in only two (9.5 %) patients (peak values 14.4 and 32.7 pg/ml, respectively). The patient with a peak value of 14.4 pg/ml developed PCP with the simultaneous elevation of serum KL-6 and BDG levels. In J-RAPID, of 32 patients who met criterion B by week 52, only 3 (9.4 %) patients (peak values 11.5, 12.3, and 18.1 pg/ml, respectively) showed abnormal, but modest, elevations of serum BDG levels that were observed in parallel with an elevation of serum KL-6 levels. These data and the favorable clinical courses of these patients indicate that the possibility of subclinical PCP was quite low in the majority of patients meeting criterion B.

Some important clinical questions arise from our findings. First, do we have to stop treatment with TNF inhibitors in RA patients with elevated serum KL-6 levels? The answer is no. We should search for reasons for the elevation, such as PCP, IP, and malignancy, as the first step, but when these adverse events are not identified, continuing treatment with TNF inhibitors under careful observation is a reasonable option for RA patients who have shown good response to the treatment. Second, is it worthwhile to monitor KL-6 every 4 weeks during treatment with TNF inhibitors? When we used criterion B to define the elevation of serum KL-6 levels, KL-6 had low positive predictive values for PCP and IP in RISING (5.9 %), HIKARI (14.3 %), and J-RAPID (0 %) and high negative predictive values (99–100 %) in all three trials. However, in these studies, there were only three PCP and three IP patients among those who met criterion B and three IP patients among those who did not met criterion B; there is, therefore, a possibility that more stringent criteria would have better predictive abilities for these adverse events. To clarify the usefulness of monitoring KL-6 serum levels during treatment with TNF inhibitors, a specifically designed clinical study is required. Therefore, we cannot provide a definite answer for the second question from our present analysis.

The potential contribution of concomitant MTX to the elevation of serum KL-6 levels in RA patients given TNF inhibitors should be mentioned. When we combined the MTX + placebo groups from J-RAPID and GO-FORTH, 3 (2.0 %) of 149 patients given MTX + placebo met criterion B by week 24 or 28 without associated pulmonary events. In our retrospective study [22], 5 (10.6 %) of 47 RA patients given MTX without biological DMARDs met criterion B, and 4 of these (8.5 %) did not have any clinical reasons for the elevation of serum KL-6 levels. These data indicate that we should consider a potential contribution of MTX to the elevation of serum KL-6 levels during treatment with TNF inhibitor + MTX.

The mechanisms of the elevation of serum KL-6 levels in RA patients given TNF inhibitors remain to be determined. Little is known about the molecular mechanisms of KL-6 expression and its transport mechanism through the alveolar–capillary barrier. Further studies are required to clarify the roles of TNF in these processes in both physiological and pathological conditions.

In summary, the transient elevation of serum KL-6 levels in patients meeting criterion B, without accompanying specific clinical events, was observed in 6.8–15.6 % of RA patients treated with TNF inhibitors by year 1 in five clinical trials. Continuing treatment with TNF inhibitors under careful observation is a clinically reasonable option when serum KL-6 levels rise.

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ORIGINAL ARTICLE

A retrospective study of serum KL-6 levels during treatment with biological disease-modifying antirheumatic drugs in rheumatoid arthritis patients: a report from the Ad Hoc Committee for Safety of Biological DMARDs of the Japan College of Rheumatology

Akito Takamura · Shintaro Hirata · Hayato Nagasawa · Hideto Kameda · Yohei Seto · Tatsuya Atsumi · Makoto Dohi · Takao Koike · Nobuyuki Miyasaka · Masayoshi Harigai

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Abstract
Objective We investigated associations between treatment with methotrexate (MTX) or biological disease-modifying antirheumatic drugs (DMARDs) and elevation of serum Krebs von den Lungen-6 (KL-6) levels in Japanese patients with rheumatoid arthritis (RA).
Methods Using a standardized form, data were collected retrospectively from medical records and analyzed descriptively.
Results Of a total of 198 RA patients with KL-6 serum levels measured at initiation of treatment (month 0) and two or more times by month 12, 27 (17.9 %) of 151 RA patients treated with biological DMARDs, including infliximab, etanercept, adalimumab, and tocilizumab (the biological DMARDs group), and 5 (10.6 %) of 47 patients treated without biological DMARDs but with MTX (MTX group), met criterion B (max. KL-6 ≥500 U/ml and >1.5-fold from baseline) by 12 months. The majority of patients ($n = 28$) meeting criterion B had no apparent interstitial lung disease or malignancy. Of these 28 patients, 21 had serum KL-6 levels available after reaching their maximum level, and 13 (61.9 %) of the 21 then met criterion R [decrease to less than 500 U/ml or to less than (baseline + 0.5 × (maximum − baseline))] by month 12.
Conclusion Serum KL-6 levels may increase during treatment with MTX or these biological DMARDs without significant clinical events.

A. Takamura, S. Hirata, H. Nagasawa, H. Kameda, Y. Seto, T. Atsumi, M. Dohi, and M. Harigai are the members of the Ad Hoc Committee for Safety of Biological DMARDs of the Japan College of Rheumatology.

A. Takamura · N. Miyasaka · M. Harigai
Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

S. Hirata
The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan

H. Nagasawa
Department of Rheumatology/Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan

H. Kameda
Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo, Japan

Y. Seto
Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan

T. Atsumi
Department of Internal Medicine II, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

M. Dohi
Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

T. Koike
Sapporo Medical Center NTT EC, Sapporo, Hokkaido, Japan

N. Miyasaka
Global Center of Excellence Program, International Research Center for Molecular Science in Tooth and Bone Diseases, Tokyo Medical and Dental University, Tokyo, Japan

M. Harigai (✉)
Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: mharigai.mpha@tmd.ac.jp

Keywords Rheumatoid arthritis · Biological disease-modifying antirheumatic drug · KL-6

Introduction

Six biological disease-modifying antirheumatic drugs (DMARDs), infliximab (IFX), etanercept (ETN), adalimumab (ADA), tocilizumab (TCZ), abatacept, and golimumab, have been approved in Japan. Today, these biological DMARDs are widely used for treatment of rheumatoid arthritis (RA). Pulmonary diseases with interstitial lesion, including rheumatoid lung, drug-induced pulmonary injury, or *Pneumocystis jirovecii* pneumonia (PCP), sometimes develop during treatment of RA with biological DMARDs [1–4]. Better prognosis for affected patients would be provided by prompt diagnosis of these diseases [5–8].

Krebs von den Lungen-6 (KL-6) is a circulating high-molecular-weight glycoprotein recently classified in humans as a cluster 9 mucin-1 (MUC1) [9]. The serum level of KL-6 was reported to be elevated in patients with idiopathic interstitial pneumonia (IIP), interstitial pneumonia (IP) associated with collagen diseases, IP associated with drug allergy, PCP, other interstitial lung diseases, and malignancy [10–15]. Measurement of serum KL-6 levels is an officially approved laboratory test in Japan, widely used as an adjunctive diagnostic or monitoring tool for patients with interstitial lung diseases and patients with RA treated with MTX or biological DMARDs.

