Journal of Microbiology, Immunology and Infection (2015) 48, 130–136

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Autoimmune diseases-related arthritis in HIV-infected patients in the era of highly active antiretroviral therapy

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Received 30 April 2013; received in revised form 1 August 2013; accepted 9 August 2013
Available online 21 September 2013

KEYWORDS
Autoimmune disease;
Highly active antiretroviral therapy;
Human leukocyte antigen

Background: Autoimmune diseases-related arthritis has been rarely reported in HIV-1-infected patients. We aimed to investigate the incidence and clinical manifestations of autoimmune diseases-related arthritis in HIV-infected patients in the era of highly active antiretroviral therapy (HAART) in Taiwan.
Methods: We retrospectively reviewed medical records of all HIV-infected patients who had a diagnosis of autoimmune arthritis between 1993 and 2013. Demographic characteristics, clinical manifestations, serial CD4 and CD8 lymphocyte counts and plasma HIV viral loads, HLA-B27 status, and treatment response to HIV and rheumatic diseases were recorded.
Results: During the 20-year study period, totally 26 HIV-infected patients with autoimmune arthritis (0.7%) were diagnosed among 3623 HIV-infected patients. There were 18 patients with ankylosing spondylitis (AS), six with rheumatoid arthritis (RA), one with psoriatic arthritis, and one with Sjögren's syndrome. HLA-B27 antigens were all detected positive of AS patients. Fifteen patients (57.7%) developed autoimmune arthritis after HAART was initiated. The median age and $CD4^+$ T lymphocyte counts at the diagnosis of autoimmune arthritis were 35 (20–62 years) and 406 (3–695 cells/μL), respectively. Three patients had typical presentations of Reiter's syndrome. Both AS and RA patients achieved a good virological response with undetectable plasma HIV RNA load 12 months after receiving HAART(85.71% vs. 80%, respectively, $p = 0.999$). The treatment response to antirheumatic medications were similar between AS patients and RA patients (77.8% vs. 50%, $p = 0.3068$), but seems to be better than that reported for the general population (30–40%).
Conclusion: A low prevalence of autoimmune arthritis among HIV-infected patients in the era of HAART was similar to that of the general Taiwanese population. Clinical manifestations of

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http://dx.doi.org/10.1016/j.jmii.2013.08.002

HIV-infected patients were similar to those described in HIV-uninfected patients. However, the treatment response to antirheumatic agents was better in HIV-infected patients in our study.

Introduction

Autoimmune arthritis occurred with a wide spectrum among HIV-infected patients.[1] In the Taiwanese general population, rheumatoid arthritis (RA) and ankylosing spondylitis (AS) were the most two common types of autoimmune arthritis, with the prevalence of 0.26—0.93% and 0.19—0.54%, respectively.[2] AS occurs more commonly in men than women, and its incidence is about 0.52% in the United States.[3] The probable pathogenic mechanism of RA involves various types of cytokines, such as transforming growth factor (TGF) and interleukins (ILs), and elicits costimulation of dendritic cells, B cells, and T cells.[4] In the era of highly active antiretroviral therapy (HAART), worsening of RA with antiretroviral therapy had been observed, and it may reveal a pivotal role of $CD4^+$ T lymphocytes in the pathogenesis of RA.[5] The precise pathogenesis of AS remains unknown, although its pathogenic mechanism in the arthritic damage may be associated with HLA-B27-related antigen presentation of arthritogenic peptides and the involvement of immune effector cells that include $CD4^+$/$CD8^+$ T lymphocytes, and natural killer cells.[6] The HLA-B27 allele that has been shown to be associated with slower progression of HIV infection is highly correlated with the development of AS.[7,8] Increasing percentage of $CD4^+$/$CCR4^+$ T cells is found among patients with AS.[9] Psoriatic arthritis (PsA), Sjögren's syndrome, and systemic lupus erythematosus (SLE) could also be found in HIV-infected patients.[10,11]

