countries in Asia. This study provides unique findings about safety of ADA and ETN because the two registries have different demographic and clinical characteristics of patients, as well as treatment profiles before starting biologic DMARDs. Some of these differences are identified as factors influencing the development of SAEs.

We found significant differences in demographic and clinical characteristics of RA patients between the two registries. First, in the RESEARCh, significantly more patients had experienced four or more nonbiologic DMARDs before starting ETN or ADA than the REAL, although patients in the RESEARCh were significantly younger with shorter disease durations than the REAL. In Korea, according to strict reimbursement guidelines, rheumatologists are required to treat a patient with at least two nonbiologic DMARDs, including MTX, for six months before confirming inadequate response to the treatment and starting TNF inhibitors. Japanese guidelines in 2007 recommend treatment with TNF inhibitors for patients who had inadequate response to treatment with at least one DMARD for 3 months [14]. Second, patients in the RESEARCh used concomitant MTX more frequently and higher dosages than those in the REAL. The maximum approved dosage for MTX in these countries apparently affects the use of the anchor drug in the two registries; i.e., 8 mg/week until February 2011, allowed up to 16 mg/week now in Japan and 20 mg/week in Korea.

The unadjusted IR of overall SAEs in the REAL was significantly higher than in the RESEARCh (IRR 2.03, 95% CI 1.38–2.99), explained at least in part by the numerically higher IR of SI in the REAL compared to the RESEARCh. The incidence of SIs in the REAL of 4.99/100 PY was comparable to Western registries incidence of 5.4–6.6/100 PY, whereas a lower incidence in the RESEARCh of 2.97/100 PY was observed [3,4,15]. We suppose that demographic features including age structure and comorbidity profiles of the two cohorts contributed to the difference. The proportion of elderly (≥65) in the general population in Japan was higher than in Korea in 2009 (22.7% in Japan vs. 10.4% in Korea) [16,17]. Compatible with these figures, the prevalence of elderly RA (≥65-year-olds) was 36.2% in a Japanese RA cohort [18] and 21.8% in Korean RA cohort [19]. Increased percentage of patients with pulmonary comorbidities, cardiovascular diseases, and diabetes mellitus in Japan may be explained by higher prevalence of elderly RA patients and longer disease duration. The prevalence of infection-related comorbidities such as pulmonary diseases, diabetes mellitus, and renal dysfunction is significantly higher in the REAL compared to the RESEARCh. It is plausible that the higher prevalence of comorbidities could be associated with the higher IR of SIs in the REAL. This association was supported by a previous comparative study showing that the difference in incidence of SIs between the American and European registries could be derived from differing comorbidity profiles of the registries [2].

Difference in the use of CSs between the two countries needs to be mentioned. It has been reported that the frequent usage of CSs at higher dosages was significantly associated with development of SIs in cohort studies from Western countries [20–22]. Japanese post marketing surveillance for ETN (HR 2.03, 95% CI 1.46–2.84) [23] and tocilizumab [24] (odds ratio 2.17, 95% CI 1.25–3.74) also revealed that concomitant use of CSs was one of the risk factors for SIs. Moreover, higher dosages of CSs significantly increased the risk for SIs in the REAL and its relative risk was the highest among the identified risk factors (2.49, 95% CI 1.08–5.50) [9]. Overall, it is apparent that use of CSs leads to a higher risk for SIs. In this study, the mean dosage of CSs at baseline was significantly higher in the REAL compared to the RESEARCh, which also explains the difference in incidence of SIs between the two registries. Furthermore, frequent usage of CSs at higher dosages may also be responsible for the higher prevalence of diabetes mellitus in Japanese RA patients, which in turn makes them more susceptible to infection. These data emphasize the importance of minimizing exposure to CSs in RA patients to decrease the risk for SIs.

Age, previous use of nonbiologic DMARDs ≥ 4, and concomitant use of CSs were significantly associated with occurrence of SAEs in the REAL as well as in the combined data, while the latter two factors were not in the RESEARCh. It has been reported that RA patients with larger number of previously used DMARDs have increased risk for SIs [20,22], which could explain the association between nonbiologic DMARDs ≥ 4 and SAE in this study because SIs account for about 40% of the SAEs (Table 3). In general, larger numbers of previously used DMARDs suggest long-standing and/or intractable disease. This may not be the case, however, for Korean patients given biologics because the patients have to be treated at least with DMARDs ≥ 2 beforehand by strict reimbursement guidelines. Such difference could lead to lack of association between previous use of nonbiologic DMARDs ≥ 4 and SAE in the RESEARCh. Weak trend toward positive association between the concomitant use of CS and SAE was observed in the RESEARCh. The small number of SAEs in the RESEARCh probably contributed to wide 95% confidence interval of the HR for the concomitant use of CS (Table 4) and the factor did not reach statistical significance.

There are certain limitations in our study. First, the difference of study design between the two registries should be mentioned. The data were obtained retrospectively from the RESEARCh registry and prospectively from the REAL registry [25], which could affect the results of this comparative study. To compensate for this difference in collecting data, we standardized the definition of SAEs, reasons for drug discontinuation, and variables such as comorbidities in two registries in this study as described in Patients and Methods. We discussed ambiguous SAE cases through regular meetings as well. A second limitation is that we did not investigate the patients with other biologics except for ETN and ADA. The safety and tolerance of a biologic DMARD can be affected by the approval status of other biologic and nonbiologic DMARDs [26]. The difference in approval status of biologic and nonbiologic DMARDs should be considered when we compare the use of biologic DMARDs between two countries. In this study, therefore, we focused on ADA and ETN, which were approved for treatment of RA within two calendar years in Korea and Japan (see Supplementary Figure S1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2013.860695). Third limitation is that RESEARCh was performed in a single institution, whereas REAL is comprised of 27 institutions, which may create selection bias in the study.

In conclusion, the differences in the demographic and clinical characteristics such as age structures, patterns of comorbidity, and treatments profile for RA between the two countries affect types and incidences of SAEs. This international collaborated study facilitates our understanding of similarity and discrepancy in the results from various biological registries, and may help applying the evidence to clinical management of patients with RA.

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Conflict of interests

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Supplementary material available online

Supplementary Figures 1 and 2.

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CASE REPORT

Recurrent mitral valve regurgitation with neutrophil infiltration in a patient with multiple aseptic abscesses

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Abstract

Aseptic abscess (AA) is characterized by accumulation of neutrophils without evidence of infection, no response to antibiotics, and rapid response to corticosteroids. We report a case of multiple abscesses in the subcutaneous tissues and joints, and severe mitral valve regurgitation. Although AA did not respond to antibiotic therapy, it improved dramatically with corticosteroid treatment. However, repeated valvuloplasty was required for the mitral valve regurgitation. The mitral valve tissue showed neutrophil infiltration without any bacterial invasion. This is the first case of AA to show involvement of cardiac valves, indicating the importance of systematic examination for patients with AA and cardiac valve involvement.

Keywords

Aseptic abscesses, Mitral valve regurgitation, Neutrophil

History

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Introduction

Aseptic abscess (AA) was first described in 1995 [1] and is characterized by accumulation of neutrophils without evidence of infection, no response to antibiotics, and rapid response to corticosteroids. It was reported that 31 of 49 patients with AA had inflammatory bowel diseases, whereas only three patients had no underlying disease [2]. We describe a case of AA with multiple abscesses in the subcutaneous tissues and joints in a patient with severe mitral valve regurgitation with neutrophil infiltration in the valve.

Case report

A 57-year-old woman without any previous medical history presented with a 3-month history of fever, and pain in the ankle and hip joints. Physical examination identified systolic murmur at the apex and tenderness and swelling of the right shoulder and pubic region. Laboratory tests showed increased leukocyte count [13,100/μl (neutrophil 81.8 %)] and C-reactive protein (CRP 22.72 mg/dl). Autoantibodies, such as antinuclear antibodies, rheumatoid factor and antineutrophil cytoplasmic antibodies, were negative. Human leukocyte antigen (HLA) typing was A24, A26, B54, and B62. Echocardiography showed mild mitral valve regurgitation without vegetation. Although bacterial endocarditis was initially suspected, repeated blood cultures were negative. Magnetic resonance imaging revealed multiple cystic lesions in the pubic joint and subcutaneous tissue of the coccygeal region (Fig. 1a, b). Contrast-enhanced computed tomography showed similar lesions around the right shoulder (Fig. 1c). Increased fluorine-18-deoxyglucose (FDG) uptake was found in both shoulders and pubic joint by positron emission tomography (FDG-PET) (Fig. 1d). Arthrocentesis from the pubic joint showed increased inflammatory cells with a cell count of 33,333/μl (polymorphonuclear cells 90 %), but cultures for bacteria and acid-fast bacilli were negative.

The patient was initially treated with several kinds of antibacterial, antituberculosis, and antifungal agents for more than 2 months, but showed no clinical response. Mitral valve regurgitation had been worsening and resulted in heart failure, which was treated with furosemide. As antibiotic therapy was not at all effective for the abscesses and the mitral valve regurgitation, in addition to negative cultures from the abscesses and blood, we finally diagnosed her as AA. Accordingly, she was treated with 30 mg/day prednisolone (PSL), which resulted immediately in resolution of the fever, marked improvement of joint pain, and reduction in CRP to an undetectable level (Fig. 2). Repeated imaging showed cystic lesions became smaller in all areas. Subsequently, PSL was gradually tapered to 15 mg/day, however; this resulted in a rise in CRP to around 1 mg/dl, necessitating the addition of methotrexate (MTX) at 8 mg/week. As severe mitral valve regurgitation persisted even with corticosteroid therapy, following the tapering of PSL to 5 mg/day, mitral valvuloplasty was performed. During surgery, perforations at the posterior leaflet and posterolateral commissure were revealed, which were sutured. She was discharged 1 month after the surgery.