In the Impact on Radiographic and clinical response of Infliximab therapy concomitant with methotrexate in rheumatoid arthritis patients by the trough Serum level in the dose-escalatING (RISING) study [16], abnormal elevation of serum KL-6 levels in RA patients treated with IFX with no pulmonary diseases was seen. Considering the prevalent use of serum KL-6 levels as a laboratory test for RA patients in Japan, the Japan College of Rheumatology (JCR) convened the Ad Hoc Committee for Safety of Biological DMARDs to investigate the abnormal elevation of serum KL-6 levels in RA patients during treatment with biological DMARDs. The committee implemented two studies, one using clinical trial data and one clinical practice data. Here, we report the results from a retrospective analysis of clinical practice data.

Patients and methods

Data source

Criteria for admission to this study included those patients (1) meeting the 1987 American College of Rheumatology criteria for RA [17], (2) ≥20 years old, (3) willing to provide informed consent, (4) starting treatment with biological DMARDs (IFX, ETN, ADA, and TCZ) or MTX, and (5) having serum KL-6 levels measured at start of treatment (month 0) and two or more times by month 12. Exclusion criteria included those patients (1) withdrawing consent to join the study, or (2) found to be unsuitable for the study at the discretion of the attending physician. Data, including age, gender, comorbidities, past history, disease duration, laboratory data [KL-6, surfactant protein-D (SP-D), beta-D-glucan, white blood cell counts, lymphocyte cell counts, lactate dehydrogenase, C-reactive protein, and erythrocyte sedimentation rate] at months 0, 6, and 12, number of tender and swollen joints at months 0, 6, and 12, the patients' global assessments at months 0, 6, and 12, and treatments during the 12 months, were collected from medical records using a standardized case report form. We also collected data on pulmonary events, including PCP, IP, and others, and any malignancies during the 12 months. Data on pulmonary events included diagnosis, date of diagnosis and prognosis of pulmonary events, and laboratory data, results of imaging analyses, and treatments at onset of pulmonary events.

Measurement of serum KL-6 levels and the criteria for increase and decrease

Serum KL-6 levels were measured using Picolumi KL-6 (Eidia Co., Ltd., Tokyo, Japan) or Lumipulse Presto KL-6 (Eidia Co., Ltd., Tokyo, Japan) by in-house laboratories or outsourced, depending on the institution. Baseline serum KL-6 levels were measured within 1 month from initiation of treatment (month 0). We defined elevation of serum KL-6 levels as follows: criterion A (max. KL-6 ≥500 U/ml and >1.25-fold from baseline), criterion B (max. KL-6 ≥ 500 U/ml and >1.5-fold from baseline), and criterion C (max. KL-6 ≥1000 U/ml and >3.0-fold from baseline). Reduction of serum KL-6 levels was defined as a decrease to less than 500 U/ml or to less than [baseline + 0.5 × (maximum − baseline)] after meeting criterion B and achieving the maximum level of an individual patient (criterion R).

Statistical analysis

In consideration of the retrospective nature of our study and unavoidable biases in selection of enrolled patients, we restricted the statistics to descriptive analysis. The chi-square test was used to compare categorical variables.

Ethics

The guidelines of the Helsinki Declaration and the ethics guidelines for epidemiological research in Japan were

followed. The study protocol was approved by the Institutional Ethics Committee of the Tokyo Medical and Dental University Hospital (protocol #853 in 2010). The ethics guideline for epidemiological research in Japan requires notifying eligible RA patients of this study and allows implementation of this study without obtaining individual written informed consent. This study was publicized by leaflets or posters in outpatient clinics of each participating institute and on the website of the Department of Pharmacovigilance of the Tokyo Medical and Dental University. Patients were excluded from the study when they expressed unwillingness to participate in this study.

Results

Of the 198 patients enrolled in the study, 151 received biological DMARDs (IFX, 44; ETN, 50; ADA, 33; TCZ, 24) (biological DMARDs group) and 47 received MTX without biological DMARDs (MTX group). Baseline characteristics of the biological DMARDs and MTX group are given in Table 1. Patients from the MTX group were numerically older, had shorter disease duration for RA, had lower serum KL-6 levels at baseline, and used lower doses of MTX. The mean observation period was 11.2 months, and 87.9 % patients were observed for 12 months.

Overall, 41 of 198 patients met criterion A, 32 criterion B, and 8 criterion C, for elevation of serum KL-6 levels at least once by month 12. Percentages (incidence rate/100 PY) of 151 patients in the biological DMARDs group patients who met the criteria by month 12 were 21.9 % (23.1/100PY) for criterion A, 7.9 % (18.9/100PY) for criterion B, and 3.3 % (3.5/100PY) for criterion C. The percentages of patients who met criterion A or B in the biological DMARDs group were higher than those for the MTX group (21.9 versus 17.0 % for criterion A, 17.9 versus 10.6 % for criterion B, respectively), but lower for criterion C (3.3 versus 6.4 %, respectively) (Table 2). In the biological DMARDs group, patients treated with TCZ showed lower incidence of elevation of serum KL-6 levels compared with tumor necrosis factor (TNF) inhibitors (8.3 % in the TCZ group versus 24.4 % in the TNF inhibitor group for criterion A, 8.3 versus 19.7 % for criterion B, 0 versus 3.0 % for criterion C) (Table 3).

Baseline characteristics of the patients in the biological DMARDs group who did and did not meet criterion B are compared in Table 4. Those who met criterion B were numerically older, had higher percentages of past illnesses

Table 1 Characteristics of the enrolled rheumatoid arthritis patients

	Biological DMARDs group ($n = 151$)	MTX group ($n = 47$)
Gender (female) (%)	75.5	70.2
Mean age (years)	59.1 ± 13.3	63.3 ± 11.3
Mean disease duration for RA (months)	99.2 ± 110.2	40.6 ± 68.0
Comorbidity		
Interstitial pneumonia (%)	30.5	19.1
Other pulmonary disease (%)	9.9	21.3
Past illness		
PCP (%)	0.0	0.0
Malignancy (%)	6.6	8.5
Drug-induced pulmonary disease (%)	2.0	2.1
Others (%)	25.2	38.3
Clinical characteristics		
Baseline KL-6 (U/ml)	375.1 ± 346.8	276.9 ± 141.7
MTX use at month 0 (%)	64.2	100
Mean dose of MTX at month 0 (mg/week)	8.5 ± 2.5	5.6 ± 1.3
Mean dose of MTX at month 12 (mg/week)[a]	8.4 ± 2.4	8.2 ± 2.3
Corticosteroid use at month 0 (%)	51.0	40.4
Mean dose of corticosteroid at month 0 (mg/day) (prednisolone equivalent)	6.2 ± 3.4	7.9 ± 8.2
DMARDs other than MTX use at month 0 (%)	25.2	17.0

Values are mean ± SD, unless otherwise stated

RA rheumatoid arthritis, *PCP Pneumocystis jirovecii* pneumonia, *MTX* methotrexate, *DMARDs* disease-modifying antirheumatic drugs, *SD* standard deviation

[a] At month 12 for patients followed up for 12 months and at last observation for patients followed up for less than 12 months

Table 2 Number and percentage of rheumatoid arthritis patients meeting the criteria for elevation of serum KL-6 levels at least once by month 12

	Biological DMARDs group ($n = 151$)		MTX group ($n = 47$)	
	n	%	*n*	%
Criterion A	33	21.9	8	17.0
Criterion B	27	17.9	5	10.6
Criterion C	5	3.3	3	6.4

Criteria A, B, and C for elevation of serum KL-6 levels are defined in "Patients and methods" section

MTX methotrexate, *DMARDs* disease-modifying antirheumatic drugs

Table 3 Number and percentage of rheumatoid arthritis patients in the biological DMARDs group meeting the criteria for elevation of serum KL-6 levels at least once by month 12

	IFX ($n = 44$)		ETN ($n = 50$)		ADA ($n = 33$)		TNF inhibitors[a] Total ($n = 127$)		TCZ ($n = 24$)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Criterion A	10	22.7	11	22.0	10	30.3	31	24.4	2	8.3
Criterion B	8	18.0	8	16.0	9	27.3	25	19.7	2	8.3
Criterion C	4	9.1	1	2.0	0	0	5	3.0	0	0

Criteria A, B, and C for elevation of serum KL-6 levels are defined in "Patients and methods" section

TCZ tocilizumab

[a] TNF inhibitors include infliximab (IFX), etanercept (ETN), and adalimumab (ADA)

other than PCP, IP, and drug-induced lung injury, and had a higher percentage of biological DMARDs-naïve patients at baseline.

