systematic literature review using transparent methodology would provide scientifically appropriate conclusions.

Correspondence to: Hiromu Ito, Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo, Kyoto 606-8507, Japan. Tel: 81-75-751-3366, Fax: 81-75-751-8409. E-mail: hiromu@kuhp.kyoto-u.ac.jp

This review is part of the clinical practice guidelines for the management of RA in Japan developed in 2014 under the support of Health and Labour Sciences Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labour and Welfare. We used the grading of recommendations, assessment, development, and evaluation (GRADE) approach to describe the quality of evidence and the strength of recommendations [2,3]. In this article, we focus on the perioperative complications of SSI and wound healing delay in patients receiving bDMARDs compared with those not receiving bDMARDs (mostly receiving conventional synthetic DMARDs [csDMARDs]) who underwent orthopedic surgery. We specifically address the following two clinical questions. (1) does the use of a bDMARD increase the risk of developing an SSI? and (2) does the use of a bDMARD increase the risk of delayed wound healing? We do not discuss other surgical complications such as thromboembolism because there was insufficient literature on these complications at the time of our review.

Materials and methods

Our review was performed according to the GRADE system [2,3]. The key components of the clinical questions according to the participants, interventions, comparisons, and outcomes or PICO plan were as follows. The participants were patients with a diagnosis of RA either confirmed by a rheumatologist or using the 1987 or 2010 classification criteria. The intervention examined was the use of bDMARDs and included anti-TNF-α inhibitors (adalimumab, etanercept, golimumab, and infliximab), abatacept, and tocilizumab. The comparison arm was any medication except bDMARDs. All of the participants underwent an elective or compulsory orthopedic surgery with continuation or discontinuation of bDMARDs. We did not ask about perioperative continuation or discontinuation of csDMARDs or steroids.

The types of studies for inclusion in our review were limited to controlled studies, all of which were cohort or observational studies with appropriate control groups. Studies that investigated only patients without RA, interventions with non-bDMARDs, or no orthopedic surgery, and/or studies that did not show separate data for bDMARDs and non-bDMARDs were excluded. Case reports, comments or letters to the editor, and articles with no control group were also excluded from the review. The primary outcomes for this systematic review were SSI and delayed wound healing reported in the literature after an orthopedic surgery.

Search methods to identify the studies

A thorough literature search was performed with a medical librarian to reduce bias by increasing the likelihood of retrieving all relevant studies. The following electronic databases were searched from January 1998 to August 2012: PubMed, Web of Science, and the Cochrane Database of Systematic Reviews (CDSR). Relevant articles were screened for additional references published by the end of December 2013. Articles written in English were considered for review. The search strategy comprised the following components, each of which was defined by a combination of Medical Subject Heading (MeSH) terms and free text terms: (1) arthritis, rheumatoid/surgery; (2) complication, adverse effect, risk factors, wound infection, or treatment outcome; and (3) antirheumatic agents or biological agents.

#1. "arthritis, rheumatoid/surgery" [MH] (MH: MeSH Terms)
#2. complication* OR adverse effect* OR risk factors OR wound infection [MH] OR "treatment outcome" [MH]
#3. "antirheumatic agents" [MH] OR (antirheumatic [TIAB] AND agents [TIAB]) OR "antirheumatic agents" [TIAB] OR "antirheumatic agents" [Pharmacological Action] OR biological agent* [TIAB] (TIAB: Title/Abstract)
#4. #1 AND #2 AND #3
#5. #4 Filters: publication date from 1998/01/01 to 2012/08/31; English

In addition, the reference lists of studies identified for inclusion in the review and in previous review papers were searched manually to find additional studies.

Data collection and analysis

Selection of studies

Titles and abstracts were assessed for all records identified through the search strategies. Two review authors (HI and MK) examined each citation, and full papers were retrieved for all those appearing to meet the inclusion criteria. Full reports were also acquired if there was any uncertainty about their inclusion or if abstracts were not available; it was not possible to exclude the study based on the title alone. All full-text articles were screened for the inclusion and exclusion criteria by the two independent review authors (HI and MK), and any disagreements regarding eligibility were resolved by discussion and the involvement of an arbiter where necessary.

Data extraction and management

For each publication, a review author (HI) retrieved the following details, which were tabulated on a standardized form: assignment to groups; follow-up periods; participants' demographics (age, sex, diagnosis, duration of disease, and sample size); medications for RA (proportions of steroid, use of methotrexate and other DMARDs, and dose of each medication); orthopedic surgery (anatomical site and type of surgery); adverse events or effects; and withdrawals. Another reviewer (MK) then checked the retrieved data and independently searched the original article(s) if there were questions or uncertainty. When the data for a particular study were unclear or missing from the article, we attempted to contact the authors. Only when the accurate data were collected from the authors was the study included for further analyses; otherwise, the study was excluded from our analyses.

Assessment of risk of bias in the included studies

To decide whether each paper retrieved would be included in the review, the two review authors (HI and MK) independently assessed the methodological quality using an adapted version of the Newcastle–Ottawa Scale for Cohort Studies [4]. This scale grades the reporting of studies according to the selection, applicability, and comparability of study groups. The maximum score was 8, and the minimum score was 0. A score of 7 or 8 was considered to indicate high methodological quality (low risk of bias), a score of 5 or 6 indicated moderate quality, and 4 or less indicated low quality (high risk of bias) [5].