While our patient was maintained by 5 mg/day PSL and 8 mg/week MTX in the outpatient clinic, any symptom such as high-grade fever or arthralgia did not develop. However, serum CRP level was around 3 mg/dl, suggesting that the disease activity was not fully controlled. Two months after discharge, she was hospitalized again because of syncope and severe anemia. Physical examination identified systolic murmur at the apex, and laboratory tests showed decreased hemoglobin (8.8 g/dl) and increased lactase dehydrogenase (2940 IU/l) and CRP (6.3 mg/dl). Severe mitral valve regurgitation was revealed again by echocardiogram. Therefore, we diagnosed her condition as mechanical hemolytic anemia due to relapsed valve regurgitation.

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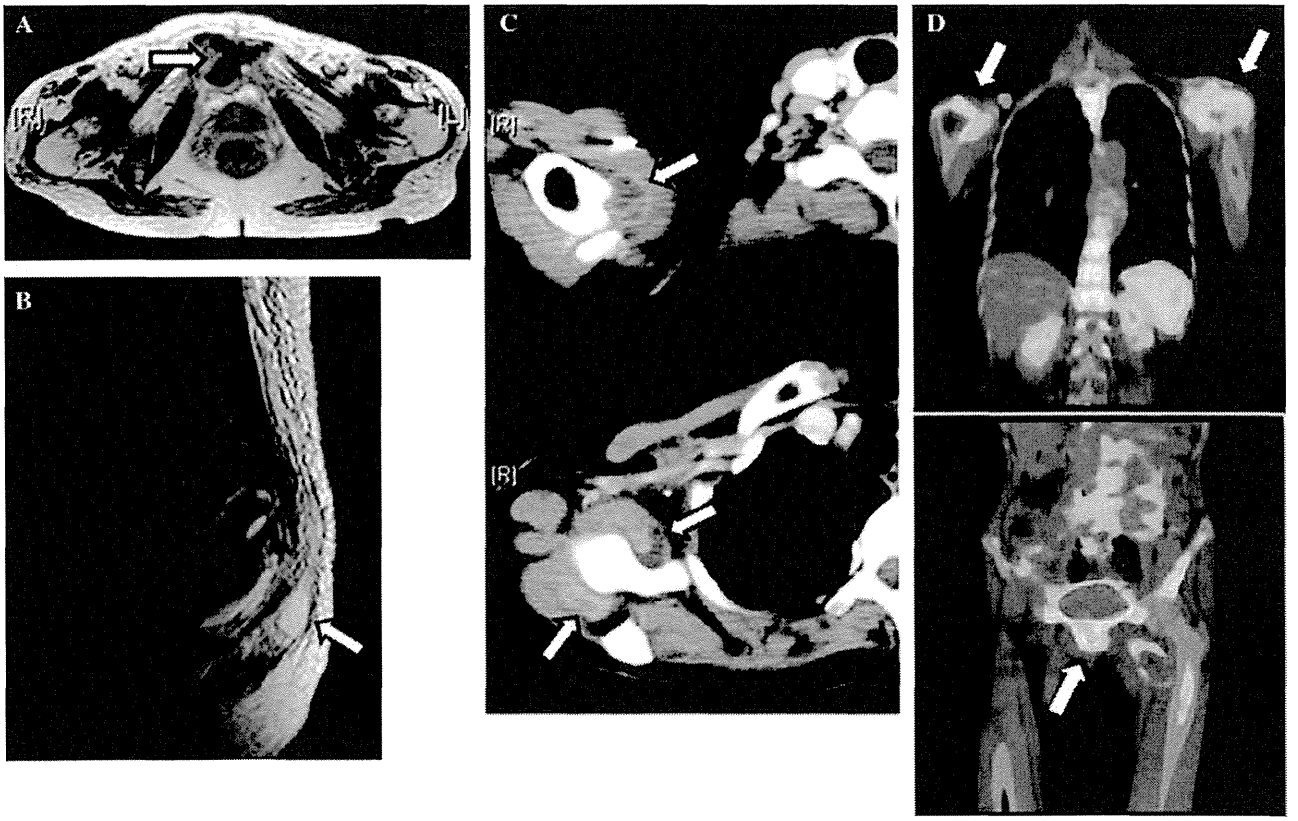

Fig. 1 Findings of magnetic resonance (MR) and computed tomography (CT) imagings. **a** Gadolinium-enhanced T1-weighted MR imaging showed low-intensity areas with enhanced margin in the pubic joint. **b** T2-weighted imaging showed high-intensity mass in the subcutaneous tissues of the coccygeal region. **c** Contrast-enhanced CT showed multiple cystic lesions with enhanced margins around the right shoulder. **d** Fluorine-18-deoxyglucose positron emission tomography (FDG-PET) showed increased FDG uptake in both shoulders and pubic joint. *Arrows* indicate affected lesions

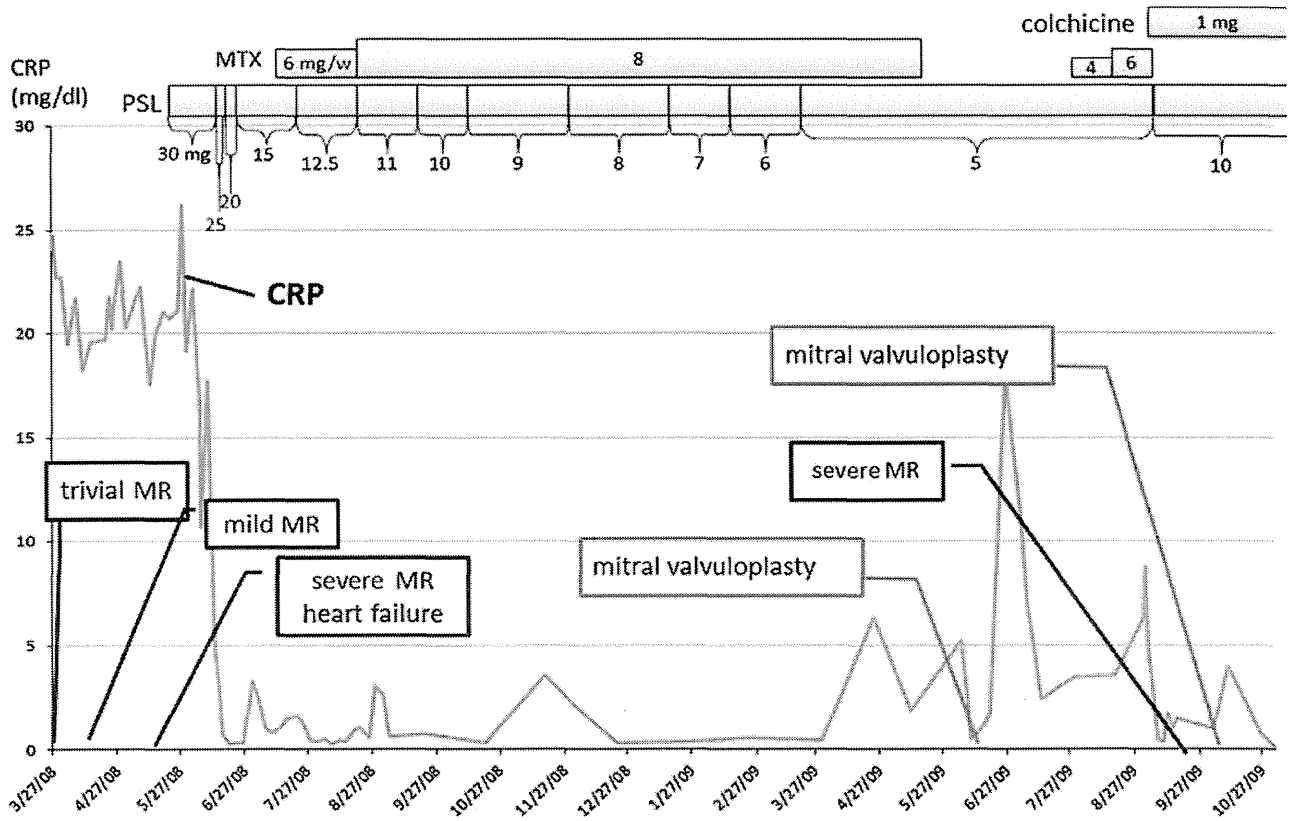

Fig. 2 Clinical course

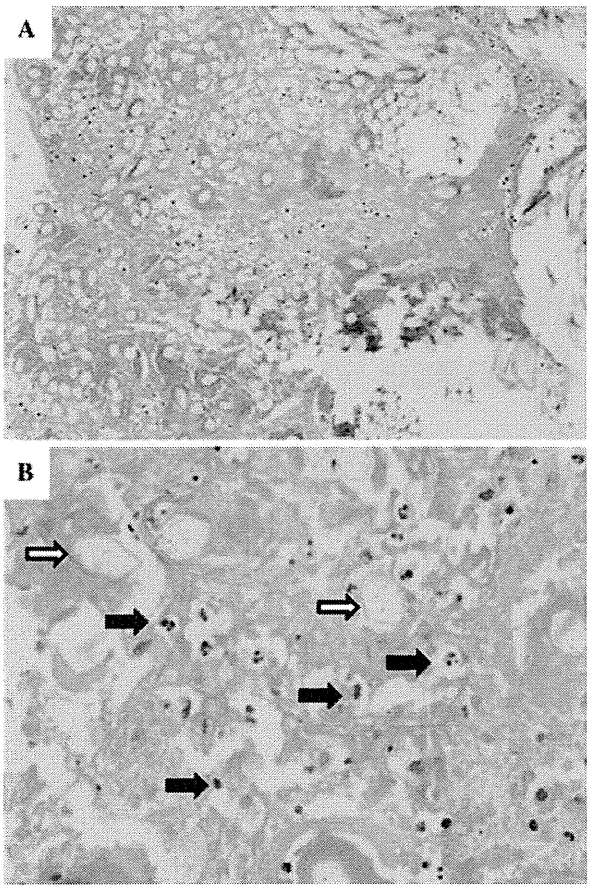

Fig. 3 Histological examination of the mitral valve. Note infiltrated polymorphonuclear neutrophils in the mitral valve (*black arrows*). *White arrows* indicate filaments of suture. Hematoxylin and eosin staining: **a** ×100, **b** ×400