We analyzed the association between elevation of serum KL-6 levels and pulmonary events. A total of 11 pulmonary events in 10 patients, including one PCP, two IP, and eight other pulmonary events such as bacterial pneumonia, pneumonia [not otherwise specified (NOS)], pulmonary tuberculosis, interstitial pulmonary shadow (ground-glass opacity and small nodules, NOS), patchy pulmonary shadow in right S10 (NOS), *Mycobacterium avium* complex, drug-induced pneumonia, and pleural effusion (NOS), were reported by month 12; however, no malignancies were reported. In two patients with bacterial pneumonia or interstitial pulmonary shadow, pulmonary lesions were depicted by chest X-ray. In the remaining eight patients, thoracic computed tomography identified the pulmonary lesions.

Five patients in the biological DMARDs group and one patient in the MTX group met both criteria A and B with one or two of these pulmonary events. In these cases, serum KL-6 levels were elevated around 1 month or less before or after the onset of the pulmonary events. When we restricted the pulmonary events to IP, PCP, and interstitial pulmonary shadow, to which elevation of serum KL-6 levels has been attributed in the literature, three patients in the biological DMARDs group and one patient in the MTX group met both criteria A and B with these pulmonary events. However, we could not identify any apparent reasons for elevation of serum KL-6 levels to the criterion B level in 24 patients (15.9 %) in the biological DMARDs group and four patients (8.5 %) in the MTX group.

Changes in serum KL-6 levels in patients who met criterion B without developing IP, PCP, or interstitial pulmonary shadow from the biological DMARDs group ($n = 24$) and MTX group ($n = 4$) are shown in Fig. 1. Of the 24 RA patients in the biological DMARDs group, 10 met criterion R by month 12 (Fig. 1a), 7 did not (Fig. 1b), and 7 lacked available data on serum KL-6 levels after meeting criterion B and reaching their maximum levels (Fig. 1c). Of the 4 RA patients in the MTX group, 3 met criterion R and 1 did not by month 12 (Fig. 1d).

Discussion

Our retrospective analysis of clinical practice data demonstrated that serum KL-6 levels increased without apparent clinical events in a substantial percentage of RA patients during treatment with MTX and/or biological DMARDs. These observations are in agreement with the report from our committee on data derived from clinical trials that were conducted in Japan.

We investigated whether the elevation of serum KL-6 levels in the DMARDs group was induced by biological DMARDs alone, or additively or synergistically by the

Table 4 Baseline characteristics of rheumatoid arthritis patients in the biological DMARDs group who did or did not meet criterion B for elevation of serum KL-6 levels

	Meeting criterion B ($n = 27$)	Not meeting criterion B ($n = 124$)
Gender (female) (%)	70.4	76.6
Mean age (years)	63.5 ± 9.7	58.1 ± 13.8
Mean disease duration (months)	100.6 ± 120.3	98.9 ± 108.4
Comorbidity		
Interstitial pneumonia (%)	44.4	27.4
Other pulmonary disease (%)	7.4	10.5
Past illness		
PCP (%)	0.0	0.0
Malignancy (%)	0.0	8.1
Drug-induced pulmonary disease (%)	0.0	2.4
Others (%)	37.0	22.6
Clinical characteristics		
Baseline KL-6 (U/ml)	419.5 ± 180.1	365.4 ± 373.3
MTX use at month 0 (%)	63.0	64.5
Mean dose of MTX at month 0 (mg/week)	8.3 ± 3.0	8.6 ± 2.5
Corticosteroid use at month 0 (%)	51.9	50.8
Mean dose of corticosteroid at month 0 (mg/day) (prednisolone equivalent)	6.5 ± 2.0	6.1 ± 3.6
DMARDs other than MTX use at month 0 (%)	22.2	25.8
Biological DMARDs-naïve (%)	92.6	74.2

Criterion B for elevation of serum KL-6 levels is defined in "Patients and methods" section

Values are mean ± SD, unless otherwise stated

RA rheumatoid arthritis, *PCP Pneumocystis jirovecii* pneumonia, *MTX* methotrexate, *DMARDs* disease-modifying antirheumatic drugs, *SD* standard deviation

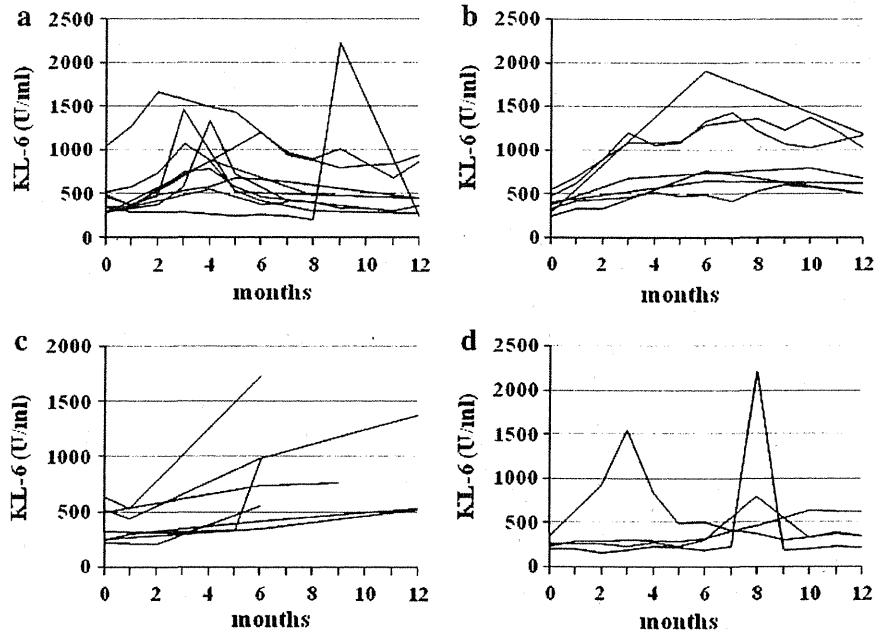

Fig. 1 Changes in serum KL-6 levels of rheumatoid arthritis patients meeting criterion B at least once during the observation period without apparent clinical events are shown. Data from the biological disease-modifying antirheumatic drugs (DMARDs) group: data from 10 patients meeting criterion R by month 12 (**a**), data from 7 patients not meeting criterion R by month 12 (**b**), and data from 7 patients without available data on serum KL-6 levels after meeting criterion B and reaching their maximum levels (**c**). **d** Data from the MTX group

combination of biological DMARDs and MTX. The percentages of patients with concomitant use of MTX were similar for patients who did and did not meet criterion B in the biological DMARDs group (63.0 versus 64.5 %) (Table 4). However, 5 (10.6 %) of 47 RA patients given MTX without biological DMARDs met criterion B (Table 2), and 4 (8.5 %) of these had any apparent reasons for the elevation of serum KL-6 levels. In our other study utilizing data from clinical trials [18], 3 (2.0 %) out of 149 patients given MTX + placebo met criterion B by week 24 or 28 without associated pulmonary events. These data indicate that we should consider potential contribution of MTX to the elevation of serum KL-6 levels during treatment with TNF inhibitor plus MTX.