Statistical analysis

We performed this meta-analysis using the method described previously [5]. Briefly, in our meta-analysis we included those studies with unadjusted estimates of SSI and delayed wound healing. After collecting the frequency data, we calculated the relative risk and 95% confidence interval (CI) for the primary outcomes (SSI and delayed wound healing) in the groups that used bDMARDs or any other medication specified. We grouped all of the data, irrespective of the follow-up period or whether the definition of complications was described. We pooled the outcome measures using the random-effects model of DerSimonian and Laird. We weighted all pooled estimates by study size and quantified heterogeneity between studies using the I^2 statistic. To assess publication bias, we constructed funnel plots to examine the sample size versus exposure effect across the included studies. We conducted all

statistical analyses using Review Manager 5.1. (Cochrane Collaboration: Review Manager [RevMan; computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

We did not find any reviews in the CDSR on this subject. We next searched PubMed and Web of Science using the terms described in "Materials and methods" and then added the manually searched manuscripts published in PubMed by the end of December in 2013, and found 75 articles that matched the search terms and parameters. Forty-four manuscripts were initially included, and 36 of these were excluded after full-text review. The actual number of cases reported in the article by Galloway et al. was not found [6], and the authors could not identify them from their record. After repeated correspondence, this manuscript was excluded from the meta-analysis. There was a possibility of duplicated cases between one article [7] and several other articles [8–12], but correspondence with the authors clarified that there were no duplicated cases except for one article [12]. The author of the article that was found to have duplicated cases was able to confirm the number of unduplicated cases. There was also a possibility of duplicated cases in two other articles, both of which were published by the same institution [9,11]. The authors could not confirm the number of duplicated cases in the two articles, but most of the cases were reportedly included in the article by Momohara et al. [11]. Thus, we decided that this article contained the representative data for the two articles. The full-text review and the correspondence resulted in the inclusion of 10 studies for SSI and five out of 10 for delayed wound healing for further review and meta-analysis (Figure 1). The structured abstracts of the 10 articles are shown in Table 1.

Surgical site infection

The prospective observational cohort study of Bibbo and Goldberg was the first to report the effects of bDMARDs on SSI [13]. The sample numbers were small (72 operations in patients taking a TNF-α inhibitor vs. 69 in those taking csDMARDs) and surgery involved only the foot and ankle. The authors concluded that the use of TNF-α inhibitory agents could be safely undertaken in the perioperative period without increasing the risk of delayed healing or infectious complications (1.4% in both groups). By contrast, in a retrospective observational cohort, Giles et al. showed that the use of TNF-α inhibitors significantly increased the risk of serious postoperative orthopedic infection (20.0% in 35 operations in patients taking a TNF-α inhibitor vs. 5.4% in 56 operations in patients taking csDMARDs) [14].

After these pioneering works, several other studies were published on this subject. Of note, the Committee on Arthritis of the Japanese Orthopaedic Association conducted a nationwide survey on the prevalence of postoperative complications in patients with RA treated in a teaching hospital between January 2004 and November 2008 [7]. The association collected 3468 cases of patients taking bDMARDs and 56339 of those taking csDMARDs. The SSI rate after all surgeries was slightly, but not significantly, higher in the bDMARD group (1.3%) compared with the csDMARD group (1.0%). The SSI rate after joint arthroplasty was significantly higher in the bDMARD group (2.1%) compared with the csDMARD group (1.0%). This is the most compelling evidence to date on this issue. Galloway et al. reported the data from the British Society for Rheumatology Biologics Registry [6]. The rate of postoperative joint infection (within 90 days) was 0.7%, and the authors concluded that the risk was not significantly increased by anti-TNF-α therapy. Their report included a sufficient number of cases (4390 in the bDMARD group and 481 in the csDMARD group), but the authors of this article did not report on individual cases of infection in both study arms, which resulted in the exclusion of this study from the meta-analysis as described above.

Overall, the incidence rate of SSI was 0–20.8% in patients taking bDMARDs, which appeared to be slightly higher than the rate of 0–5.4% in the control groups taking csDMARDs or any other drug. The incidence rate of SSI after large joint surgery was 2.1–20.8%