The valvuloplasty was thus repeated. In the open heart surgery, another perforation was found next to the sutured one at the posterior leaflet. Histological findings of mitral valve tissue showed neutrophil infiltration (Fig. 3). No bacterial invasion was detected by Gram staining. Disease activity was subsequently well controlled with maintenance therapy of 10 mg/day PSL and 1 mg/day colchicine.

Discussion

Aseptic abscess is diagnosed based on criteria by André et al. [2]: (1) deep abscess detected by radiologic examination associated with neutrophilia; (2) negative cultures of blood and pus from abscess; (3) lack of response to antibiotic therapy; (4) rapid clinical improvement following initiation of corticosteroids. Previous case series reported AA appeared mostly in viscera, such as spleen (70 %), abdominal lymph nodes (53 %), liver (40 %), lung (17 %), pancreas (10 %), and brain (10 %). In addition, involvement of soft tissue in AA patients was also reported [2–4]. All patients were treated with corticosteroids; however, some patients required additional drugs, such as azathioprine (30 %), colchicine (27 %), cyclophosphamide (17 %), antitumor necrosis factor agent (10 %), and MTX (3 %) [2]. We treated our patient with 30 mg/day (0.6 mg/kg/day) of PSL with MTX. Furthermore, colchicine was added with the expectation of suppressing augmented neutrophil activity.

In this case, mitral valve regurgitation without vegetation occurred with multiple abscesses. Antibiotics were not effective, and cultures from the abscesses and blood were negative. The mitral valve regurgitation relapsed during maintenance therapy, with CRP elevation, suggesting disease activity was not well controlled. Moreover, histological findings of the mitral valve revealed neutrophil infiltration without bacterial invasion. Taken together, we considered that this mitral valve regurgitation was derived from AA. To our knowledge, this is the first case in the literature to show involvement of the cardiac valves in AA.

Although autoinflammatory diseases such as familial Mediterranean fever, hyperimmunoglobulinemia D with periodic fever syndrome, pyogenic arthritis, pyoderma gangrenosa and acne syndrome, tumor-necrosis-factor-receptor-associated periodic syndrome, and cryopyrin-associated periodic syndromes were suspected in our patient, she did not have any disease-related nucleotide polymorphisms [5]. Genetic abnormalities of AA have not been reported.

It is reported that 7–46 % of patients with Behçet's disease develop cardiovascular complications—including valve diseases, which frequently relapse [6, 7]—and some require valvuloplasty [8]. However, this patient showed no typical manifestations of Behçet's disease, such as oral ulcerations, urogenital lesions, cutaneous lesions, or ocular disease.

In conclusion, ours is the first case of AA affecting the mitral valve reported in the literature. Patients with AA should be systemically and carefully examined, including cardiac valve involvement. Furthermore, once AA is diagnosed, disease activity should be tightly controlled.

Conflict of interest

None.

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Clinical Investigations

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Serodiagnosis of *Mycobacterium avium* Complex Pulmonary Disease in Rheumatoid Arthritis

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Key Words
Glycopeptidolipid · *Mycobacterium avium* complex pulmonary disease · Rheumatoid arthritis · Sensitivity · Specificity

Abstract
Background: *Mycobacterium avium* complex (MAC) pulmonary disease (PD) is often difficult and complicated to diagnose or to discriminate from follicular bronchitis, bronchiectasis, or other conditions associated with rheumatoid arthritis (RA) lung in the clinical setting. ***Objective:*** We investigated whether a serologic test for anti-glycopeptidolipid (GPL) antibody was useful for distinguishing MAC-PD from RA lung in diagnosis. ***Methods:*** Serum IgA antibody to MAC-specific GPL core antigen was measured by an enzyme immunoassay. Antibody levels were measured in sera from 14 RA patients with MAC-PD (RA + MAC), 20 RA patients with bronchial or bronchiolar lesions without MAC-PD (RA w/o MAC), 20 RA patients without pulmonary lesions (RA only), and 25 healthy volunteers (HV). ***Results:*** The levels of serum anti-GPL antibodies were higher in the RA + MAC group than in the RA w/o MAC, RA-only, and HV groups (2.87 ± 2.83 vs. 0.50 ± 0.45, 0.31 ± 0.24, and 0.38 ± 0.10 U/ml, respectively; $p < 0.001$). With the cutoff point in receiver-operating characteristic analysis set at 0.7 U/ml, the serologic test differentiated RA + MAC from RA w/o MAC with a sensitivity of 100% and specificity of 90%. ***Conclusions:*** This serologic test for anti-GPL antibody is useful for diagnosing MAC-PD in RA.

Introduction

Recent reports have shown a rising prevalence of disease caused by nontuberculous mycobacteria (NTM) [1–5]. Seventy percent of patients with NTM disease in Japan are diagnosed with *Mycobacterium avium* complex (MAC) [6]. MAC causes chronic and progressive pulmonary disease (PD) in immunosuppressed patients and immunocompetent patients alike. Chest computed tomography (CT) of patients with rheumatoid arthritis (RA) reveals bronchial and/or lung abnormalities along with various other distinguishing features [7]. While only 1–3% of RA patients exhibit bronchiectasis clinically, as many as 30% manifest bronchiectasis in high-resolution CT [8]. MAC-PD is therefore difficult to diagnose or to differentiate from follicular bronchitis, bronchiectasis, or other conditions associated with RA lung in the clinical setting.

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The tumor necrosis factor (TNF)-α antagonists infliximab and etanercept are used for the treatment of RA, as well as sarcoidosis and other collagen diseases and inflammatory conditions that interfere with granuloma formation [9]. Infections with intracellular pathogens such as NTM have been exacerbated in patients treated with TNF-α antagonists [10]. Because TNF-α antagonists pose a high risk for NTM-infected patients, they are not indicated for NTM under the guidelines from the American College of Rheumatology 2008. Whether TNF-α antagonists can be administered for RA remains an important issue [10, 11]. For this reason, we normally expect to conduct specific screening tests whenever we plan to administer anti-TNF-α drugs to RA patients.

In this study, we investigated whether a serologic test for anti-glycopeptidolipid (GPL) antibody was useful for distinguishing MAC-PD from RA lung in diagnosis.

Materials and Methods

Subjects

All subjects were enrolled between April 2009 and September 2011. Serum samples were collected from 14 RA patients with MAC-PD (RA + MAC), 20 RA patients with bronchial or bronchiolar lesions without MAC-PD (RA w/o MAC), 20 RA patients without pulmonary lesions (RA only), and 25 healthy volunteers (HV). Blood was collected from 11 of the 14 RA + MAC patients after the start of the MAC-PD treatment. Three of the 14 RA + MAC patients were treated with a 3-drug regimen, 3 received no drugs, and 8 were treated with a 1-drug treatment. Among the 8 RA + MAC patients treated with the 1-drug treatment, they received the single drugs for the following reasons: 4 were diagnosed after blood collection, 2 failed to properly comply with the multidrug regimen, 1 was elderly, and 1 had been treated with the 3-drug regimen but required dose reduction. The Research and Ethics Committees of the Tokyo Medical and Dental University approved the study as a study on human subjects (identification No. 984), and all of the subjects provided written informed consent.

Criteria

Our study subjects were selected retrospectively from patients who regularly visited our hospital because of RA and/or abnormal chest shadows. First, the RA patients were divided into two groups, namely patients without abnormal shadows on chest X-ray (RA only) and patients with abnormal shadows. Then, in the latter group, the patients with radiologic findings compatible with MAC-PD were divided into two subgroups: those in whom MAC was detected by sputum culture or bronchoscopy (RA + MAC) and those in whom no MAC was detected (RA w/o MAC). All patients with MAC-PD met the diagnostic criteria of the American Thoracic Society (ATS) guideline [1]. Clinical criteria included: (1) pulmonary symptoms, nodular or cavitary opacities on chest radiograph or a high-resolution CT scan manifesting multifocal bronchiectasis with multiple small nodules, and (2) appropriate exclusion of other diagnoses. Microbiologic criteria included: (1) positive culture results from at least two sputum samples, (2) positive culture results from at least one bronchial wash or lavage, or (3) transbronchial or other lung biopsy with mycobacterial histopathological features. All cases of RA + MAC and RA w/o MAC underwent chest CT, and the findings were compatible with MAC-PD.