A possible explanation for the elevation of serum KL-6 levels without apparent clinical events would be the presence of subclinical IP or PCP. We had 22 patients with serum levels of SP-D, another serum marker for interstitial lung disease [19], at both baseline and at least one additional time point, and we exploratory analyzed these data. Of the 22 patients, only two showed significant elevation of SP-D [defined as max. SP-D $\geq$110 ng/ml (upper limit of normal in Japan) and >1.5-fold from baseline] and both of these patients met criterion B. One of them developed PCP with simultaneous elevation of serum KL-6 and SP-D levels while he was receiving MTX without a biological DMARD. The other met criterion B without any pulmonary events 6 months after commencement of IFX with MTX and showed elevation of serum SP-D level 6 months after meeting criterion B. This patient did not have other available data for serum SP-D levels. Of the remaining 20 patients with serum SP-D levels reported, 5 patients met and 15 did not meet criterion B without significant elevation of SP-D. It appeared to be difficult to draw a definite conclusion from these data. In 20 of 33 patients who met criterion A in the biological DMARDs group, serum levels of β-D-glucan, a marker for PCP [15], were measured at the time of the elevation of serum KL-6 levels (data not shown), but did not increase throughout the observation period. These data suggest that subclinical PCP has a relatively low possibility of being the reason for the elevation of serum KL-6 levels.

In the normal state, bronchiolar epithelial cells and bronchial gland cells, as well as type II alveolar epithelial cells, produce KL-6. When lung injury occurs, proliferation or regeneration of alveolar type II cells and increased alveolar–capillary permeability have been reported to be mechanisms for the elevation of serum KL-6 levels [20]. However, the relationship between these mechanisms and the use of biological DMARDs or MTX is unknown, and further pathophysiological studies will be required to clarify the mechanism for spontaneous elevation of serum KL-6 levels during treatment with these drugs.

In our study, patients treated with TNF inhibitors had higher incidence of elevation of serum KL-6 levels meeting criterion A or B than patients treated with TCZ (Table 3). Because we could not avoid selection bias and recall bias in our study, we deliberately did not perform further statistical analyses. Prospective studies or analysis of clinical trial data may help clarify whether abnormal elevation of serum KL-6 levels is more frequently observed in patients given TNF inhibitors than in those given other classes of biological DMARDs.

How should rheumatologists manipulate treatment for RA patients given biological DMARDs when their serum KL-6 levels are elevated in clinical practice? Taking the established evidence for KL-6 into account, rheumatologists initially should compare chest X-ray or thoracic CT at baseline and at elevation of serum KL-6 levels and search for reasons for the elevation, such as PCP, IP, and malignancy. When these adverse events are not identified, continuing treatment with biological DMARDs under careful observation is a reasonable option for RA patients who have shown good responses to the treatments.

In summary, serum KL-6 levels may increase without associated clinical conditions in patients receiving biological DMARDs or MTX. Spontaneous reduction of serum KL-6 levels was observed in the majority of these patients; therefore continuing treatment with biological DMARDs under careful observation is a reasonable option in this clinical situation.

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OPEN ACCESS

EXTENDED REPORT

Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA)

Maxime Dougados,[1,2] Martin Soubrier,[3] Anna Antunez,[4] Peter Balint,[5] Alejandro Balsa,[6] Maya H Buch,[7,8] Gustavo Casado,[9] Jacqueline Detert,[10] Bassel El-zorkany,[11] Paul Emery,[7,8] Najia Hajjaj-Hassouni,[12] Masayoshi Harigai,[13] Shue-Fen Luo,[14] Reka Kurucz,[5] Gabriel Maciel,[15] Emilio Martin Mola,[16] Carlo Maurizio Montecucco,[17] Iain McInnes,[18] Helga Radner,[19] Josef S Smolen,[19] Yeong-Wook Song,[20] Harald Erwin Vonkeman,[21] Kevin Winthrop,[22] Jonathan Kay[23]

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For numbered affiliations see end of article.

Correspondence to
Professor Maxime Dougados, Rhumatologie B, Hôpital Cochin, 27 rue du Fg Saint-Jacques, Paris 75014, France; maxime.dougados@cch.aphp.fr

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ABSTRACT

Background Patients with rheumatoid arthritis (RA) are at increased risk of developing comorbid conditions.

Objectives To evaluate the prevalence of comorbidities and compare their management in RA patients from different countries worldwide.

Methods *Study design*: international, cross-sectional. *Patients*: consecutive RA patients. *Data collected*: demographics, disease characteristics (activity, severity, treatment), comorbidities (cardiovascular, infections, cancer, gastrointestinal, pulmonary, osteoporosis and psychiatric disorders).

Results Of 4586 patients recruited in 17 participating countries, 3920 were analysed (age, 56±13 years; disease duration, 10±9 years (mean±SD); female gender, 82%; DAS28 (Disease Activity Score using 28 joints)–erythrocyte sedimentation rate, 3.7±1.6 (mean±SD); Health Assessment Questionnaire, 1.0±0.7 (mean±SD); past or current methotrexate use, 89%; past or current use of biological agents, 39%. The most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5%; chronic obstructive pulmonary disease, 3.5%. High intercountry variability was observed for both the prevalence of comorbidities and the proportion of subjects complying with recommendations for preventing and managing comorbidities. The systematic evaluation of comorbidities in this study detected abnormalities in vital signs, such as elevated blood pressure in 11.2%, and identified conditions that manifest as laboratory test abnormalities, such as hyperglycaemia in 3.3% and hyperlipidaemia in 8.3%.

Conclusions Among RA patients, there is a high prevalence of comorbidities and their risk factors. In this multinational sample, variability among countries was wide, not only in prevalence but also in compliance with recommendations for preventing and managing these comorbidities. Systematic measurement of vital signs and laboratory testing detects otherwise unrecognised comorbid conditions.