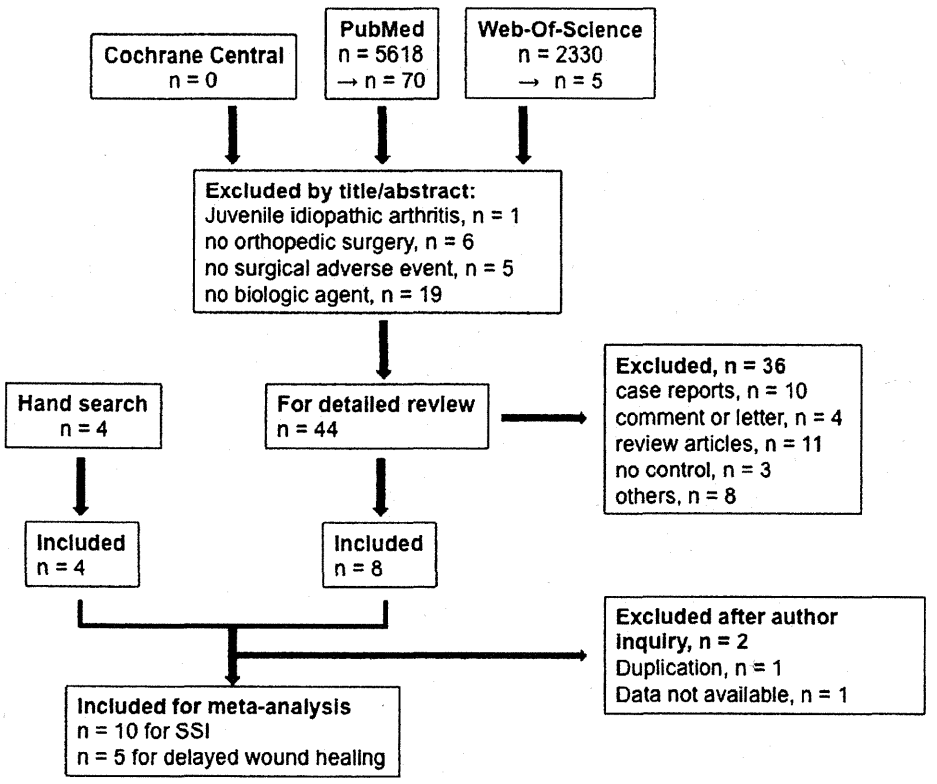


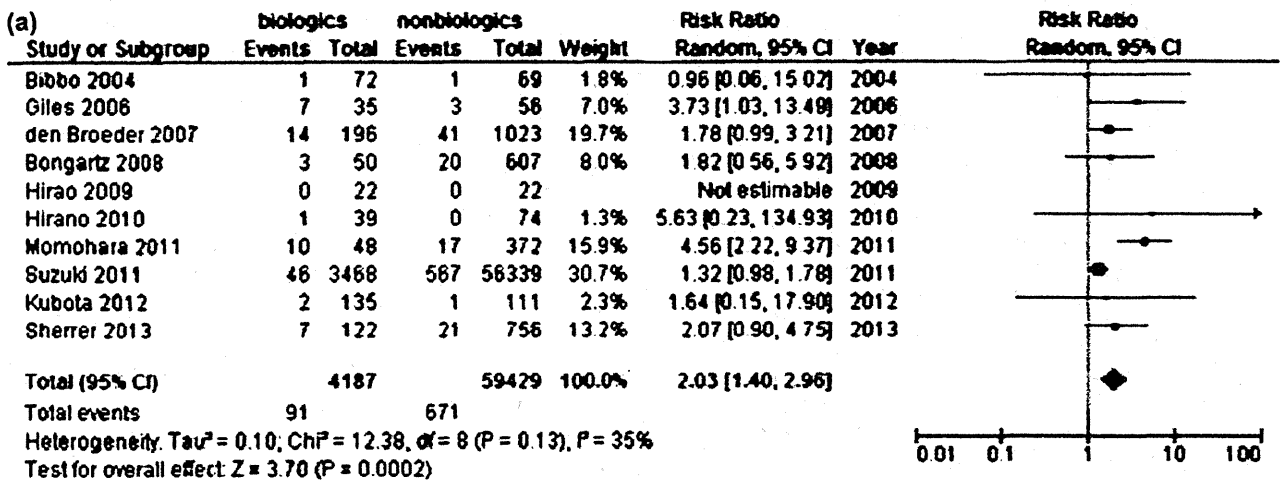
Figure 1. Literature search of 75 articles. Twelve articles were met the inclusion criteria. Ten articles were used for meta-analyses.

Table 1. Study and patient characteristics for the included studies.

Characteristics of observational studies included in systematic review of SSI in rheumatoid arthritis.

Author	Year	Study design	Patient characteristics: Anti-TNF agent user	Patient characteristics: Non-anti-TNF agent users	Multiple operation	Time of surgery	Follow-up	Definition of outcomes	Last administration of biologics before operation	NOS* quality index	Risk of bias
Bibbo and Goldberg	2004	Prospective cohort study	$N = 16$, mean age: 50 (range, 40–66) years	$N = 15$, mean age: 60 (range, 41–73) years	Unclear	Unspecified	1 year	Unclear	1–10 days for ETN, 2–45 days for IFX	3	High
Giles et al.	2006	Questionnaire survey to patients with verification by hospital charts	Total $N = 91$; Patient with infection, $N = 10$, age: 59.7 ± 9.66; no infection, $N = 81$, age: 59.4 ± 12.5.		No	1999,1~2004,3	30 days	Clear	Unspecified	3	High
den Broeder et al.	2007	Retrospective cohort study	$N = 104$, mean age: 54 ± 16; $N = 92$, mean age: 57 ± 13.	$N = 1023$, mean age: 61 ± 13.	Included	1997.1~2004,9	30 days/1 year	1992 CDC criteria	Within four times the half-life of the anti-TNF agent	7	Low
Bongartz et al.	2008	Retrospective cohort study, Registry data	Total of 462 patients, 657 procedures; mean age: 64 years; mean disease duration: 21.1.		Included	1996,1~2004,7	4.3 years (mean)	Clear	1–8 days for ETN, 1–57 for IFX, 1–15 for Adalimumab, and 1–8 days for Anakinra	5	Moderate
Hirao et al.	2009	Case–control study	Total of 22 joint surgeries	Total of 22 joint surgeries	No	Unspecified	2 weeks	Unclear	3–27 days	2	High
Hirano et al.	2010	Retrospective cohort study	$N = 39$, mean age: 58.9 ± 9.0.	$N = 74$, mean age: 62.6 ± 9.1.	No	2004,4~2007,7	4 weeks	Clear	3–4 weeks	3	Moderate
Momohara et al.	2011	Retrospective cohort study	Total $N = 420$; Patient with infection, $N = 27$, age: 61 (56.5–68); no infection, $N = 393$, age: 61 (54–68)		No	2005.1~2009,12	Unspecified	1999 CDC criteria	2–4 weeks	6	Moderate
Suzuki et al.	2011	Questionnaire survey to 2019 hospitals (returning 61.7%)	3,468 procedures	56,339 procedures	Included	2004.1~2008.11	Unspecified	1999 CDC criteria	2–4 weeks	4	High
Kubota et al.	2012	Retrospective cohort study	276 procedures, age 59.2 ± 10.1.	278 procedures, age 65.5 ± 10.1.	Unclear	2006.1~2010.12	Unspecified	1999 CDC criteria	2–4 weeks	4	High
Sherrer et al.	2013	Retrospective cohort study, Registry data	Total $N = 2,472$, mean age: 60.0 ± 12.7; 2,050 cases with RA.		Included	2000~2008	30 days, 10 weeks, 2 years	Clear	Within three times the half-life of the anti-TNF agent	6	Moderate

*NOS, Newcastle–Ottawa Scale



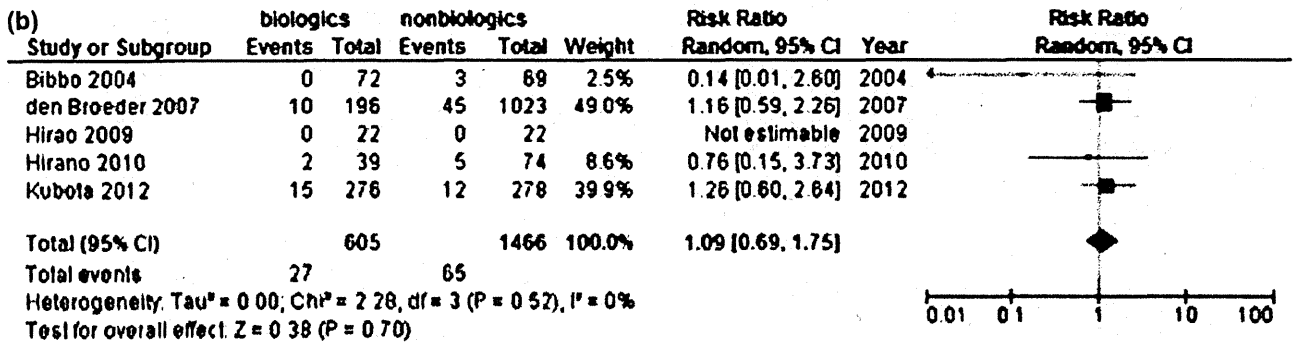


Figure 2. (a) Meta-analyses of SSI and (b) Meta-analysis of delayed wound healing.