Enzyme Immunoassay for Anti-GPL Antibody

All serum samples were measured by an enzyme immunoassay (EIA) kit for anti-GPL antibody (Tauns Laboratories, Inc., Shizuoka, Japan). All sera were stored at –20°C until assayed for IgA antibodies to GPL antigen according to the manufacturer's instructions [12]. The interfering substance, rheumatoid factor (RF), was <500 IU/ml, a level too low to affect the EIA, in every sample.

Radiological Analysis

The patients with MAC-PD were classified into two groups, namely fibrocavitary (FC) disease and nodular-bronchiectatic (NBE) disease, based on the chest radiographic findings [1]. FC disease was defined as the presence of cavitary forms in the upper lobes. NBE disease was defined as the presence of bronchiectasis and multiple nodular shadows on chest CT. Disease conforming to neither of these types was considered unclassifiable. To localize the infection, the lungs of each patient were divided into 10 fields (right lung, S^{1+2}, S^{3}, S^{4+5}, S^{6}, and $S^{7+8+9+10}$, and left lung, S^{1+2}, S^{3}, S^{4+5}, S^{6}, and S^{8+9+10}) according to Moore's [13] definition. Each field was evaluated with reference to the presence of bronchiectasis, centrilobular nodules, air space disease, cavities, and nodules >10 mm in diameter. The extent of disease was expressed as the number of MAC-involved segments, as described in previous studies [14, 15]. Chest CT findings were assessed by a consensus reading by two respiratory physicians and one radiologist (Y.M., Y.K., and Y.M.).

Statistical Analysis

All statistical analyses were performed using SPSS version 19 (IBM Japan Inc., Tokyo, Japan). Antibody levels in all groups were expressed as means ± SD. To compare mean values of multiple groups, data were compared using the Kruskal-Wallis test. The Steel-Dwass test, a nonparametric post hoc multiple comparison test, was used to evaluate differences between the groups when appropriate. Spearman's rank correlation coefficient was used for correlation analysis and the χ^2 test was used to assess the degree of compatibility. A probability value of $p < 0.05$ was regarded as significant.

Results

Characteristics of the Study Subjects

Table 1 summarizes the characteristics of the study subjects at blood sampling. None of the patients was seropositive for HIV type 1 or type 2, and none of the patients was suspected of MAC colonization. Among the 14 patients in the RA + MAC-PD group, 1 patient had diabetes mellitus, 2 had sequelae of pulmonary tuberculosis,

and 1 had chronic kidney disease. The HV group was younger than every other group ($p < 0.001$). No significant difference was seen among the groups in patient age at the onset of RA. The RA w/o MAC group used prednisolone (PSL) more frequently than the RA only group ($p < 0.05$). According to the radiological findings of the 14 patients in the RA + MAC-PD group, 2 were determined to have FC disease, 11 were determined to have NBE disease, and 1 was unclassifiable. The radiological findings of the 20 patients in the RA w/o MAC group were similar: 1 was determined to have FC disease, 19 manifested a predominant finding of NBE disease in the baseline CT, and 1 was determined to have FC disease. Figure 1 shows representative CT images of the RA + MAC and RA w/o MAC.

Levels of Anti-GPL Antibodies

The levels of serum anti-GPL antibody in the RA + MAC, RA w/o MAC, RA only, and HV groups were 2.87 ± 2.83, 0.50 ± 0.45, 0.31 ± 0.24, and 0.38 ± 0.10 U/ml, respectively (fig. 2). Serum anti-GPL antibody was significantly higher in the RA + MAC group than in the other three groups ($p < 0.001$).

Sensitivity and Specificity

A receiver-operating characteristic (ROC) curve constructed for RA + MAC and RA w/o MAC had an area under the curve of 0.95 (fig. 3). Fourteen RA + MAC patients and 20 RA w/o MAC patients were included in the ROC analysis. The best cutoff value obtained by measuring the shortest distance between the coordinate point (0, 100) and the respective points on the ROC curve was 0.7 U/ml. A cutoff value of 0.7 U/ml resulted in 90.0% (18/20) specificity and 100% sensitivity (14/14).

Treatments and Levels of Anti-GPL Antibodies

The levels of serum anti-GPL antibodies were compared according to the treatment regimen in the 14 RA + MAC patients. No significant differences in the levels of anti-GPL antibodies were found among these regimens (fig. 4).

Correlations between the Extent of Disease and Levels of Anti-GPL Antibodies

Correlations between the extent of disease and levels of anti-GPL antibodies were investigated in 14 RA + MAC patients who underwent chest CT and serologic tests at the same time. No correlations were found between the extent of disease and the levels of anti-GPL antibodies (fig. 5).

Table 1. Characteristics of the study subjects

Characteristics	RA + MAC	RA w/o MAC	RA only	HV
Patients	14	20	20	25
Age	66.0±9.5[a]	66.0±10.2[a]	60.9±9.9[a]	54.1±6.1
Range	50–87	38–80	35–75	45–67
Sex				
Male/female	2/12	2/18	1/19	4/21
Duration				
MAC disease	2.3±1.7	N/A	N/A	N/A
Age at RA onset	52.0±11.0	56.5±14.7	55.5±12.8	N/A
CT classification				
FC	2	1		
NBE	11	19	N/A	N/A
Unclassifiable	1	0		
Therapy for RA				
DMARDs total	14	19	19	
PSL	2	10*	2	
MTX	8	12	14	N/A
TAC	2	4	1	
Anti-TNFα	0	6	5	
Therapy for MAC-PD				
3 drugs	3			
1 drug	8	N/A	N/A	N/A
No treatment	3			

Data are shown as mean ± SD years or numbers. N/A = Not available; DMARDs = disease-modifying anti-rheumatic drugs; MTX = methotrexate; TAC = tacrolimus. * $p < 0.05$ vs. RA only, [a] $p < 0.001$ vs. HV.

Discussion

The present study showed that EIA for anti-GPL antibody can be a useful tool for detecting MAC-PD in patients with RA. With the cutoff value set at 0.7 U/ml, the ROC analysis had a sensitivity of 100% and specificity of 90%.

In 2007, a new set of diagnostic guidelines for NTM disease was published by the ATS and Infectious Disease Society of America (IDSA). Not long after, Japanese counterparts published new NTM guidelines with modifications almost identical to those of the ATS and IDSA. The bacteriological criteria are now somewhat simpler than those described under the ATS diagnostic criteria from 1997 [16]. It remains difficult, however, to reach an MAC-PD diagnosis bacteriologically in RA patients who manifest abnormal shadows characteristic of MAC-PD, particularly when bronchoscopy is unfeasible or the culture for bronchial lavage fluid is negative.

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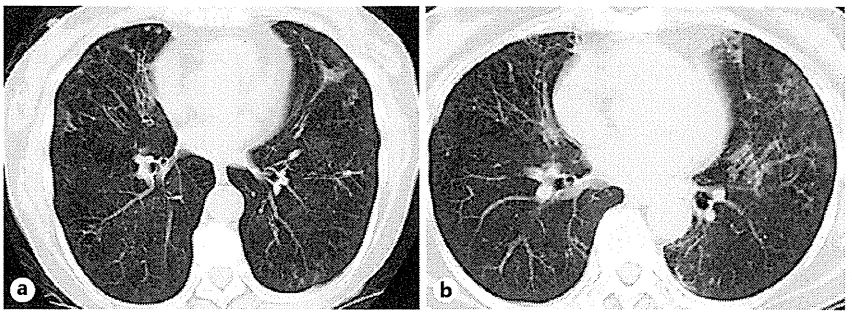

Fig. 1. a RA + MAC: axial CT shows cylindrical bronchiectasis and independent nodules in the right middle lobe and a larger nodule in the left upper lobe. **b** RA w/o MAC: axial CT shows cylindrical bronchiectasis in the right middle lobe and centrilobular opacities in the left upper lobe.

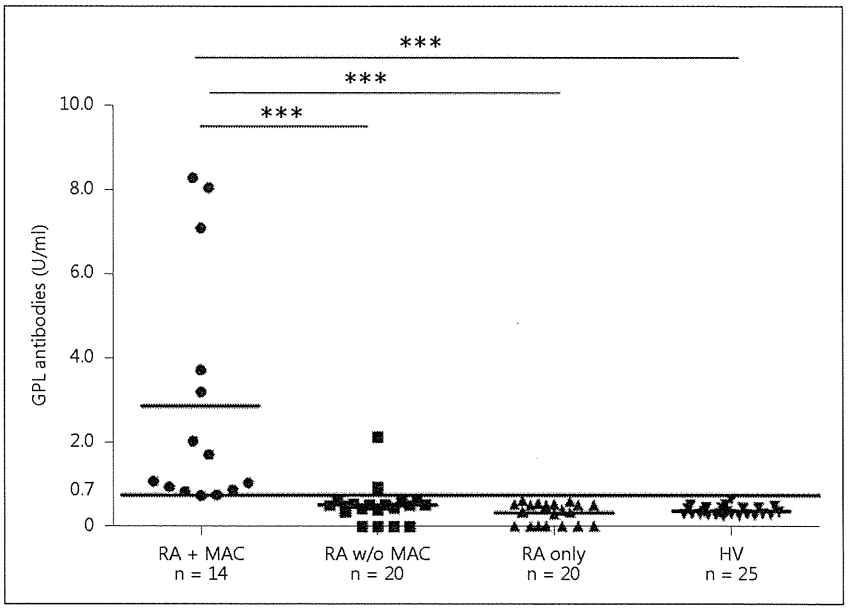

Fig. 2. Levels of serum anti-GPL antibody in the RA + MAC, RA w/o MAC, RA-only, and HV groups. All results were expressed as individual data, and the horizontal bars indicate the respective means. *** $p < 0.001$.