With the initiation of HAART, $CD4^+$ T lymphocyte counts increase significantly in HIV-infected patients. Increased inflammatory responses, also termed immune reconstitution inflammatory syndrome have been widely reported in HIV-infected patients with opportunistic infections when combination antiretroviral therapy is concurrently initiated.[12] Therefore, immune reconstitution after HAART may increase the risk for autoimmune arthritis. In this study, we aimed to know the prevalence of autoimmune diseases-related arthritis and describe the clinical manifestations of autoimmune arthritis in HIV-infected patients in Taiwan, where HIV infections occur predominantly in men (male-to-female ratio: 13.38).[8]

Materials and methods

Study population

We identified patients with HIV infection (ICD-9-CM code V08, 042) by using our computer-based international classification of disease (ICD) code database at the National Taiwan University Hospital (NTUH) between 1993 and 2013. We further identified HIV-infected patients with AS (ICD-9-CM code 720.0), RA (ICD-9-CM code 714.0), SLE (ICD-9-CM code 710.0), PsA (ICD-9-CM code 696.1), and Sjögren's syndrome (ICD-9-CM code 710.2). We then retrospectively reviewed the medical records of the HIV-infected patients with autoimmune diseases-related arthritis who sought medical attention at NTUH. The diagnosis of AS was made by according to the modified New York criteria.[13] The criteria include one of the three symptomatic presentations (low back pain or stiffness, limitation of motion of the lumbar spine in the sagittal and frontal planes, and limitation of chest expansion relative to normal values correlated for age and sex), and radiographic evidence of sacroileitis. If both symptomatic and radiographic criteria are fulfilled, he or she will be classified as being a definite case of AS. The diagnosis of RA was based on the criteria set by American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee.[14] RA diagnosis requires clinical scoring for more than six points (full score: 10 points).

We used a standardized case record form to collect information on demographic characteristics, smoking status, alcohol consumption, comorbidities, concomitant medications, opportunistic infections during the HIV disease course, and antiretroviral regimens. We also recorded associated extra-articular manifestations, CD4 and CD8 lymphocyte counts, and plasma HIV RNA loads before and after the start of HAART, clinical response to antirheumatic regimens, serum creatinine value, liver function profiles, viral hepatitis coinfection, Rapid plasma reagin titer, autoimmune profiles (antinuclear antibody, rheumatoid factor, C3, C4, IgG, IgA, IgM, or other autoimmune antibodies), and HLA-B27 status. The treatment response was defined as good symptomatic control with no pain after 12 month's follow-up.

Laboratory investigations

HLA-B27 was detected by flow cytometry for leukocyte surface markers. Plasma HIV RNA load was quantified using the COBAS AMPLICOR HIV-1 MONITOR test (v1.5, Roche Diagnostics Corporation, IN) with a lower detection limit of 40 copies/mL, and the CD4 lymphocyte count was determined using FACFlow (BD FACSCalibur, Becton Dickinson, CA).

The study was approved by the Research Ethics Committee of the hospital (Registration no. 201212177RINB) and written or oral informed consent was waived.

Statistical analysis

The Cochran—Armitage Test for Trend was performed to analyze the prevalence of autoimmune arthritis among the different time periods. We used Fisher's exact test or

Chi-squared test for categorical variables among the two groups of patients (AS and RA), and utilized the Wilcoxon test for the examination of continuous variables. A p value <0.05 was considered statistically significant. The confidence interval was set at 95%. The analysis was conducted using the statistical package SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

During the 20-year study period, 3623 HIV-infected patients had sought HIV care at the hospital at least once; 26 patients had a diagnosis of autoimmune diseases-related arthritis. There were 18 patients with AS (0.49%), six with RA (0.16%), one with PsA (0.03%), and one with primary Sjögren's syndrome (0.03%). The prevalence of autoimmune arthritis by different disease categories is shown in Fig. 1, and the prevalence among the general Taiwanese population is also revealed. The prevalence of autoimmune arthritis within different time periods is shown in Fig. 2. The trend of prevalence changes was not statistically significantly associated with pre-HAART, early-HAART, and late-HAART ($p = 0.391$).

The overall clinical characteristics of the 26 HIV-infected patients with autoimmune arthritis are shown in Table 1. The median age was 35 years at the diagnosis of autoimmune arthritis. The median CD4 T lymphocyte counts was 205 cells/μL at the diagnosis of HIV infection, and 81.8% of these achieved an undetectable plasma HIV viral load 12 months after taking HAART.