in patients using bDMARDs, which was higher than that in controls (1.0–4.6%). Our meta-analysis showed that the relative risk of bDMARDs was 2.03 with a 95% CI of 1.40–2.96 (Figure 2a). Of note, the patients taking bDMARDs were younger than the controls. Older age is accepted as a risk factor for complications including SSI, and this relative risk provides compelling evidence of the risk of SSI in association with the use of bDMARDs.

To summarize, the relative risk of SSI after orthopedic surgery is marginally higher in patients using bDMARDs compared with those using csDMARDs or any other drug. bDMARD use may increase the relative risk of SSI in patients, especially those undergoing a total joint replacement. All of the reviewed studies were observational studies. The definition of SSI varied between articles, and the differences between deep and superficial infection could not be determined. Most articles dealt with only anti-TNF-α inhibitors. There was little evidence about IL-6 inhibitors and none about T-cell function modulators.

Delayed wound healing

The prospective observational cohort study of Bibbo and Goldberg was also the first to report the effects of bDMARDs on wound healing delay [13]. They showed that the rate of delayed wound healing for patients taking bDMARDs (0%) was similar to or even lower than that for patients taking csDMARDs (4.3%). Several research groups have reported on this issue since then, and most of the results show similar rates of delayed wound healing for patients taking bDMARDs and controls [8,10,12,15]. However, an article published by researchers in Japan reported a higher rate of delayed wound healing (12.4%) in patients taking tocilizumab compared with the rates reported in other articles and experienced in normal clinical practice [16]. The article did not have a control group (csDMARDs or other drugs), but the high incidence rate observed in this study should be noted.

Overall, the incidence rate of delayed wound healing was 0–5.4% in patients taking bDMARD, which seemed similar to the rate of 0–6.8% in controls (csDMARDs or other drugs). Our meta-analysis showed that the relative risk of bDMARDs was 1.09 with a 95% CI of 0.69–1.75 (Figure 2b), indicating that the use of bDMARDs does not increase the risk of delayed wound healing. However, these results were based on only five articles and a relatively a small sample size (605 in the bDMARD groups and 1466 in the controls).

To summarize, the relative risk of delayed wound healing after orthopedic surgery is similar in patients using bDMARDs and those using csDMARDs or any other drugs. The definition of delayed wound healing varied between articles, and most articles dealt with only anti-TNF-α inhibitors. As noted above for SSI, there was little evidence about the effects of IL-6 inhibitors and none about the effects of T-cell function inhibitors on the risk of delayed wound healing.

Discussion

Several reports have focused on the increased risk of SSI attributed to bDMARDs and a few review articles have been published [17–21], but their conclusions have been ambiguous and conflicting. Delayed wound healing is a clinical concern for surgeons and patients taking bDMARDs, but few articles have been written on this issue. We, therefore, focused on SSI and delayed wound healing in this systematic review. Our analysis shows that the use of bDMARDs appears to have certain effects on perioperative complications of orthopedic surgery, and thus bDMARDs should be used with appropriate caution. The data from the Brit-

ish national registries of patients with RA receiving bDMARDs showed an increased risk of serious infection, especially within the first 6 months after initiation of treatment [22]. Thus, there is a reasonable concern about the increased risk of SSI in patients using bDMARDs compared with csDMARDs.

SSI is one of the most devastating complications after surgery, especially joint-replacement surgery. It is thus important to clarify the effects of bDMARDs on the risk of SSI. Despite the scientific and statistical limitations related to the ethical and clinical aspects of this issue, the current review concludes from the 10 included studies that the use of a bDMARD appears to increase the rate of SSI slightly, especially after large joint-replacement surgery. Several articles have reported infection rates of 0–6.5%, although some of these reports lacked controls or sufficient data for statistical analysis [23–29]. Johnson recently reported a slightly higher rate of SSI in a group of patients taking anti-TNF-α agents (3.26%, 3/92) compared with a control group (2.10%, 3/143) [30]. These results seem to support our conclusion. However, the data are far from sufficient to justify applying them to specific strategic therapies or preventive interventions in clinical practice. Further collection and analysis of data are needed to be able to draw more reliable, precise conclusions.

Delayed wound healing has received much less attention from physicians because the consequences of this complication are usually less severe than those of SSI. However, delayed wound healing can last a long time and can be annoying to patients. It can also lead to superficial infection, especially in the ankle and foot, and to intractable osteomyelitis or deep infection of an implant in the worst-case scenario. Fewer articles focused on this topic, but the present analysis found that the rates of delayed wound healing are similar between bDMARDs and csDMARDs. One article reported a high rate of this complication in patients taking tocilizumab [16], and clinicians should continuously be aware of this topic.

TNF-α inhibitors were first introduced into clinical practice for RA treatment and are used worldwide, and so it is reasonable that there are more data for TNF-α inhibitors than for other bDMARDs. IL-6 inhibitors (e.g., tocilizumab) and T-cell or B-cell function modifiers are being used increasingly, but reports about these bDMARDs are still lacking. The available data for IL-6 inhibitors appear to show similar infection rates to those for other bDMARDs [7,8,11,12], although Momohara et al. reported a higher rate of delayed wound healing in patients receiving tocilizumab than that seen in normal practice [16]. This finding and the underlying mechanism require confirmation. Godot et al. recently reported that, of 94 orthopedic surgeries on patients with RA who received rituximab, six patients (6.4%) experienced a superficial or deep infection [31]. This rate does not seem to be higher than that for other bDMARDs. Nishida et al. reported a small case series of treatment with abatacept [32], but the effects of T-cell function modifiers should be observed in a large number of cases. This project is now underway.