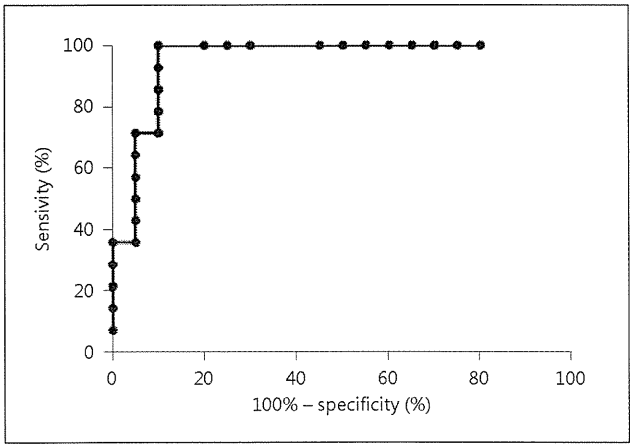

Fig. 3. ROC constructed for RA + MAC and RA w/o MAC patients.

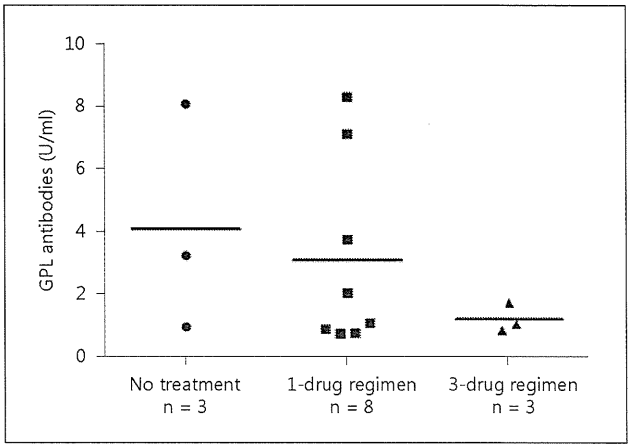

Fig. 4. Comparison of antibody levels between 3-drug, 1-drug, and no-treatment regimens. Horizontal bars indicate the means.

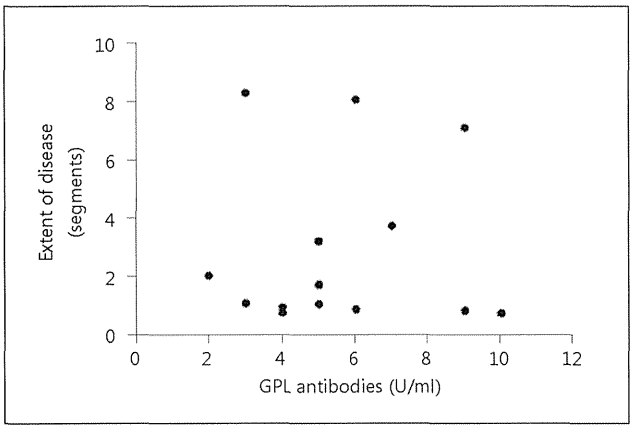

Fig. 5. Correlation between antibody levels and radiographic severity by chest CT in 14 RA patients with MAC-PD.

RA patients have pulmonary lesions such as follicular bronchitis and bronchiectasis [7, 8]. Lesions of the respiratory tract on chest CT are reportedly found in 40% of RA patients [17]. While the frequency of NTM infection has yet to be identified in RA, Wickremasinghe et al. [18] reported a 2% rate of NTM infection in bronchiectasis patients in their study. This radiological similarity between MAC-PD and RA lung has often made a differentiation between both diseases difficult. In the present study, we were able to distinguish the levels of serum IgA antibody to GPL core between RA + MAC and bronchitis or bronchiectasis associated with RA.

The most critical tool for MAC-PD diagnosis is generally thought to be smear results and culture of bronchial washing. Among 57 MAC-PD patients tested by Yamazaki et al. [19], sputum acid-fast smears were positive in 11 patients (19.2%) and sputum MAC cultures were positive in 21 (36.8%). In the deteriorated patient group of their study, cultures obtained by fiberoptic bronchoscopy proved to be positive for MAC in 49 patients (85.9%) and negative for MAC in 17% [19]. In serodiagnosis studies by Kitada et al. [20, 21], the EIA for anti-GPL antibody had a sensitivity and specificity of 84.3 and 100%, respectively, in a Japanese population and 87.9 and 94.2%, respectively, in an American population. The sensitivity and specificity in the present study were similar to those reported previously [21, 22].

Two patients manifesting anti-GPL antibodies above our cutoff value of 0.7 were mixed into the RA w/o MAC group in the present study. Though still unable to identify the cause of this discrepancy, RF stands out as a possible culprit. RF interferes with immunoassay in two ways, namely, in how it reacts with polyethylene glycol in the reagent and in how it recognizes animal antibodies in the reagent as antigens and produces immunoprecipitate in response. RF nonspecifically binds to the Fc region of IgG and IgM-RF immunocomplex in the RF family and can form a bridge structure when it reacts with latex reagent [23]. False-positive results can also result from diseases of other mycobacteria such as *Mycobacterium fortuitum*, *chelonae*, *abscessus*, or *scrofulaceum*, organisms that similarly possess GPLs on their cell wall surfaces [24–26].

False negatives occurred in 15.7% of the patients with MAC-PD in the study by Kitada et al. [21]. HLA genes may govern the immune responses to GPL core, and variation in these responses among individuals may be one cause of false negatives [27]. Another possible cause is the immunosuppressive agents the RA patients may have received. In our study, 14 patients received PSL (2 in RA + MAC, 10 in RA w/o MAC, and 2 in RA only), and 34 (8 in RA + MAC, 12 in RA w/o MAC, and 14 in RA only; table 1) received methotrexate. While most of our patients used >1 drug for RA treatment, a significant number of patients in the RA w/o MAC group received PSL alone. The levels of anti-GPL antibodies did not significantly differ between the patients receiving PSL and patients not receiving PSL (2.40 ± 1.87 vs. 2.95 ± 3.01 in RA + MAC, $p = 0.584$, and 0.633 ± 0.552 vs. 0.386 ± 0.310 in RA w/o MAC, $p = 0.224$, Mann-Whitney U test).

The recommended treatment for NTM-PD since the release of the ATS guideline in 1997 has been a 3-drug regimen of clarithromycin (CAM), ethambutol (EB), and rifabutin (RBT) or rifampicin (RFP) for 12 months for negative smear results. For more severe cases, the recommendation has been a 4-drug regimen (CAM, EB, streptomycin, and RBT or RFP) for 2 months, followed by a switch to a 3-drug regimen for 12 months after the smear results are negative [28]. Sixty to 80% of MAC-PD cases were reported to be smear negative after the first treatment using this standard regimen [29, 30]. In our study, 14 patients with RA w/o MAC were classified into three categories according to the treatment received. There were no significant differences in the levels of GPL antibodies among the three regimens, though the antibodies did tend to be lower in the patients on the 3-drug regimen. Eight of the RA + MAC patients received a 1-drug treatment for MAC infection for the reasons indicated in the Materials and Methods. We have not measured anti-GPL antibodies in our subjects since the end of the study. When Kitada et al. [12] compared serum IgA antibodies

to GPL before and after chemotherapy in both cured (14 MAC patients) and uncured patients (13 MAC patients), they found significantly decreased GPL core antibodies in the cured MAC patients who had responded to the chemotherapy.

Finally, Kitada et al. [14] reported that the levels of GPL core-specific IgA antibodies correlated with the number of involved chest CT segments in patients with MAC lung disease. In our study, we found no such correlations between the extent of the disease and GPL antibody levels (fig. 4). We may have overestimated the lung lesions with MAC in our study because of the RA lesions.

Our study has several limitations. First, the sample size of 74 cases is small. Our sample for RA + MAC, only 14 patients, is especially small, as few cases of RA + MAC presented at our institution between April 2009 and September 2011. Second, the timing for the blood collection varied since our data were retrospective. Among our 14 RA + MAC patients, blood was collected before the MAC diagnosis in 9 patients and after the diagnosis in 5. Finally, this study was a derivation cohort but not a validation cohort.

In conclusion, a serologic test for anti-GPL antibody is useful for the diagnosis of MAC-PD in RA.

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Financial Disclosure and Conflicts of Interest

None of the authors has financial relationships with commercial entities that have interests in the subject of this paper.

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Amelioration of Small Bowel Injury by Switching from Nonselective Nonsteroidal Anti-Inflammatory Drugs to Celecoxib in Rheumatoid Arthritis Patients: A Pilot Study

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Key Words
Nonsteroidal anti-inflammatory drugs · Cyclooxygenase-2 selective inhibitor · Small bowel injury · Video capsule endoscopy

Abstract
Background/Aims: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in patients with rheumatoid arthritis (RA) but have several side effects including mucosal damage in the small intestine. We aimed to evaluate whether the small bowel injury is ameliorated by switching from nonselective NSAIDs to celecoxib in patients with RA. ***Methods:*** Sixteen patients with RA who were treated with nonselective NSAIDs were enrolled in this study. Nonselective NSAIDs were converted to celecoxib for 12 weeks. Capsule endoscopy was performed before and after treatment with celecoxib. Videos were screened by gastroenterologists blinded to the patients' treatment. ***Results:*** Before the administration of celecoxib, reddened folds, denuded areas, petechiae/red spots and mucosal breaks were observed in 63, 63, 88 and 69% of the patients, respectively. In the 14 patients who completed this study, conversion to celecoxib significantly reduced the number of petechiae/red spots, the number of mucosal breaks, and Lewis scores. RA activity and cytokine levels in the peripheral blood were not significantly different before and after treatment with celecoxib. ***Conclusions:*** The incidence of small bowel injury by nonselective NSAIDs is high in patients with RA. Conversion from nonselective NSAIDs to celecoxib can be useful for protecting patients with RA from small bowel injury.