We compare with two most common autoimmune arthritis, AS versus RA. The clinical characteristics of the 18 HIV-infected patients with AS and six with RA are shown in Table 2. The patients who received the diagnosis of RA had a higher median age at the diagnosis of autoimmune arthritis (46 vs. 34; $p = 0.018$). The AS group had a significantly higher proportion of patients carrying HLA-B27 alleles (100% vs. 0%, $p = 0.0022$). There were no other statistically significant differences in the proportion of

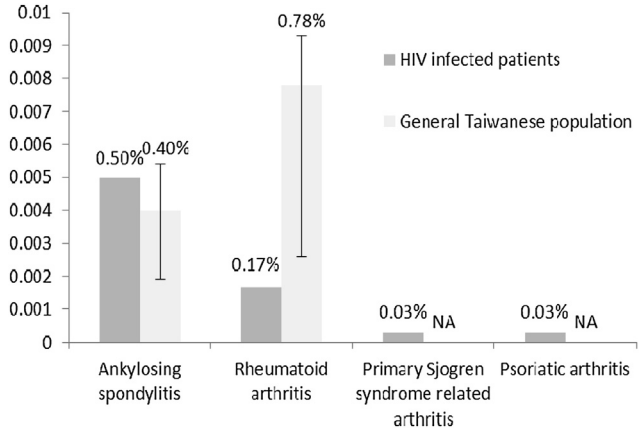

Figure 1. The prevalence of autoimmune arthritis among HIV-infected patients (category by diseases) compared to the general Taiwanese population.[2] AS = ankylosing spondylitis; NA = not available; PsA = psoriatic arthritis; RA = rheumatoid arthritis.

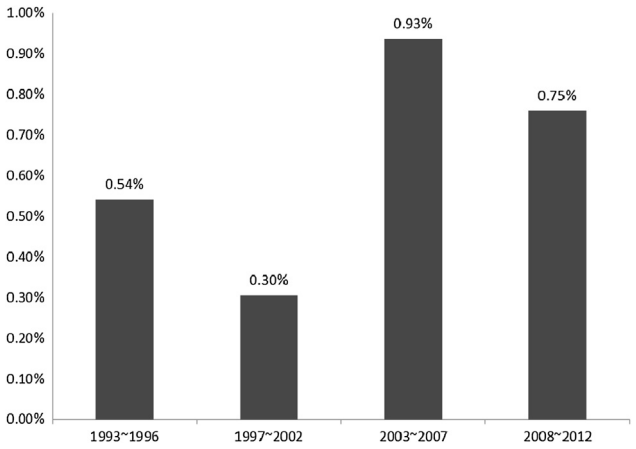

Figure 2. The prevalence of autoimmune arthritis among HIV-infected patients (category by calendar years) (trend analysis, $p = 0.391$).

Table 1 Overall clinical characteristics of the 26 HIV-infected patients with autoimmune arthritis

Characteristics	Autoimmune arthritis ($n = 26$)
Age at the diagnosis of autoimmune arthritis, y	35 (20–62)
Male, sex	24 (92.3)
Body weight, kg	62 (47–92)
HIV risk factors	
Homosexual	20 (76.9)
Heterosexual	2 (7.69)
Bisexual	1 (3.85)
IDU	3 (11.5)
Cigarette smoking	13 (50)
Alcohol consumption	5 (19.2)
Comorbidities	
Diabetes mellitus	1 (3.85)
Chronic lung disease	2 (7.69)
Chronic hepatitis B	4 (15.4)
Chronic hepatitis C	4 (15.4)
CD4 count at diagnosis of HIV	205 (0.5–763) [$N = 23$]
CD8 count at diagnosis of HIV	754 (78–2392) [$N = 19$]
CD4 count change 12 mo after initiating HAART	+175 (−14–578) [$N = 22$]
Plasma HIV RNA load at the diagnosis of HIV, log10 copies/mL	5.39 (3.77–6.75) [$N = 21$]
Achieved undetectable plasma HIV load 12 mo after initiation of HAART	18 (81.8) [$N = 22$]
Autoimmune arthritis diagnosed after HAART	15 (57.7)

Data represent the median value (total range) for continuous variables and the number of cases (%) for categorical variables.
N indicates the number of patients being tested.
IDU = intravenous drug abuser.