INTRODUCTION

The long-term prognosis of rheumatoid arthritis (RA) has improved dramatically following the introduction of highly effective medications, such as methotrexate leflunomide and biological agents,[1 2] and as the result of close monitoring and regular adjustment of treatment to the targets of low disease activity or remission.[3] However, comorbidities may shorten the life span of patients with RA.[4–6] This higher death rate appears to be the consequence of an increased prevalence of cardiovascular disease, a greater incidence of infections, and the development of certain malignancies in patients with RA.[7–11] Also, osteoporotic fractures are more commonly observed in patients with RA and significantly affect the prognosis for functional decline.[12 13] In addition, RA patients with more comorbidities experience greater functional impairment.[14]

Some of these comorbidities are observed more often among RA patients because of the medications with which they are treated, especially glucocorticoids,[10] and because of traditional risk factors, such as tobacco smoking.[15] However, chronically active inflammation also predisposes to the development of these comorbidities.[16]

Unfortunately, comorbidities are not well managed in RA patients.[17–20] To address this disparity, the European League Against Rheumatism (EULAR) proposed specific recommendations for detecting and managing specific comorbidities and preventing their development when possible. These include recommendations that all patients with RA should be vaccinated against influenza every year and against pneumococci every 5 years[21] and should be evaluated for cardiovascular risk annually. Because chronically active inflammation contributes to the development of cardiovascular disease, these recommendations suggest that the cardiovascular risk score be multiplied by a factor of 1.5 when two of the following three criteria are met: (1) disease duration longer than 10 years; (2) presence of circulating rheumatoid factor or anti-citrullinated protein antibodies; (3) presence of extra-articular manifestations.[22]

The COMORA (COMOrbidities in Rheumatoid Arthritis) Study had two major objectives. The first was to evaluate variability in the prevalence of comorbidities and their risk factors between participating countries. The second was to assess whether there is a disparity between existing national recommendations and the actions implemented in daily clinical practice to detect and prevent the development of these comorbidities.

PATIENTS AND METHODS

Study design

This was a cross-sectional, observational, multicentre, international study.

Patient recruitment

The scientific committee chose national principal investigators for this study. Their task was to select rheumatologists who would be representative of their country and to conduct the study in accordance with good clinical practice. The protocol was reviewed and approved by all local institutional review boards or ethics committees. Consecutive patients visiting the participating rheumatologists were invited to enrol in the study if they were at least 18 years of age, fulfilled the 1987 American College of Rheumatology classification criteria for RA,[23] and were able to understand and complete the questionnaires that were administered. Written informed consent was obtained from all subjects before enrolment.

Sample size

The sample size calculation was based on the precision (width) of the 95% CI of the proportions of expected events (eg, prevalence of each comorbidity). For example, it was calculated that a sample of 4000 patients would allow the 35% prevalence of a given comorbidity, X, to be estimated with a precision of 1.5% (95% CI 33.5% to 36.5%), or the 1% prevalence of another comorbidity, Y, to be estimated with a precision of 0.3% (95% CI 0.7% to 1.3%).

Investigators in each participating country were expected to enrol at least 200 patients.

Data collected

A case report form specifically created for this study was used to collect four categories of data.

1. *Characteristics of demographics and the disease.* Patients' demographic characteristics included: age, gender, body mass index, smoking status, alcohol intake, marital status, socioeconomic status and highest level of education completed. Disease activity was assessed using the DAS28 (Disease Activity Score using 28 joints)–erythrocyte sedimentation rate (ESR)[24] and the C-reactive protein level. Disease severity was evaluated from the history of joint surgery to address structural damage caused by RA (eg, total joint arthroplasty, arthrodesis, metacarpophalangeal or metatarsophalangeal joint resections). Past and current medications used to treat RA were also recorded, including non-steroidal anti-inflammatory drugs, corticosteroids and conventional and biological disease-modifying antirheumatic drugs (DMARDs).
2. *History or current evidence of comorbidities.* Ischaemic cardiovascular disease (myocardial infarction, stroke), cancers (colon, skin, lung, breast and uterus for women, prostate for men) and lymphoma, gastrointestinal diseases (diverticulitis, ulcers), infections (hepatitis), lung disease (chronic obstructive pulmonary disease (COPD), asthma) and psychiatric disorders (depression).
3. *Coexisting risk factors.* Risk factors for cardiovascular diseases (hypertension, diabetes, dyslipidaemia, family history of myocardial infarction or sudden death), risk factors for infectious diseases and vaccination status, risk factors for cancers (family history of prostate, breast or colon cancer; adenomatosus polyposis and/or personal history of inflammatory bowel disease (for colon cancer) and history of numerous (>40) nevi for skin cancer).
4. *Compliance with current national recommendations regarding management (prevention, detection and treatment) of these comorbidities.* For example, annual estimation of cardiovascular risk.

For each patient, information was gathered by a study investigator during a face-to-face interview at a dedicated study visit and through review of the medical record.

Data analysis

The first step of the analysis was to describe the baseline characteristics of the enrolled patients, by country, including the prevalence of each comorbidity and associated disease risk factors (% and 95% CI).

To estimate any disparity that might exist between published recommendations and daily clinical practice in the prevention, detection and management of these comorbidities, the percentage of patients monitored and managed according to national guidelines was calculated. The definition of 'optimal' management for the evaluated comorbidities was primarily based on recommendations made by international scientific societies[17 18] and/or national healthcare systems[25] and/or the recommendations of the French Society of Rheumatology to prevent, detect and control comorbidities in patients with inflammatory rheumatic diseases.[26]

For cardiovascular diseases, a patient was considered to be optimally monitored when risk factors for cardiovascular events (eg, blood pressure, blood glucose level, low-density lipoprotein (LDL) cholesterol level) were evaluated annually. Patients older than 50 years were considered to be managed optimally if they were receiving an antithrombotic drug, in the setting of a past thrombotic cardiovascular event, or if their Framingham Risk Score[27] was calculated to be 20% or more above the upper limit of normal after being adjusted for RA (multiplied by a factor of 1.5), in the presence of specific RA characteristics.[22] Finally, we evaluated the proportion of patients in whom the systematic evaluation of risk factors for cardiovascular diseases during the conduct of the study detected hypertension (eg, systolic pressure >140 mm Hg or diastolic pressure >80 mm Hg or >130 mm Hg and 70 mm Hg, respectively, in the setting of concomitant diabetes mellitus[26]), elevated LDL cholesterol (above the targeted value defined with regard to the number of concomitant additional cardiovascular risk factors[28]) and hyperglycaemia (random blood glucose level >1.26 g/L[28]).

A patient was considered to be monitored optimally for infectious diseases if he or she had had (1) a dental examination within the previous year, (2) an influenza vaccination within the previous year, and (3) a pneumococcal vaccination within the previous 5 years.

A patient was considered to be monitored optimally for cancer if age- and sex-appropriate cancer screening recommendations for the general population were followed. A male patient without known prostate cancer was considered to have been screened optimally for prostate cancer if a digital rectal examination and prostate-specific antigen (PSA) level had been performed between the ages of 50 and 75 years (or between the ages of 45 and 75 years for patients of African ancestry) or with at least two first-degree relatives who had prostate cancer. Subsequently, this

evaluation had to have been repeated every 3 years for those with PSA <1 ng/mL and annually for those with PSA between 1 and 4 ng/mL. For men with PSA >4 ng/mL, evaluation by an urologist was required for the patient to be considered to have been monitored optimally.[28] For breast cancer detection, a woman between the ages of 50 and 74 years without known breast cancer was considered to have been screened optimally if a mammogram had been performed within 2 years of the study visit.[28] For uterine cancer detection, a woman between the ages of 25 and 65 years without known uterine cancer was considered to have been monitored optimally if a Papanicolaou smear of the cervix had been performed within 3 years of the study visit.[28] For colon cancer screening, a patient over 50 years old without known colon cancer was considered to have been optimally monitored if stool had been tested for occult blood and at least one colonoscopy had been performed. For those patients at high risk of developing colon cancer (eg, those with inflammatory bowel disease or with at least two first-degree relatives who had colon or rectal cancer or at least one first-degree relative with adenomatous polyposis or with Lynch syndrome), a colonoscopy had to have been performed in the 2 years before the study visit for a patient to be considered to have been optimally monitored.[28] For skin cancer detection, a patient was considered to be optimally monitored if he or she had been examined at least once by a dermatologist; if more than 40 nevi were present, annual evaluation by a dermatologist was required for optimal monitoring.[28] For lung cancer screening, a patient was considered to have been monitored optimally if a chest radiograph had been performed after the onset of RA.[26]