Introduction

Recent progress in the development of biologics, including disease-modifying antirheumatic drugs, has changed the treatment strategy for rheumatoid arthritis (RA) [1]. However, nonsteroidal anti-inflammatory drugs (NSAIDs) are still widely used because of their high efficacy for pain control and cost-effectiveness [2]. In spite of the usefulness of NSAIDs for reducing pain, patients who take NSAIDs are at a high risk for severe in-

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jury in the mucosa of the stomach and duodenum [3, 4]. Chronic NSAID users are estimated to suffer from ulcer complications (bleeding or perforation) at a rate of 1–4% each year, and NSAID use has been shown to be associated with up to 2,500 deaths per year in the UK population [5]. Previous randomized trials primarily focused on damage in the upper gastrointestinal (GI) tract, but recent reports have shown that lower GI events were also observed in patients with RA who use NSAIDs [6, 7].

NSAIDs act by inhibiting cyclooxygenase (COX), which converts arachidonic acid to prostaglandins [8, 9]. COX exists in two isoforms: COX-1, an essential enzyme to produce prostaglandins involved in the cytoprotective functions in the GI mucosa [10, 11]; COX-2, a predominantly cytokine-induced enzyme, produces prostaglandins to mediate pain and inflammation. Nonselective NSAIDs inhibit both COX-1 and COX-2, and gastroduodenal injury is suggested to mainly result from COX-1 inhibition. A selective COX-2 inhibitor has a characteristic of reducing mucosal damage compared to NSAIDs [12, 13], and celecoxib is one of the most commonly used selective COX-2 inhibitors. Several randomized controlled trials have compared the efficacy and side effects between celecoxib and nonselective NSAIDs and have shown that celecoxib reduced the relative risk of gastroduodenal ulcers compared to nonselective NSAIDs to 79% [12, 14, 15]. Over 24 weeks, the prevalence of endoscopically identified gastroduodenal ulcers in patients with RA taking celecoxib was nearly 4-fold lower than that of diclofenac. In addition, the incidence of mucosal injury to the small intestine was significantly lower in healthy subjects who received celecoxib than the subjects who received nonselective NSAIDs plus omeprazole [16, 17]. Available data, however, were limited to studies regarding the administration of nonselective NSAIDs or celecoxib in healthy volunteers.

Recently, video capsule endoscopy (VCE) enabled noninvasive visualization of the whole small intestine [18, 19]. VCE revealed approximately 90% of patients with RA suffer from small bowel injury regardless of NSAID use [20]. To date, clinical trials investigating the effect of COX-2 selective inhibitors on damage to the small intestine are lacking. In addition, the efficacy of switching from nonselective NSAIDs to celecoxib has not been investigated in patients taking NSAIDs. In this study, patients with RA with long-term use of nonselective NSAIDs were evaluated for mucosal damage of the small intestine by VCE. After the evaluation of mucosal injuries in the small intestine, nonselective NSAIDs were switched to celecoxib. We investigated whether the switching from nonselective NSAIDs to celecoxib ameliorates small bowel injury.

Patients and Methods

Study Subjects

Patients with RA who were older than 20 years and had been regularly treated with NSAIDs (loxoprofen, diclofenac, indomethacin, etc.) for more than 3 months (median 24 months; range 4–164 months) were consecutively recruited in the Department of Respiratory Medicine, Allergy and Rheumatic Disease, Osaka University Hospital, from January 2009 to April 2011. Exclusion criteria included: patients under treatment with biologics [anti-tumor necrosis factor (TNF)-α antibody, anti-interleukin (IL)-6 receptor antibody, etc.], high-dose corticosteroids (>10 mg/day of prednisolone), aspirin, or anti-ulcer drugs (misoprostol, teprenone, rebamipide, etc.); active GI ulcers; known or suspected complete or partial stenosis of the small intestine; inflammatory bowel disease; severe cardiovascular disease; malignancies; mental disorders; severe liver, renal and hematopoietic diseases, and patients who were pregnant or breastfeeding. Participants were not allowed to change their medications during the study, except for NSAID and celecoxib usage.

Study Design

This was a prospective, open-label, endoscopist-blinded, single-arm, and single-center study. Patients with RA treated with NSAIDs were assigned to receive celecoxib 200 mg twice daily for 12 weeks after the discontinuation of NSAIDs. VCE was performed before and after the treatment with celecoxib. Patients were evaluated for changes in the serologic markers of RA, serum cytokine concentrations, joint pain, and adverse events or side effects of celecoxib. The study protocols and informed consent forms were approved by the institutional review boards of Osaka University Hospital, and all patients signed a written consent form before being included in the study. The trial is registered at UMIN-CTR, No. UMIN000002554. The full trial protocol can be accessed at http://www.umin.ac.jp/ctr/.

Video Capsule Endoscopy

The VCE (Given video capsule system with the PillCam SB1 capsule; Given Imaging Ltd., Yoqneam, Israel) was performed as previously described [21]. Briefly, one day before the VCE examination, the subjects were required to fast after 9 p.m. After the subjects were fitted with sensor array and data recorder on the following morning at 9 a.m., they swallowed the VCE. Patients were not allowed to drink fluids until 2 h after swallowing the VCE, and only a light meal was allowed after a subsequent 2 h. The subjects avoided exposure to magnetic fields or radio transmitters, which may have interfered with image capture; otherwise, they were allowed to perform their daily activities. The sensor array and data recorder were removed 8 h after swallowing the capsule and were returned to the investigator to download the images onto a computer workstation for analysis. Videos were blinded before analysis by deletion of information including patients' name, date of birth, and examination date.

Methodology for Reviewing the VCE

The blinded videos were viewed by a physician with vast experience in VCE, and thumbnail pictures of potential abnormalities were created. These thumbnails were reviewed by three investigators. The damage scale from a previous classification for acute NSAID-induced small bowel damage by Maiden et al. [21] was used

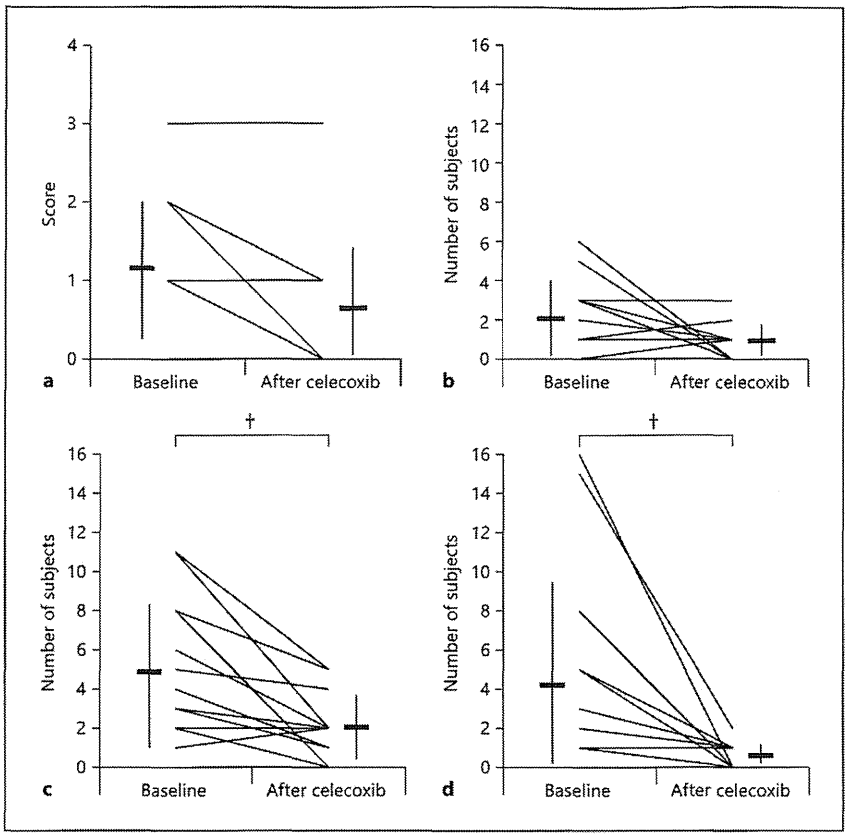

Fig. 1. Effect of the conversion from nonselective NSAIDs to celecoxib on the damage scale of small bowel lesions. The scores or number of lesions with each VCE finding [reddened folds (n = 14; **a**), denuded areas (n = 14; **b**), petechiae/red spots (n = 14; **c**) and mucosal breaks (n = 14; **d**)] were evaluated at baseline and after celecoxib treatment in the 14 patients who completed this study. † $p < 0.05$ after Bonferroni's correction. Bars indicate mean ± SD.

to evaluate mucosal injury as follows: category 1: reddened folds (≥1 valvulae conniventes showing discrete patchy or continuous erythema); category 2: denuded area (loss of villous architecture without a clear breach of the epithelium, may or may not be associated with surrounding erythema); category 3: petechiae/red spot (demarcated, usually circular, area of crimson mucosa with preservation of villi); category 4: mucosal break (mucosal erosions and/or ulcers, both represent discrete lesions with central pallor and surrounding hyperemia and loss of villi aphthae around the ulcer, and a punched out ulcer), graded by aphthae, circular ulcer, and punched out ulcer, and category 5: presence of blood. The severity of reddened folds was scored as 0 for none, 1 for mild, 2 for moderate, and 3 for severe. Additionally, the damage scale by Gralnek et al. [22], a capsule endoscopy scoring index for small bowel mucosal inflammatory change (Lewis score), was calculated for every patient by one endoscopist according to the judged thumbnails.