Table 2 Clinical characteristics of the 24 HIV-infected patients with AS and RA

Characteristics	AS ($n = 18$)	RA ($n = 6$)	p
Age, y	34 (20–44)	46 (23–62)	0.018
Male sex	18 (100)	5 (83.3)	0.250
Body weight, kg	63.5 (47–85)	59 (50–92)	0.685
HIV risk factors			
Homosexual	15 (88.3)	4 (66.7)	0.568
Heterosexual	1 (5.6)	1 (16.7)	0.446
Bisexual	1 (5.6)	0 (0)	0.999
IDU	1 (5.6)	1 (16.7)	0.446
Cigarette smoking	8 (44.4)	3 (50)	0.999
Alcohol use	3 (16.7)	2 (33.3)	0.568
Underlying medical diseases			
Diabetes mellitus	0 (0)	1 (16.7)	0.250
Chronic lung disease	0 (0)	2 (33.3)	0.054
Chronic hepatitis B	2 (11.7)	1 (16.7)	0.999
Chronic hepatitis C	2 (11.7)	1 (16.7)	0.999
Patients who had OIs during the course of HIV infection	4 (22.2)	3 (50)	0.307
Pneumocystosis	1 (5.6)	1 (16.7)	0.446
CMV disease	2 (11.1)	1 (16.7)	0.999
MAC infection	2 (11.1)	1 (16.7)	0.999
Tuberculosis	0 (0)	1 (16.7)	0.250
Kaposi sarcoma	1 (5.6)	0 (0)	0.999
Extra-articular manifestations	6 (33.3)	0 (0)	0.277
Psoriasis	1 (5.56)	0 (0)	0.999
Uveitis	4 (16.7)	0 (0)	0.539
Ulcerative colitis	1 (5.56)	0 (0)	0.999
HLA-B27(+) status	12 (100) [$N = 12$]	0 (0) [$N = 3$]	0.002
Laboratory data at the diagnosis of autoimmune arthritis			
Elevated ANA titer	3 (60) [$N = 5$]	1 (20) [$N = 5$]	0.524
RF titer (U/mL)	0 (0–27.8) [$N = 4$]	0 (0–30.9)	0.999
CRP level (mg/dL)	2.68 (0.08–14.74) [$N = 13$]	1.05 (0.04–4.21)	0.125
ESR level (mm)	67.6 (9–120) [$N = 11$]	34.3 (1–93)	0.159

Data represent the median value (total range) for continuous variables and the number of cases (%) for categorical variables. *N* indicates the number of patients being tested.
ANA = antinuclear antibody; AS = ankylosing spondylitis; CMV = cytomegalovirus; CRP = C reactive protein; ESR = erythrocyte sedimentation rate; IDU = intravenous drug abuser; MAC = *Mycobacterium avium-intracellulare* complex; OIs = opportunistic infections; RA = rheumatoid arthritis; RF = rheumatoid factor.

males, HIV infection risk factors, baseline medical comorbidities, and opportunistic infections during the HIV disease course, and the C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels at the diagnosis of autoimmune arthritis. Six of the AS patients had extra-articular manifestations, but none of the RA patients had extra-articular involvement (Table 1). Three of the AS patients also fulfilled the criteria of Reiter's syndrome (arthritis and uveitis). One had concurrent co-infection of syphilis (VDRL titer 1:1024). The other had biopsy-proven ulcerative colitis. All the three patients with Reiter's syndrome improved after the anti-HIV treatment. All the clinical presentations of Reiter's syndrome may be due to the presentations of HIV-related arthritis.

In two patients of the AS group, the diagnosis of HIV infection and AS were made at the same time; and in seven AS patients (50%) and one RA patient (16.7%), the diagnosis of autoimmune arthritis was made before using HAART. Only one patient of the AS group had aggravating arthritis symptoms after initiating HAART, and needed to add Plaquenil for better symptomatic control.