A patient was considered to have been screened optimally for osteoporosis if at least one bone densitometry study had been performed after the onset of RA and if he or she was taking vitamin D supplementation at the time of the study visit.[26]

RESULTS

Patients and study course

A total of 4586 patients were recruited by investigators in the 17 participating countries between 2011 and 2012. Because a disproportionately high number of subjects were enrolled in South Korea (n=1052) compared with each of the other 16 countries, 400 patients from South Korea were randomly selected for inclusion in the analysis. Fourteen patients from a single centre were excluded from the current analysis because of too many missing data, leaving a total of 3920 patients for further evaluation.

The baseline characteristics are summarised in table 1. There was enormous intercountry variability for some characteristics: patients in North Africa tended to have more active and more severe disease, and fewer patients in some South American countries had been treated with biological agents. Detailed comparisons of the baseline characteristics for each individual country are provided in online supplementary tables S1 and S2.

Prevalence of comorbidities

The prevalence of those comorbidities that were evaluated is depicted in figure 1. Depression (past or current symptoms) was the most commonly observed comorbidity (mean 15.0%, 95% CI 13.8% to 16.1%); however, the prevalence of depression varied widely among countries (from 2% in Morocco to 33% in the USA).

There was a history of ischaemic cardiovascular disease (myocardial infarction or stroke) in 6.0% (95% CI 5.3% to 6.8%) of the patients. This prevalence ranged from a low of 1% in Morocco to a high of 17% in Hungary. A history of any solid tumour, excluding basal cell skin cancers, was found in 4.5% (95% CI 3.9% to 5.2%) of the patients and ranged from a low of 0.3% in Egypt to a high of 12.5% in the USA). Hepatitis B infection was observed more frequently in Italy (9%) and Taiwan (7%) than in other countries (2.8% (95% CI 2.3% to 3.3%)). The prevalence of hepatitis C infection was highest in Italy (6.6%), Egypt (6.8%) and Taiwan (4.8%). The overall prevalence of past or present gastrointestinal ulcer was 10.8% (95% CI 9.8% to 11.8%). This ranged from a low of 1% in Morocco to a high of 22% in Egypt. Episodes of diverticulitis that had required surgical intervention were rarely observed (0.4% (95% CI 0.2% to 0.6%)). Pulmonary diseases, especially COPD, were observed less commonly in Asian countries (Japan, 1.4%; Korea, 1.3%; Taiwan, 0.3%) than in European countries or the USA (Hungary, 8.0%; USA, 7.5%). Detailed listings by country of the prevalence of the various comorbidities, grouped by category, are presented in online supplementary tables S3–S7.

Table 1 Baseline patient and disease characteristics of the 3920 analysed patients enrolled in the COMORA Study

	Results	
Variable	**Global results**	**Extremes (countries)**
Number	3920	From 30 (Uruguay) to 411 (France)
Female gender (%)	81.7	From 66 (Netherlands) to 91 (Venezuela)
Age (years), mean±SD	56±13	From 48 (Morocco/Egypt) to 63 (Japan)
Smoking status (% current smokers)	13.2	From 0.9 (Morocco) to 48 (Austria)
Educational level (% university or graduate school)	24.5	From 5.3 (Italy) to 75 (Netherlands)
Marital status (% married)	69.7	From 50 (Venezuela) to 86 (Netherlands)
BMI (% overweight or obese)	50.7	From 0 (Netherlands) to 69 (USA)
Work status (% currently employed)	31.4	From 16 (Morocco) to 46 (USA)
Disease duration (years), mean±SD	9.6±8.7	From 7 (Morocco) to 14 (France)
DAS28–ESR, mean±SD	3.7±1.6	From 2.6 (Netherlands) to 5.3 (Egypt)
HAQ, mean±SD	1.0±0.7	From 0.7 (Taiwan) to 1.5 (Morocco)
Prednisone (% currently taking)	54.3	From 9 (UK) to 82 (Morocco)
NSAID use (% having taken dose during previous 3 months)	55.2	From 25 (Morocco) to 94 (Taiwan)
MTX (% ever treated)	88.6	From 79 (Italy) to 98 (UK)
Any biological therapy (% ever treated)	38.9	From 3 (Uruguay) to 77 (UK)

BMI, body mass index; DAS28–ESR, Disease Activity Score using 28 joints–erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug.

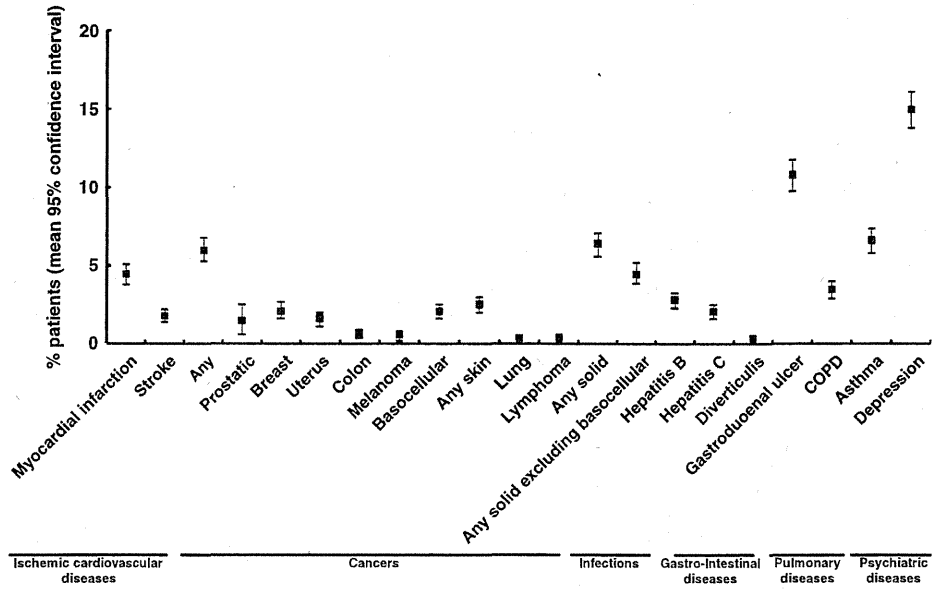

Figure 1 Prevalence of evaluated comorbidities in the 3920 patients with rheumatoid arthritis. COPD, chronic obstructive pulmonary disease.

Prevalence of risk factors for comorbidities

The prevalence of various risk factors for cardiovascular disease and several malignancies is depicted in figure 2. As might be expected, given the increased prevalence of cardiovascular disease associated with RA, the most prevalent risk factors were those that predispose to cardiovascular disease, such as increased Framingham Risk Score (42.8% (95% CI 41.2% to 44.3%)), hypertension (40.4% (95% CI 38.9% to 41.9%)) and hypercholesterolaemia (31.7% (95% CI 30.3% to 33.2%)). As with the prevalence of comorbidities, there was considerable intercountry variability in the prevalence of risk factors. For example, the prevalence of smoking ranged from 3% in Morocco to 48% in Austria. Detailed listings by country of the prevalence of the various risk factors, grouped by comorbidity, are presented in online supplementary tables S8 and S9.