One of the current interests in relation to the use of bDMARDs is the perioperative discontinuation of these drugs. If bDMARDs increase the rates of SSI and delayed wound healing, it may be better to stop these drugs before surgery. This is one reason why some guidelines suggest discontinuation of bDMARDs for a certain time before and after an operation [33,34]. Conversely, several reports have shown that continuation of bDMARDs does not increase the rate of SSI and suggested justification of continuation of the drug when it is needed [15,23–26,28,30,35], while otherwise was documented by an article [36]. There is insufficient literature on this subject [21], and further studies are required to draw a definite conclusion. Given that the most serious concern about discontinuation of bDMARDs is a flare-up of disease activity, compared with the most serious concern about continuation, namely SSI, our analysis suggests that discontinuation during the perioperative period should be considered unless a reasonable factor to warrant continuation exists.

This study has several limitations. First, the articles reviewed were mostly retrospective single-center observational cohort studies. One prospective cohort study had only a small sample size with high bias [13]. Prospective randomized studies cannot be conducted from an ethical point of view, and the level of evidence was, and will always be, less than optimum. Second, surgery inevitably involves a variety of uncontrollable biases, such as surgical indications and the backgrounds of the patient and surgeon. This unavoidably leads to ambiguity when drawing conclusions from this type of study, even in a systematic review. We conducted a meta-analysis, but the results should be interpreted with caution in mind. Third, the definitions of SSI and delayed wound healing are inconsistent between studies, and several articles included in our analysis did not describe the definitions sufficiently. Finally, new medications are being developed, and the indications for medication change accordingly. Therefore, at any given time, there will always be insufficient evidence on newly developed drugs. However, information about new drugs should be collected and published as soon as practical to help surgeons avoid surgical complications.

In summary, the use of bDMARDs appears to increase the rate of SSI slightly, especially after large joint-replacement surgery. The risk of delayed wound healing does not appear to be increased by the use of bDMARDs. The use of bDMARDs appears to have certain effects on perioperative complications of orthopedic surgery, and these medications should be used with appropriate caution. The slight increase in the risk of SSI in patients taking bDMARDs should not prevent consideration of an appropriate combination of bDMARDs and orthopedic surgery.

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Conflict of interest

H.I. has received grant and research support from Takeda, Mitsubishi-Tanabe, Chugai, Pfizer, Astellas, and Daiichi-Sankyo; K.N. has received research funding from Abbvie, Astellas, Chugai, Mitsubishi-Tanabe, Eisai, and Bristol-Myers-Squibb; I.M. has received lecturer's fee from Takeda, Mitsubishi-Tanabe, Chugai, Pfizer, Astellas, Bristol-Myers-Squibb, AbbVie, and Eisai; T.K. received speakers' bureau from Mitsubishi-Tanabe, Takeda, Eisai, Abbvie, Bristol-Myers-Squibb, Pfizer, Chugai, Janssen, and Astellas and research grants from Takeda, Janssen, and Astellas; Y.K. has received research honorarium for the lecture from Abbvie, Eisai, Chugai, Bristol-Myers-Squibb, Astellas, Mitsubishi-Tanabe, Pfizer, Janssen, and UCB; Y.K. has received honorarium for the lecture or consultancy from AbbVie, Asahikasei Pharma, Astellas, Bristol-Myers-Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Ono Pharma, Pfizer, Takeda, UCB, and Santen and has received research grant from AbbVie, Asahikasei Pharma, Astellas, Bristol-Myers-Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Ono Pharma, Pfizer, Taisho-Toyama, and Takeda.; M.K. received speaking fees and/or honoraria from Santen, Mitsubishi-Tanabe, Pfizer, Eisai, Teijin Pharma, and Ono Pharma; Y.S. has received speaker fee from AbbVie; N.K. received payments from StaGen, SRL, and Teijin Pharma; A.I. has received grant and research support from Pfizer, AbbVie, and Chugai; N.M. has received research grants from AbbVie, Astellas, Bristol-Myers-Squibb, Chugai, Dainihon-Sumitomo, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Novartis, and Takeda and received consulting fee or honorarium from AbbVie, Bristol-Myers-Squibb, and Janssen; HY has received honorarium for the lecture or consultancy from Teijin Pharma, Chugai, Astellas, Bristol-Myers-Squibb, AbbVie, Daiichi-Sankyo, Nihon-Kayaku, Mitsubishi-Tanabe, Pfizer, Takeda, and UCB and has received research grant from AbbVie, Asahikasei Pharma, Astellas, Bristol-Myers-Squibb, Chugai, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi-Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taisho-Toyama, Takeda, and Teijin Pharma.; M.K., T.N., H.E., S.H., K.T., and M.H. declared that no conflict of interest exists. The sponsors were not involved in the study design; in the collection, analysis, and interpretation of data; in the writing

of this manuscript; or in the decision to submit the article for publication. The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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ORIGINAL ARTICLE

The process of collecting and evaluating evidences for the development of Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014: Utilization of GRADE approach

Masayo Kojima[1], Takeo Nakayama[2], Yutaka Kawahito[3], Yuko Kaneko[4], Mitsumasa Kishimoto[5], Shintaro Hirata[6], Yohei Seto[7], Hirahito Endo[8], Hiromu Ito[9], Toshihisa Kojima[10], Keiichiro Nishida[11], Isao Matsushita[12], Kiichiro Tsutani[13], Ataru Igarashi[13], Naoyuki Kamatani[7], Mieko Hasegawa[14], Nobuyuki Miyasaka[15], and Hisashi Yamanaka[7]

[1]*Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan,* [2]*Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan,* [3]*Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan,* [4]*Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan,* [5]*Division of Allergy and Rheumatology, St Luke's International Hospital, Tokyo, Japan,* [6]*The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan,* [7]*Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan,* [8]*Division of Rheumatology, Department of Internal Medicine, School of Medicine, Toho University Tokyo, Japan,* [9]*Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan,* [10]*Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan,* [11]*Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan,* [12]*Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama, Toyama, Japan,* [13]*Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan,* [14]*The Japan Rheumatism Friendship Association, Japan, and* [15]*Tokyo Medical and Dental University, Tokyo, Japan*