The virological response, $CD4^+/CD8^+$ T lymphocyte counts at the initiation of HAART, and change of $CD4^+/CD8^+$ T lymphocyte counts 12 months after the initiation of HAART are shown in Table 2. There were no statistically significant differences between the AS and RA groups. About 80% of both two groups achieved undetectable plasma HIV RNA load. The median $CD4^+$ T lymphocyte increases at 12 months after the initiation of HAART were 175 and 168 cells/μL, respectively ($p = 0.668$).

Nine of the AS patients (50%) and five of the RA patients (83.3%) received the diagnosis of autoimmune arthritis after initiating HAART. The time interval from the initiation of HAART to the diagnosis of AS and RA ranged from 1 month to 46 months, and 8 months to 144 months, respectively. At the start of combination antiretroviral therapy, none of the 14 patients had symptoms and signs suggestive of autoimmune arthritis, such as low back pain, knee pain, or

Table 3 Medication, virological, and immunological response to HIV between AS and RA

	AS ($n = 18$)	RA ($n = 6$)	p
HAART medications			
NNRTI usage	12 (66.7)	5 (83.3)	0.629
PI usage	6 (33.3)	2 (33.3)	0.999
Diagnosis of autoimmune arthritis before using HAART	9 (50)	1 (16.7)	0.489
Time to development of autoimmune arthritis after taking HAART, mo	13 (1–46)	67 (8–144)	0.160
CD4 T lymphocyte count			
At the diagnosis of HIV	205 (39–163) [$N = 17$]	144 (42–507) [$N = 4$]	0.622
At the start of HAART	186 (2–456)	186.5 (11–507)	0.764
12 mo after initiating HAART	360 (0–705) [$N = 15$]	437.5 (68–745)	0.726
Interval change 12 mo after initiation of HAART	175 ((−14)–578) [$N = 15$]	168 (57–358)	0.668
CD8 T lymphocyte count			
At the diagnosis of HIV	754 (379–1354) [$N = 13$]	1333 (569–2392) [$N = 5$]	0.610
At the start of HAART	754 (189–1486) [$N = 17$]	1282 (666–3150)	0.086
12 mo after initiating HAART	902 (18–1602) [$N = 15$]	1080 (619–1944)	0.436
Interval change 12 mo after initiation of HAART	90 ((−651)–943)) [$N = 11$]	−100.5 ((−1829)–287)	0.102
Plasma HIV RNA load before the initiation of HAART, log10 copies/mL	5.27 (4.13–6.75)	5.69 (4.94–6.18) [$N = 5$]	0.146
Achieve undetectable plasma HIV RNA load 12 mo after the initiation of HAART	12 (80) [$N = 15$]	5 (83.3)	0.456

Data represent the median value (total range) for continuous variables and the number of cases (%) for categorical variables. *N* indicates the number of patients being tested.
HAART = highly active antiretroviral therapy; NNRTI = non-nucleotide reverse transcriptase inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs; PI = protease inhibitor.

hand joint pain. As the $CD4^+$ T lymphocyte counts increased, low back pain or stiffness gradually occurred in all of the nine AS patients, and knee pain or hand joints pain developed in all of the five RA patients. The diagnosis of AS was made by the presenting symptoms, positive tests of HLA-B27, and radiography of the lumbosacral spine and pelvis several weeks to months after the onset of symptoms. Three of the nine AS patients developed extra-articular manifestations with uveitis, and one of them developed ulcerative colitis. The diagnosis of RA was made by the clinical symptoms, radiographic evidence of bony erosions, and serology markers for elevated rheumatoid factor, anticitrullinated protein antibody, or CRP. None of them had extra-articular presentations.

The clinical responses to rheumatological disease are shown in Table 3. The AS group had a higher proportion of achieving good symptomatic control at a 1-year follow-up period (77.8% vs. 50%, $p = 0.307$), while the RA group had a greater need for the use of Plaquenil and methotrexate with a borderline significance (11.1% vs. 50%, $p = 0.0785$) (Table 4).

Discussion

In this study of autoimmune arthritis among HIV-infected Taiwanese patients who sought HIV care at a referral hospital, it is estimated 0.49% of the patients had AS, which was similar to the prevalence (0.19～0.54%) reported in the general Taiwanese population. However, it is estimated 0.16% of the patients had RA, which was lower than the general Taiwanese population reported (0.26～0.93%). [2] RA was much more prevalent among the female population, and thus our study population may have had a lower prevalence due to the predominantly male composition. Although immune reconstitution with HAART may precipitate development of autoimmune arthritis in patients at risk, our research failed to demonstrate the increasing prevalence before and after the HAART era.