Assessing the Severity of RA

Changes in laboratory data including serum C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3) and blood hemoglobin (Hb) concentration were measured. Additionally, changes in serum cytokine concentrations were studied using the Bio-Plex human cytokine assay kit (Biorad, Hercules, Calif., USA) for platelet-derived growth factor-BB, IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor, granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, interferon (IFN)-γ, IFN-inducible protein-10, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, regulated and normal T cell expressed and secreted, TNF-α, and vascular endothelial growth factor. Arthritis scores were evaluated before and after the treatment of celecoxib by Disease Activity Score in 28 joints calculated by using CRP (DAS28-CRP) as described previously [23]. The number of the joints with swelling (SJC28) and the number of the joints with tenderness (TJC28) among 28 joints were counted by the rheumatologist. The DAS28-CRP was calculated from SJC28, TJC28, pain visual analogue scale and serum CRP values.

Statistical Analysis

The mucosal injury scores and the blood test results were analyzed before and after the treatment with celecoxib among the 14 patients who had completed a previous study using Wilcoxon paired signed rank test and paired t test, respectively. The Bonferroni method was used to adjust for multiple comparisons; therefore, p values $<0.05/5 = 0.01$ for the mucosal injury parameters (fig. 1, 2) and $<0.05/4 = 0.0125$ for the blood test parameters (fig. 3) were considered statistically significant. JMP Pro version 10.0 (SAS Institute Inc., Cary, N.C., USA) was used for all the analyses.

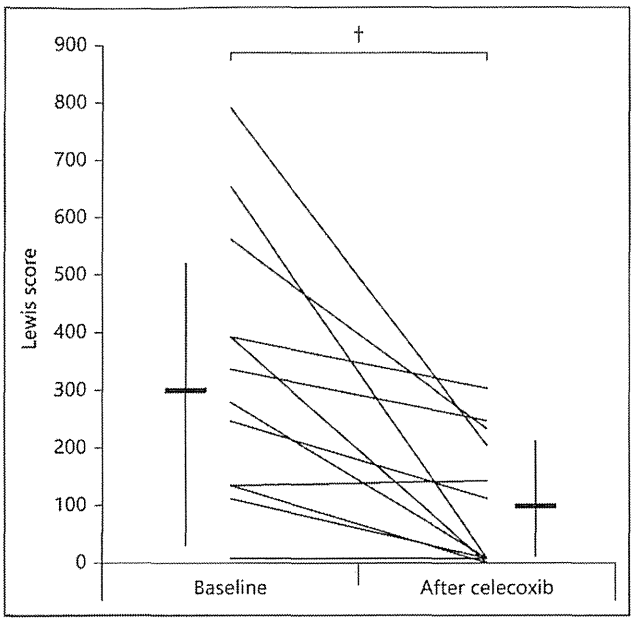

Fig. 2. Effect of conversion from nonselective NSAIDs to celecoxib on the scoring index for small bowel mucosal inflammatory change (Lewis score). The scoring index was evaluated at baseline and after celecoxib treatment in the 14 patients who completed this study. † $p < 0.05$ after Bonferroni's correction. Bars indicate mean ± SD.

Results

Patients

Sixteen patients underwent baseline VCE during the study period. Baseline characteristics for each subject are shown in table 1. Thirteen patients took loxoprofen; 3 patients took diclofenac, and 1 patient took indomethacin. One patient took both loxoprofen and diclofenac. Six patients took proton pump inhibitor (PPI) and 2 patients took histamine H2 receptor antagonist. Two patients dropped out because of general fatigue and disc herniation, which were not suggested as being related to celecoxib. Among the 14 patients who completed the study, no serious complications or side effects were observed.

Baseline VCE

Small bowel lesions were observed in 14 of 16 patients (88%) at baseline VCE. Reddened folds, denuded areas, petechiae/red spots and mucosal breaks were observed in 10 (63%), 10 (63%), 14 (88%) and 11 patients (69%), respectively. The presence of blood was not observed in any patient. The numbers of red spots and mucosal breaks were 5.5 ± 35.7 and 3.7 ± 5.1, respectively.

Efficacy of Switching from Nonselective NSAIDs to Celecoxib

Small bowel lesions were observed in 12 of 14 patients (86%) at posttreatment VCE. Similar to baseline VCE, the presence of blood was not observed in any patient. VCE findings were compared before and after treatment with celecoxib in the 14 subjects who completed this study. The proportion of patients having reddened folds, denuded areas, petechiae/red spots and mucosal breaks decreased from 71 to 50%, 64 to 50%, 93 to 79% and 71 to 36%, respectively. We performed quantitative analyses of small bowel injury in each patient before and after treatment with celecoxib. The numbers of petechiae/red spots and mucosal breaks were significantly decreased from 4.9 ± 3.5 to 1.9 ± 1.7 ($p = 0.002$; Bonferroni-adjusted $p = 0.010$) and 4.1 ± 5.4 to 0.4 ± 0.6 ($p = 0.004$; Bonferroni-adjusted $p = 0.0195$), respectively (fig. 1c, d). The scores of reddened folds and the number of denuded areas did not significantly differ before and after the treatment of celecoxib ($p = 0.031$, Bonferroni-adjusted $p = 0.157$; $p = 0.094$, Bonferroni-adjusted $p = 0.469$, respectively; fig. 1a, b). Lewis scores significantly decreased from 290 ± 248 to 92 ± 112 ($p = 0.002$; Bonferroni-adjusted $p = 0.010$; fig. 2).

Assessment of the Severity of RA

We next assessed serum and clinical markers for the disease activity of RA. There were no significant differences in Hb ($p = 0.029$; Bonferroni-adjusted $p = 0.114$), CRP ($p = 0.734$; Bonferroni-adjusted $p = 1$), MMP-3 ($p = 0.786$; Bonferroni-adjusted $p = 1$) and DAS28-CRP ($p = 0.167$; Bonferroni-adjusted $p = 0.667$) before and after treatment with celecoxib (fig. 3). We assessed serum cytokine concentrations by multiplex cytokine assay. There were no cytokines whose expressions were significantly different before and after treatment with celecoxib (table 2). Thus, we observed a significant reduction in small bowel injury by switching from nonselective NSAIDs to celecoxib after the 12 weeks of administration in patients with RA without a significant difference in the effectiveness of the medication on RA.

Discussion

Recently, VCE enabled to evaluate NSAID-induced small bowel injury, and we showed celecoxib use could reduce small bowel injury compared with nonselective NSAIDs. Goldstein et al. [16, 17] reported two randomized controlled trials using VCE in healthy volunteers and

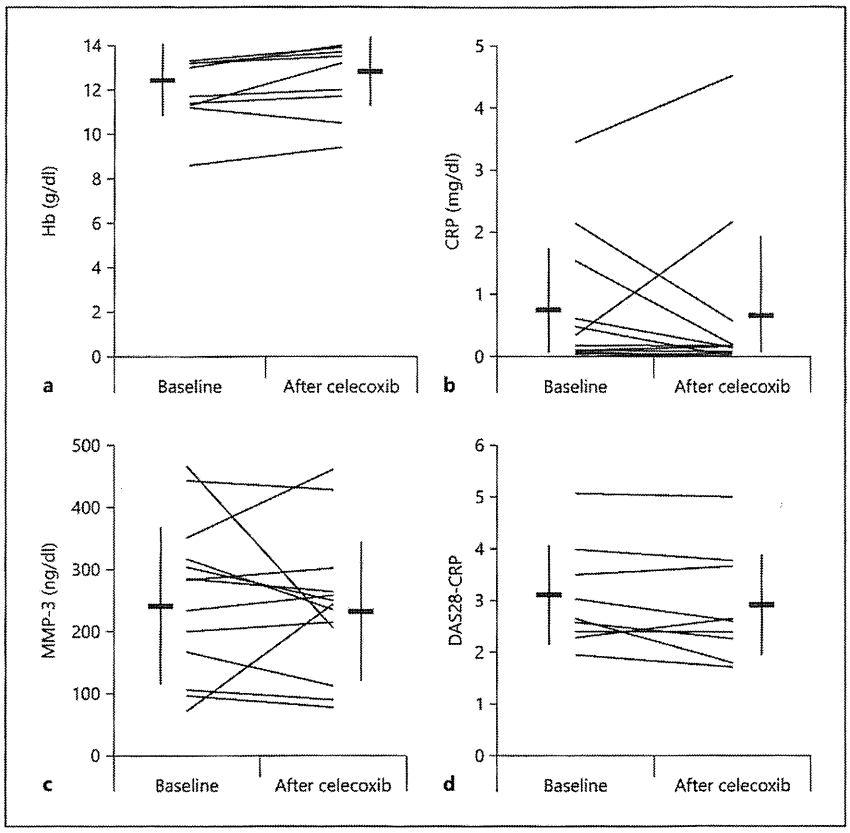

Fig. 3. Effect of conversion from nonselective NSAIDs to celecoxib on the activity of RA. Blood tests and disease activity scores were evaluated at baseline and after celecoxib treatment in 14 patients. **a** Blood Hb concentration (n = 14). **b** Serum CRP (n = 14). **c** MMP-3 (n = 14). **d** DAS28-CRP (n = 9). Bars indicate mean ± SD.