Abstract

Objectives. To describe the process of collecting and evaluating evidence for treating rheumatoid arthritis (RA) for developing clinical practice guidelines (CPGs) for rheumatologists in Japan.
Methods. The task force comprised rheumatologists, epidemiologists, health economists, and patients. First, the critical outcomes were determined according to a three-round Delphi method, and eight topics with 88 clinical questions (CQs) were formulated. A systematic review of CQs was conducted using the Cochran Database of Systematic Reviews, MEDLINE, and Japana Centra Revvo Medicina (2003–2012). A questionnaire survey and focus group interview were performed to capture the patients' values and preferences. Data from the National Health Insurance drug price list and product information provided by pharmaceutical companies were collected to evaluate drug cost and safety. The GRADE approach was used to describe the evidence quality and determine the strength of recommendations. Recommendations were developed using a modified Delphi method by a multidisciplinary panel including patients.
Results. Eight meetings and frequent e-mail communications were conducted to draft a quality assessment of evidence and recommendations. For 88 CQs, recommendation statements were determined.
Conclusions. Using the GRADE approach, new CPGs successfully addressed important clinical issues for treating RA patients. Timely updating of recommendations should be routinely considered.

Keywords:
Clinical practice guidelines, GRADE, Rheumatoid arthritis, Systematic review

History
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Introduction

The use of biologics created major and dramatic changes to rheumatoid arthritis (RA) treatment. In response, the European League Against Rheumatism published recommendations for RA management using synthetic and biological anti-rheumatic drugs in 2010 [1], following the recommendations of the American College of Rheumatology published in 2008 [2]. In Japan, the latest clinical practice guidelines (CPGs) were developed by a research group supported by the Nippon Arthritis Foundation and Ministry of Health, Labour and Welfare in 2004 [3]. Therefore, to reflect the rapid and recent progress in treating RA, a task force was formed to develop new CPGs based on available evidence to match clinical practice in Japan. This project was a component of a multilayered study on standardizing RA treatment in Japan supported by a Health and Labour Sciences Research Grant to study immune allergic diseases (2011–2013).

This paper describes the process of collecting and evaluating evidence to develop the new CPGs for treating RA patients in Japan. The new CPGs were designed for RA specialists and published on October 10, 2014. To develop new CPGs, we adopted several new strategies. First, the new CPGs were designed to

Correspondence to: Associate Prof. Masayo Kojima, The Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Kawasumi 1, Mizuho-cho, Mizuho-Ku, Nagoya 467-8601, Japan. Tel: + 81-52-853-8176. Fax: + 81-52-842-3830. E-mail: masayok@med.nagoya-cu.ac.jp

follow the most recent standards for CPGs, described in the report of the United States Institute of Medicine (IOM) of the National Academies released in 2011 [4]. According to them, CPGs that can be trusted should be based on the highly systematic and transparent process that rates the quality of evidence and the strength of the recommendations. To follow the IOM standards, we adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [5,6]. To collect the vast clinical evidence and summarize it as the body of evidence in accordance with the GRADE system, we utilized the available Cochran Reviews (Cochran reviews, http://community.cochrane.org/cochrane-reviews).

Materials and methods

Figure 1 illustrates the development process flowchart of our new CPGs. First, a multidisciplinary task force was assembled. Then, clinical topics to be addressed were chosen and clinical questions (CQs) were built for evidence evaluation. Critical and important outcomes were determined based on three-round Delphi method. Successively, literature search and evidence evaluation were conducted. All necessary information was integrated to determine the strength of recommendations. Finally, recommendation statements were formulated and approved by a consensus of the multidisciplinary panel. The CPGs were finalized and published after having peer comments in an academic society for RA, Japanese Congress of Rheumatology (JCR).

Task force

The task force comprised eight internists [Nobuyuki Miyasaka (the chair, NM) Hisashi Yamanaka (the task force leader, HY), Yutaka Kawahito, Yuko Kaneko, Mitsumasa Kishimoto, Shintaro Hirata, Yohei Seto, and Hirahito Endo], four orthopedic surgeons (Hiromu Ito, Toshihisa Kojima, Keiichiro Nishida, and Isao Matsushita), two epidemiologist (Takeo Nakayama and Masayo Kojima), one biostatistician (Naoyuki Kamatani), and the president of a patient society, the Japan Rheumatism Friendship Association, JRFA [7] (Mieko Hasegawa). The internists and orthopedic surgeons were all board-certified as senior rheumatologists from JCR. All task force members attended face-to-face meetings, participated in discussions via e-mail, and accordingly shared the work. The rheumatologist members, excluding NM and HY, performed the literature review and prepared a draft statement of recommendations. The first meeting was held in Tokyo on July 20, 2011. All members of the task force declared any potential conflict of interest (COI) and confirmed that no COI influenced the interpretation of the guidelines by the COI management committee of JCR.

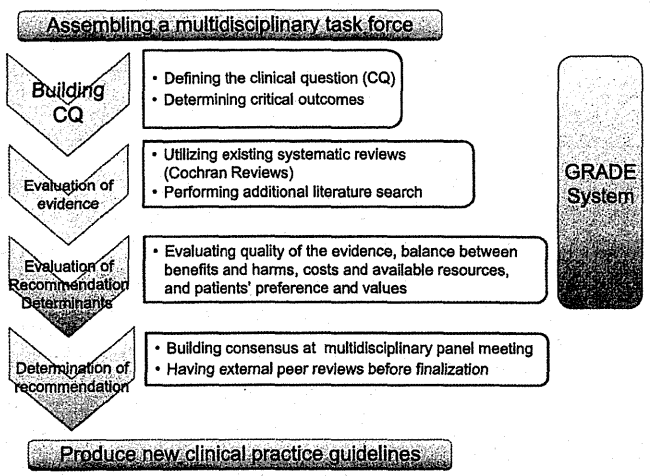

Figure 1. Flowchart of the development process of the Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014.