Management of comorbidities

Cardiovascular diseases

Annual evaluation of cardiovascular risk, including measurement of blood pressure, total serum cholesterol (high-density lipoprotein (HDL) and LDL), blood glucose and serum creatinine, was performed in 59.4% (95% CI 57.9% to 60.9%) of the patients. Of the 236 patients who had a prior myocardial infarction or stroke, 162 (68.6%) were currently receiving an antithrombotic drug, but 74 (31.4%) were not. Among the other 3684 patients who had no history of myocardial infarction or stroke, 366 would appropriately have been given prophylactic antithrombotic drug treatment because they were older than 50 years and had a calculated Framingham Risk Score above 20%; however, of these, 299 were not receiving any antithrombotic agent. Thus, 373 (9.5%) of the total number of patients

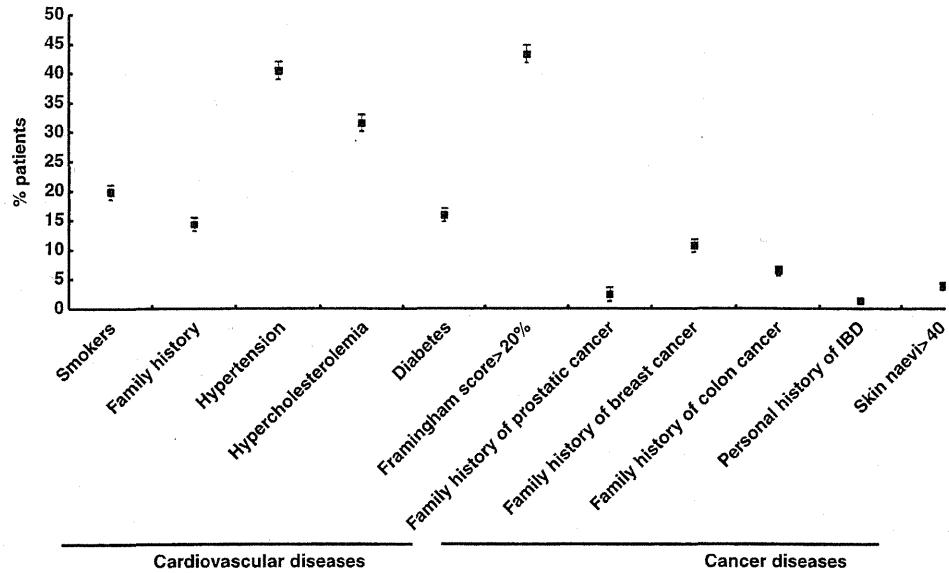

Figure 2 Prevalence of risk factors for cardiovascular and cancer diseases in the 3920 patients with rheumatoid arthritis. IBD, inflammatory bowel disease.

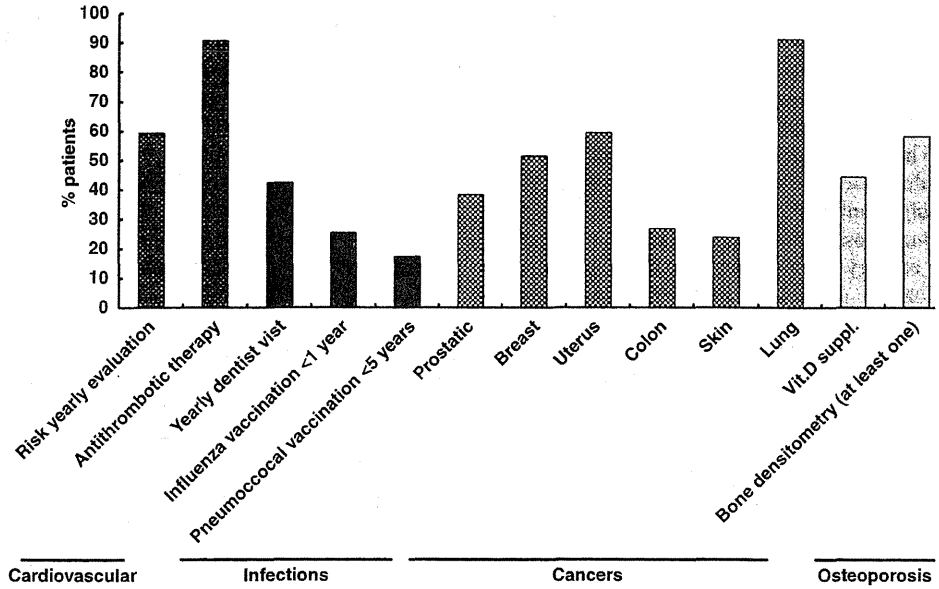

Figure 3 Percentage of patients optimally monitored with respect to some comorbidities. Vit.D suppl., vitamin D supplementation.

enrolled in this study should have been treated with antithrombotic drug prophylaxis, but were not being managed optimally to prevent cardiovascular events (figure 3).

The systematic assessment of certain cardiovascular risk factors in this study allowed their detection in previously undiagnosed patients. Among the 2489 patients without known hypertension, elevated blood pressure was detected in 454 (18%). An elevated blood glucose level was detected in 131 (3.7%) of the 3522 patients without previously diagnosed diabetes mellitus. An LDL cholesterol level above the optimal target was detected in 325 (11.0%) of the 2966 patients not previously diagnosed to have a dyslipidaemia or not receiving lipid-lowering therapy.

Infectious diseases

During the year before the study visit, 42.3% (95% CI 40.8% to 43.9%) of all 3920 enrolled patients had undergone a dental examination. However, fewer patients were vaccinated in accordance with current recommendations: an influenza vaccination had been performed during the year before the study visit in only 938 (25.3% (95% CI 23.9% to 26.7%)) of the patients and a pneumococcal vaccination had been performed within 5 years of the study visit in only 636 (17.2% (95% CI 16.0% to 18.4%)) of the patients. Both an influenza and a pneumococcal vaccination were performed according to current recommendations in only 316 (10.3% (95% CI 9.3% to 11.4%)) of the patients.

Cancers

Optimal screening for malignancies, according to recommended guidelines, was performed in only 909 (23.9%) of the patients for skin cancers, 608 (26.7%) of the patients for colon cancer, 202 (38.2%) of the patients for prostate cancer, 938 (51.5%) of the patients for breast cancer, and 1383 (59.3%) of the patients for uterine cancer.

Osteoporosis

Bone densitometry had been performed at least once in 2281 (58.2% (95% CI 56.6% to 59.7%)) of the 3920 patients. Of all enrolled patients, 1733 (44.4% (95% CI 42.9% to 46.0%)) were receiving vitamin D supplementation at the time of the study visit.

Detailed listings by country of the percentage of patients optimally monitored for cardiovascular, infectious and cancer diseases are presented in online supplementary tables S10–S12.