Table 1. Details of patients and treatment for RA

Age, years	59.0±11.8[a]
Sex	
Male	6 (38%)
Female	10 (62%)
Body mass index	23.5±3.9[a]
Prior NSAID therapy	
Loxoprofen	13 (81%)[b]
Diclofenac	3 (19%)[b]
Indomethacin	1 (6%)
Treatments for RA other than NSAIDs	
Corticosteroids	12 (86%)
Methotrexate	11 (69%)
Salazosulfapyridine	6 (38%)
Bucillamine	2 (13%)
Laboratory tests	
CRP, mg/dl	0.65±0.96[a]
MMP-3, ng/dl	222±135[a]
DAS28-CRP	3.2±1.1[a]
Hb, g/dl	12.6±1.6[a]

[a] Mean ± SD.
[b] One patient took a combination of loxoprofen and diclofenac.

concluded that celecoxib was effective for decreasing small bowel injury in comparison to nonselective NSAIDs. Mizukami et al. [24] also reported that celecoxib reduced small bowel injury compared with loxoprofen. Although their reports clearly showed the efficacy of celecoxib in comparison to NSAIDs for reducing small bowel injury, these reports had limitations. The duration of the celecoxib/NSAID treatment was relatively short (2 weeks), and the subjects were not diseased patients who required NSAIDs. Chan et al. [25] reported that anemia caused by small bowel injury was lower in celecoxib than diclofenac and omeprazole in patients with RA taking either medication for 6 months. However, they did not directly evaluate this small bowel damage by radiologic or endoscopic methods such as VCE. Our results revealed that celecoxib reduced the number of petechiae/red spots and mucosal breaks. Lewis scores were significantly decreased after the conversion to celecoxib. Thus, we demonstrated for the first time that small bowel injury was significantly improved by switching from NSAIDs to celecoxib in RA patients.

Table 2. Multiplex immunobead assay at baseline (B) and after celecoxib treatment (P)

Cytokine	B, pg/ml	P, pg/ml	Fold change P/B[a]	p value[b]
PDGF-BB	105,441 (31,476–1,164,451)	97,588 (46,382–1,216,712)	0.89	0.58
IL-1β	37 (15–490)	30 (15–965)	0.96	0.5
IL-1ra	1,226 (526–1,911)	1,134 (500–2,721)	1.15	0.58
IL-2	3 (0–18.79)	18 (0–45.4)	5.26	0.84
IL-4	55 (34–94)	55 (33–86)	0.99	1
IL-5	25 (9–130)	27 (6–105)	1.02	0.47
IL-6	152 (28–1,430)	92 (47–5,369)	1.96	0.95
IL-7	158 (84–351)	170 (78–296)	1.05	0.67
IL-8	246 (108–39,611)	219 (126–90,527)	1.18	0.63
IL-9	568 (51–3,923)	656 (16–9,347)	1.25	1
IL-10	132 (12–14,014)	113 (21–14,527)	1.05	0.36
IL-12	331 (64–9,501)	324 (85–5,704)	0.74	0.76
IL-13	85 (23–311)	88 (17–297)	1.12	1
IL-15	1 (0–10)	19 (0–252)	30.93	0.63
IL-17	107 (0–307)	84 (0–1,117)	1.28	0.91
Eotaxin	730 (0–6,917)	726 (0–8,988)	1.44	0.5
Basic FGF	253 (110–447)	218 (100–6,136)	2.61	0.71
G-CSF	218 (123–350)	226 (120–363)	1.05	0.81
GM-CSF	46 (0–434)	59 (0–772)	1.30	0.97
IFN-γ	2,312 (1,052–4,574)	2,721 (1,059–5,314)	1.06	0.5
IP-10	21,271 (10,152–189,971)	27,085 (12,249–216,373)	1.28	0.27
MCP-1	252 (85–451)	324 (173–1,067)	1.41	0.1
MIP-1α	58 (14–5,554)	62 (24–4,666)	0.52	0.63
MIP-1β	1,143 (471–45,475)	957 (618–22,649)	0.47	0.86
RANTES	22,134 (13,799–39,568)	22,134 (17,876–40,407)	1.01	0.88
TNF-α	624 (220–1,543)	412 (282–1,665)	0.90	1
VEGF	2,650 (581–9,218)	2,537 (656–12,726)	1.23	0.39

Values for B and P are expressed as median (range). PDGF = Platelet-derived growth factor; FGF = fibroblast growth factor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte/macrophage colony-stimulating factor; IP-10 = IFN-inducible protein-10; MCP-1 = monocyte chemoattractant protein-1; RANTES = regulated and normal T cell expressed and secreted; VEGF = vascular endothelial growth factor.

[a] Fold change in mean cytokine level.

[b] Wilcoxon paired signed-rank test.

It has been reported that patients with RA have small bowel injury in high frequency regardless of their NSAIDs use [20]. In addition, Sugimori et al. [20] showed that patients with RA taking NSAIDs were at high risk of severe small bowel injury. Consistent with previous reports [16, 20, 21], we obtained the results that patients with RA taking NSAIDs had a high frequency of small intestinal injury. Although the proportion of RA patients who had mucosal injury was not significantly changed by switching NSAIDs to celecoxib, the severity of small bowel injury was significantly improved. In addition, the efficacy of pain control in patients with RA by celecoxib was not inferior to that of nonselective NSAIDs. These results indicate that COX-2 selective inhibition by celecoxib is beneficial for the protection of mucosal damage in the small intestine without sacrificing the efficacy of pain control in patients with RA. In spite of the absence of abdominal symptoms in most RA patients in this study, 71% of the patients with RA presented mucosal breaks by VCE and 50% presented abnormal Hb concentrations. Although it may not be necessary to switch from nonselective NSAIDs to celecoxib in all the patients, evaluation of the small intestine should be considered when the RA patients with chronic NSAID users develop persistent severe anemia but do not have diseases in the upper and lower GI tract. In such cases, switching from nonselective NSAIDs to celecoxib may be beneficial.

Maiden et al. [21] previously reported that long-term COX-2 selective agents caused small-bowel damage comparable to NSAIDs. The discrepancy in the effectiveness

of COX-2 selective agents between long- and short-term use might be caused by the fact that the majority of the subjects analyzed in their study were patients with osteoarthritis, and only 24–33% of RA patients were included. In addition, COX-2 selective agents other than celecoxib were used in 40% of the patients in their study (etoricoxib, 20%; rofecoxib, 15%; valdecoxib, 5%). Furthermore, they did not quantitatively evaluate the severity of small bowel injury. Even in their analysis, small bowel injury was observed in a lower percentage by COX-2 selective agents than by NSAIDs. Further long-term studies using celecoxib for the patients with RA are necessary to clarify this issue.

Consistent with the previous reports, we found that celecoxib did not worsen the severity of RA, including blood Hb concentration, CRP, MMP-3 and DAS28-CRP. No patients discontinued celecoxib because of a worsening of pain caused by RA. When we assessed serum cytokine concentrations by multiplex cytokine assay, which had been reported to correlate with disease activity of RA [26–28], there were no cytokines whose expressions were significantly different before and after treatment with celecoxib. These results indicate that the conversion from NSAIDs to celecoxib was tolerable without diminishing the efficacy of pain control for RA patients. We did not include patients on biologics, such as anti-TNF and anti-IL-6 receptor antibodies, because these medications might be protective for small bowel injury [29–31]. Infliximab has been reported to be protective for indomethacin-induced small bowel damage in rats [32]. Similarly, there are several reports showing the efficacy of antiulcer drugs on preventing NSAID-induced small bowel injury [33–36]. We excluded patients taking these drugs, although those were the majority of long-term NSAIDs users. On the other hand, we included patients taking gastric acid suppressants such as PPI and H2 receptor antagonist because it is still controversial whether the inhibition of gastric acid exacerbate small intestinal injury. Lansoprazole has been reported to ameliorate NSAID-induced small bowel injury in rats by inhibiting inducible nitric oxide synthase expression, while omeprazole has no effect [37, 38]. Conversely, there are some recent reports showing the opposite result that PPIs exacerbate or have no effect on NSAID-induced small intestinal injury [39–41]. Moreover, these reports concerned indomethacin-induced rat models and not humans. Additionally, because corticosteroids were reported to be either ulcerogenic [42, 43] or gastroprotective [44, 45], patients on high-dose corticosteroids were eliminated from our study. We tried to avoid medications which may affect the small intestinal injury as well as the severity of RA.

There are some limitations to this study; the sample size of the study is relatively small. This is neither a placebo-controlled study nor a crossover study. There was no control group continuing nonselective NSAIDs. Thus, we cannot completely deny the possibility that the lesions would have improved if the prior NSAIDs had been continued or switched to different nonselective NSAIDs. We did not set a washout period after the cessation of NSAIDs use because the joint pain of arthritis is not tolerable without medication with NSAIDs. The duration of medication by celecoxib in this study was relatively short. In spite of these limitations, this study clearly demonstrates that the COX-2 selective inhibitor celecoxib has a clinical benefit for the improvement of small bowel injury in RA without diminishing the efficacy of its pain control. Additional long-term and large-scale studies are necessary to clarify the role of celecoxib in small bowel injury.

In conclusion, the incidence of small bowel injury by nonselective NSAIDs is high in patients with RA. Conversion from nonselective NSAIDs to celecoxib can become a useful therapeutic option for the treatment of small bowel injury in patients with RA.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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