GRADE system

GRADE is a systematic and explicit approach to grade the quality of evidence and the strength of recommendations. It was proposed by the GRADE Working Group, founded in 2000, with the aim of developing high standards of quality and clarity for the formulation of recommendations and evaluation of evidence (GRADE working group, http://www.gradeworkinggroup.org/index.htm). Since the GRADE Working Group began its activities, the World Health Organization, the Cochrane Collaboration, and a number of organizations worldwide adopted the GRADE system. The Appraisal of Guidelines for Research and Evaluation or AGREE Instrument [8] and the Conference on Guideline Standardization or COGS checklist [9] are well-known tools to improve the quality of CPGs. They illuminate the elements that are necessary in CPGs; however, they are not intended to define the process. A systematic approach to grading the quality of the evidence and strength of recommendations can minimize bias and facilitate interpreting guidelines [10].

The first step of the GRADE system is to frame the CQ and decide on the importance of outcomes [10,11]. Further, it rates the quality of the body of evidence for each outcome across studies [12] and creates a summary of findings in tables that show the evidence quality and the information regarding the reason for the evidence quality rating [10]. Finally, the direction (for/against) and grade strength (strong/weak) of recommendation were determined by balancing their advantages and disadvantages, patients' values and preferences, and consideration of costs and available resources [13,14].

Utilization of existing systematic reviews

The Cochrane Collaboration (About us, http://community.cochrane.org/about-us) is a global independent network to produce credible and accessible health information. Its main activity is to produce Cochran Reviews with regular updates that review the latest scientific evidence. Cochran Reviews investigate the effects of interventions for prevention, treatment, and rehabilitation with a preplanned method that includes a comprehensive search of all potentially relevant studies and the use of explicit, reproducible criteria in the selection of studies for review. Cochrane Reviews are published in the Cochrane Database of Systematic Reviews (CDSR), one of several databases in the Cochrane Library (Cochran Library, http://www.cochranelibrary.com/).

The Cochrane Collaboration recommends the use of GRADE in assessing the evidence quality [15], and recent Cochrane Reviews include all necessary information to rate the quality of the body of evidence according to the GRADE criteria [10]. If the CQ that is addressed in the CPGs matches the Cochrane Review, the process of qualifying evidence can be greatly reduced. Therefore, the task force decided to first search the CDSR. If a Cochrane Review corresponding to CQ was not available, other databases were used for further literature searches.

Results

Building CQs

Extraction and determination of CQs

The task force determined that CQ covered in the new CPGs should be limited to "treatment" and should not target the diagnosis. The task force members e-mailed the task force leader (HY) lists of clinical issues they considered important for RA treatment. One hundred ninety-nine CQs were listed, and the research

leader categorized them into 22 topics. Finally, at the face-to-face meeting, the task force chose 96 CQs.

Choosing critical and important outcomes

GRADE encourages guideline developers to specify all potential patient-important outcomes and rate them numerically on a scale of 1–9 to distinguish between important categories: 7–9, critical; 4–6, important; and 1–3, limited importance [11]. A total of 44 outcomes were listed and the three-round Delphi method by the task force members was used to determine their importance levels. Finally, mortality was determined as the most critical outcome, and the following outcomes were judged as critical: RA disease activity index (DAS-28, SDAI, CDAI, and RAPID3), HAQ, the quality-adjusted life year, frequency of severe adverse effects, severe infection, remission rate, and total Sharp Score (indicators of joint destruction). Table 1 presents the critical and important outcomes determined by the task force.

Table 1. Critical and important outcomes for patients with rheumatoid arthritis determined by the clinical practice guidelines task force using the modified Delphi technique.

Outcomes	Rating of importance
Critical outcomes (7–9)	
Mortality rate	9
DAS28, SDAI, CDAI, RAPID3	8
HAQ	8
Quality-adjusted life year	8
Remission rate	8
Incidence of severe adverse effect	8
Incidence of severe infection	8
Total sharp score	8
Patient global assessment	7
Pain	7
Patient satisfaction	7
SF-36	7
EQ-5D	7
ACR20,50,70	7
Tender joint count	7
Swelling joint count	7
Recurrence rate	7
Drug continuation rate	7
Incidence of adverse effects	7
Incidence of infection	7
Incidence of interstitial pneumonia	7
Incidence of tuberculosis	7
Incidence of malignancy	7
Replacement rate of joint prosthesis	7
Postoperative complications	7
Productivity losses	7
Important but not critical outcomes (4–6)	
Physician global assessment	6
JOA score	6
MRI	6
Ultrasonographic grading	6
Incidence of cardiac disorders	6
Incidence of gastrointestinal disorders	6
Incidence of bone fracture	6
Incidence of hospitalization	6
Incidence of hepatitis	6
Pregnancy outcomes	6
Fatigue	5
Grip strength	5
Bone mineral density	5
Surgical operation time	5
RA development	5
Duration of morning stiffness	4

DAS28 Disease Activity Score in 28 joints, *SDAI* Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *RAPID3* Routine Assessment of Patient Index Data 3, *HAQ* Health Assessment Questionnaire, *SF-36* Short Form 36, *EQ-5D* EuroQol 5 dimension, *ACR* American College of Rheumatology, *JOA* Japanese Orthopaedic Association, *MRI* magnetic resonance imaging, *RA* rheumatoid arthritis.

Evaluation of evidence

Literature search

Each working member took charge of 1–3 topics/1–28 CQs and built search queries in PICO (participants, interventions, comparisons, and outcomes) format. The types of study participants included in the literature search were limited to patients with RA. The publication dates of the studies searched were between January 1998 and August 2012. The availability of the Cochran Reviews relevant to the CQ was confirmed by searching CDSR. We performed a further search of PubMed to find studies published after the Cochran Reviews. Furthermore, we searched PubMed when we were unable to find Cochran Reviews corresponding to CQs. An independent search of the relevant literature written in Japanese available from Japana Centra Revvo Medicina (ICHUSHI, a Japanese medical literature database) was conducted as well. The literature search was performed by the Japan Medical Library Association, and this literature search was reviewed by two task force members. Some CQs were combined in the process, and total of 8 topics with 88 CQs were formulated.