Although the rate of RA is lower among HIV-infected patients as compared with the general population, we might have underestimated the incidence because of the

Table 4 Rheumatologic treatment outcomes of AS and RA

	AS ($n = 18$)	RA ($n = 6$)	p
Antirheumatic medications			
Sulfasalazine	10 (55.6)	4 (66.7)	0.999
Plaquenil	2 (11.1)	3 (50)	0.079
Methotrexate	2 (11.1)	3 (50)	0.079
Steroid	0 (0)	1 (20)	0.215
NSAIDs	15 (83.3)	6 (100)	0.546
Adalimumab	0 (0)	1 (16.7)	0.250
Good symptomatic control at 12-mo follow-up	14 (77.8)	3 (50)	0.307

Data represent the number of cases (%) for categorical variables.
NSAIDs = nonsteroidal anti-inflammatory drugs.

younger median age than the general population. An older onset age of RA had been found to be related to higher activation status of peripheral blood $CD4^+$ T lymphocyte and disease activity.[15] In this study, the age at the diagnosis of RA is significant higher than that of AS. Whether longer survival and progressive increases of CD4 count with prolonged courses of combination antiretroviral therapy may increase the incidence of AS, warrants further study.

Previous studies by Massabki and colleagues have suggested that HIV infection was associated with an increased incidence of presence of autoantibodies.[16] In the era of HAART, several different autoimmune diseases such as SLE, Graves' disease, and autoimmune hepatitis, have been observed to occur during the course of combination antiretroviral therapy.[11,17,18] Some autoimmune phenomena may be considered as one manifestation of immune reconstitution inflammatory syndrome.[12,19] However, AS related to immune reconstitution inflammatory syndrome was rarely reported before. Most of our patients carried the HLA-B27 allele, which has been known to be a predisposing factor to developing AS.[20] As the immune reconstitution occurs with combination antiretroviral therapy, some HIV-infected patients with autoimmune diathesis may develop autoimmune disease, such as the HLA-B27-positive patients in our study.

Reiter's syndrome was found in 0.4～10% of the HIV-infected subjects, most of whom had asymmetric oligoarthritis,[21] compared with 0.0035% in the general population.[22] It may overlap with AS with the presentations of sacroileitis and carrying HLA-B27 allele.[23] In our study, three of the 18 AS patients also matched the diagnosis of Reiter's syndrome, a kind of reactive arthritis. All the clinical presentations of Reiter's syndrome may be because of the presentations of HIV-related arthritis.

The treatment response to antirheumatic agents for AS and RA with good symptomatic control was estimated as 30～40% on the basis of the previous studies.[24–26] However, the treatment responses in the AS and RA patients of our study were 77.8% and 50%, respectively, with a better rate of symptomatic control. The better control for autoimmune arthritis may result from the relative immune deficiency state of the HIV-infected patients.

The major limitations of our study included low case numbers of autoimmune arthritis and retrospective method. Therefore, several laboratory data, such as antinuclear antibody, antineutrophil cytoplasmic antibody, C3, C4, and other autoantibodies were missed or incomplete. A large longer observation is mandatory for this issue. Owing to the lack of baseline $CD4^+/CD8^+$ T lymphocyte counts at the diagnosis of AS or RA in these eight patients who had autoimmune arthritis before initiating HAART, it was difficult to evaluate the changes in $CD4^+/CD8^+$ T lymphocyte counts and their effect on the disease severity of AS or RA. Owing to the unknown percentage of HIV-infected patients that were lost to follow-up, we may have underestimated the incidence of autoimmune arthritis among the study population, although the percentage of HIV-infected patients lost to follow-up is quite low (<5%) at NTUH.

In conclusion, autoimmune arthritis remains a rare complication among the HIV-infected patients receiving HAART. The virological and immunological responses are good in HIV-infected patients with autoimmune arthritis, who are receiving HAART. The clinical manifestations are no different from those in the general population, but the treatment responses to antirheumatic medications seemed to be better than those in the general population.

Conflicts of interest

The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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