Quality assessments

The quality of the body of evidence was evaluated according to the GRADE system. The GRADE system defines the evidence quality to be assessed for each outcome across studies. The factors considered to diminish the evidence quality were as follows: bias risk [16], imprecision [17], inconsistency of results [18], indirect evidence [19], and publication bias [20]. Factors judged to increase the evidence quality were the magnitude of the effect, dose dependence, and plausible confounders [21]. According to the types of studies, randomized controlled trials and observational studies were initially considered to provide high- or low-quality evidence, respectively. The final rating of the evidence quality for each outcome was graded as high, moderate, low, or very low. The member in charge of the systematic review of each CQ prepared an evidence profile table summarizing the findings according to outcomes. Table 2 shows an example of an evidence profile table.

Evaluation of recommendation determinants

According to the GRADE system, the guideline developers should consider the direction (for or against) and strength (strong or weak) of recommendations according to the following four factors: evidence quality, balance between advantages and disadvantages, costs and available resources, and patients' preferences and values [5].

We collected the National Health Insurance drug price list and product information provided by the pharmaceutical companies to evaluate cost and safety. To capture patients' values and preferences for RA treatments, we submitted a questionnaire to 2,222 patients with RA who were randomly selected from the sample stratified by prefecture and age. Furthermore, we conducted a focus group of five representative patients to verify the findings of the questionnaire. The details of the patient survey will be reported elsewhere.

Formulation of recommendation statements

Finally, we determined the direction and strength of recommendations at an in-person, two-day meeting, using the modified Delphi's method. In addition to the original task force members, two health economists and three patients were included in the multidisciplinary panel to determine the recommendations. Therefore, the consensus was reached by 12 rheumatologists, four patients, three epidemiologists, and two health economists. All information

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Table 2. Example of evidence profile. Methotrexate once weekly versus twice weekly or daily in rheumatoid arthritis.

Outcomes	No. of studies	Design	Quality Assessment					No of participants		Effect		Quality of evidence	Reference
			Limitation	Inconsistency	Indirectness	Imprecision	Publication bias	Twice or more per week	Once weekly	Relative effect	Absolute effect		
ACR20	1	RCT	Serious	–	No indirectness	Serious	–	22/41	24/39	RR = 0.92 (95% CI = 0.58 to 1.45)	Absolute risk difference = −0.03 (95% CI = −0.03 to 0.20)	Low	Pandya 2002[a]
Swollen joint count	2	RCT, randomized crossover design	Serious	Serious	No indirectness	Serious	–	41 20	39 20	(Pandy) Mean change from baseline in the two groups: 3.36 ± 3.88 vs 4.92 ± 7.22 at 8 week. (Seideman) Baseline 2 ± 2, daily 3 ± 1 vs weekly 2 ± 1 at 8 week.	(Pandy) Cohen's $d = 0.27$, (Seideman) NA	Low	Pandya 2002[a], Seideman 1993[b]
Patient global assessment	2	RCT, randomized crossover design	Serious	Serious	No indirectness	Serious	–	41 20	39 20	(Pandy) Mean change from baseline: 2.87 ± 2.68 vs 3.36 ± 3.59 at 8 week. (Seideman) Baseline 4.1 ± 1.0, daily 4.1 ± 1.1 vs weekly 3.9 ± 1.1 at 8 week.	(Pandy) Cohen's $d = 0.16$, (Seideman) NA	Low	Pandya 2002[a], Seideman 1993[b]

RCT randomized control trial, *RR* relative risk, *CI* confidence interval, *NA* not available.
[a]Pandya S, et al. Rheumatol Int. 2002;22:1–4.
[b]Seideman P. Clin Rheumatol. 1993;12:210–13.

regarding evidence, cost and safety, and patient surveys were sent in advance by mail to the panel members. The authors of the evidence summary presented brief accounts of the drafts, and all panel members were requested to evaluate the degree of agreement according to the recommendations at five levels. Arriving at a consensus required an average level of agreement ≥4.0. When the agreement level was <4.0, we conducted further discussions and voted again.

The key recommendations were presented at the 58th annual general assembly and scientific meeting of the JCR on April 24, 2014 and discussed by the panel and audience members. Then, the drafts of the guidelines were posted on the web site of the JCR for peer review by the end of May, 2014. After making some minor revisions in descriptions according to the comments from the external peer reviewers, the final product was published as the guidelines for the management of RA, JCR 2014 [22].

Discussion

Here, we summarize the process of collecting and evaluating evidence regarding the RA treatment to develop new CPGs in Japan. Using the GRADE approach, we successfully addressed current important clinical issues for treating RA patients and integrated the body of evidence to determine the strength of recommendations.

We employed new strategies in this project, and utilizing the Cochran Review was one of them. Numerous reports on health care are published every year, and the number of systematic reviews is increasing as well [23]. Since some topics, such as surgery, were not included in the Cochran Review, we were required to conduct new systematic reviews [24]. However, if there is an adequate summary of the evidence corresponding to CQ, it should be utilized to develop recommendations [25]. Starting the evidence search with the limitation as systematic review is becoming the standard procedure [25]. If several systematic reviews of the same topics are available, they can be synthesized [26]. For example, the Cochran Collaboration has already introduced several systematic reviews of Cochran Reviews [27,28].

To utilize the existing systematic reviews for developing guidelines, we note several issues. First, the quality of the systematic reviews should be critically appraised. Numerous instruments are available to evaluate the quality of systematic reviews. For example, A Measurement Tool to Assess systematic reviews or AMSTAR assesses the methodological quality of systematic reviews [29] and was selected as the best and most reliable tool [30]. Second, updating the systematic reviews should be considered. Considering the rapid progress in the management of RA during the last 10 years, further development of new treatments should be realized in the next several years. According to a review of 17 guidelines published by the Agency for Healthcare Research and Quality, approximately half of the guidelines become outdated in 5.8 years [31]. Therefore, the guidelines must reflect the latest evidence, and routine updates of the guidelines should be considered by relying on high-quality systematic reviews.

In conclusion, we developed the new CPGs for rheumatologists using the GRADE approach. Timely updating of the recommendations should be routinely considered.

Conflict of interest

None.

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