DISCUSSION

This is the first population-based, cross-sectional observational study to assess multiple comorbidities and their management among a relatively large sample of patients with RA who were enrolled by rheumatologists in 17 participating countries on five different continents. This study confirms not only the relatively high prevalence of comorbidities among patients with RA, but also considerable intercountry variability in the prevalence of these comorbidities.[29] It demonstrates that, at present, the management of comorbidities in patients with RA is far from optimal. As in this study, the systematic evaluation of RA patients for evidence of comorbidities may uncover previously undiagnosed conditions in some patients.

An important aim of this study was to evaluate the gap between current recommendations for detecting, managing and preventing comorbidities and their implementation in observed daily practice. To accomplish this objective, the scientific committee for the study created an a priori definition of optimal monitoring based largely on current recommendations provided by various international medical organisations. The optimal LDL cholesterol level on which the analysis of this study was based is that currently recommended by the French Ministry of Health,[28] and this standard was applied to all study subjects in all participating countries regardless of local recommendations. However, for comorbidities such as cardiovascular disease, definitions were country-specific, and recommendations for monitoring or prevention varied slightly between participating countries. For example, the indication for initiation of antithrombotic drug prophylaxis was a history of a prior cardiovascular event in some countries and a >20% risk of experiencing a cardiovascular event based on the Framingham Risk Score in others.[27] Had this study used other standards for the detection, management and

prevention of comorbidities,[30 31] it might have found slightly different proportions. Regardless, this study demonstrates that compliance with recommended strategies is far from perfect and that this varies significantly among countries.

Although this study has numerous strengths, it also has several weaknesses. The comorbidities evaluated were selected for the study by the scientific committee and were not all-inclusive; some important comorbidities, such as tuberculosis, were not among those assessed. Despite the principal investigators in each country having been instructed to recruit rheumatologists working in different practice settings to enrol RA patients, it cannot be guaranteed that the prevalent cohort of 3920 patients studied here were fully representative of all RA patients in the participating countries. The study did not enrol RA patients from general practices who were not under the care of a rheumatologist. Moreover, some of the intercountry variability in the degree of RA disease activity observed in this study might reflect differences in the reason for which the patient was visiting the rheumatologist at the time of study participation: in some countries, patients are evaluated routinely even when their RA is under good control, whereas, in other countries, patients go to see their rheumatologist only when they experience a flare of disease activity. Also, cultural differences among patients recruited from different countries might lead to diverse interpretations of questions included in the questionnaire. Varied interpretation of the term 'depression' by subjects in different countries could account, in part, for the wide differences observed across countries in the prevalence of depression.

Several different types of bias are inherent in a prevalent cohort study of a chronic disease. The prevalence of some comorbidities might be overestimated because of diagnostic bias, in that patients with RA may more likely be offered screening for recognised comorbidities, or because of reporting bias, in that RA patients may more likely be diagnosed with comorbidities known to be associated with this inflammatory disease. The prevalence of other comorbidities might be underestimated because of truncation bias, in that RA patients with potentially life-threatening comorbidities may have been lost from the population before the cohort was enrolled. These biases may produce diverse effects in different countries. The lack of a comparator group without RA did not allow comparison in this study between the observed prevalence of comorbidities and their optimal management among RA patients with that in the general population or among patients with another disease state.

This study achieved its main objective, which was to evaluate and demonstrate intercountry variation in the detection, management and prevention of comorbidities among RA patients. It shows clear differences in the prevalence of certain risk factors, which might influence national policies regarding prevention strategies. For example, the high prevalence of tobacco smoking found among RA patients in the Netherlands (41.2%) and Austria (47.5%) might prompt targeted programmes to reduce this behaviour, which clearly predisposes not only to the development of RA,[32] but also to cardiovascular disease[33] and lung cancer,[34] both of which are also significant comorbidities of RA. Other studies that have compared the prevalence of comorbidities among RA patients with those in the general population have shown a higher prevalence of cardiovascular events,[8] infections,[10 11] osteoporotic fractures[12] and lung cancer[14] among RA patients. Nevertheless, the relatively large sample of RA patients who were enrolled from 17 countries on various continents allowed the present study to confirm the high prevalence of hepatitis in Asian[35 36] and southern European countries[37] and in Egypt.[38 39]

This study confirms the observation that monitoring of RA patients for cardiovascular risk is suboptimal[19 40–42] and extends this assumption to other comorbidities. Moreover, it demonstrates that systematic assessment of RA patients for comorbidities facilitates the detection of abnormalities such as elevated blood pressure, hyperglycaemia and hypercholesterolaemia. These findings are in agreement with those of previous studies that suggested that cardiovascular risk factors are not optimally monitored and managed in 30–50% of RA patients.[40 41]

Given the findings of the present study, the question arises as to how best to improve this situation. The treating rheumatologist should consider the periodic assessment of comorbidities as one of the tasks involved in treating a patient with RA. This should be carried out in collaboration with primary care providers and other specialists who are involved in the care of these patients. However, the increasing complexity of managing treatment of RA with effective combinations of traditional and biological DMARDs in the setting of progressively decreasing amounts of time available for direct interaction with the patient makes this additional responsibility challenging. The development and implementation of standardised programmes to detect, manage and prevent comorbidities in daily clinical practice, working in partnership with other healthcare providers such as nurses,[42 43] might greatly facilitate the identification of and intervention to reduce the prevalence of comorbidities among patients with RA.

Author affiliations
[1]Medicine Faculty, Paris-Descartes University, Paris, France
[2]Rheumatology B Department, APHP, Cochin Hospital, Paris, France
[3]Department of Rheumatology, CHU Clermont-Ferrand, France
[4]Rheumatology Unit, Central Hospital "Dr Urquinaona", Maracaibo, Venezuela
[5]3rd Rheumatology Department, National Institute of Rheumatology and Physiotherapy, Budapest, Hungary
[6]Rheumatology Unit, La Paz University Hospital, Madrid, Spain
[7]Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds, UK
[8]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS, UK
[9]Department of Rheumatology, Hospital Militar Central, Buenos Aires, Argentina
[10]Rheumatology Department, Charité University Medicine, Berlin, Germany
[11]Department of Rheumatology, Cairo University, Cairo, Egypt
[12]Rheumatology Department, El Ayachi Hospital, Salé, Morocco
[13]Department of Pharmacovigilance, Tokyo Medical and Dental University, Tokyo, Japan
[14]Department of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital and Chang Gung University, Tao-Yuan, Taiwan
[15]Clínica Médica 1, Hospital Maciel, Universidad de la República, Montevideo, Uruguay
[16]Department of Rheumatology, La Paz University Hospital, Madrid, Spain
[17]Division of Rheumatology, IRCCS policlinico S. Matteo foundation, University of Pavia, Pavia, Italy
[18]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, Scotland
[19]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, and 2nd Department of Medicine, Hietzing Hospital, Vienna, Austria
[20]Department of Rheumatology, Seoul National University Hospital, Seoul, Korea
[21]Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente and University of Twente, Enschede, The Netherlands
[22]Division of Infectious Diseases, Public Health and Preventive Medicine, Oregon Health and Science University, Portland, Oregon, USA
[23]Division of Rheumatology, Department of Medicine, University of Massachusetts Medical School and UMass Memorial Medical Center, Worcester, Massachusetts, USA

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A Delphi Exercise to Identify Characteristic Features of Gout — Opinions from Patients and Physicians, the First Stage in Developing New Classification Criteria

Rebecca L. Prowse, Nicola Dalbeth, Arthur Kavanaugh, Adewale O. Adebajo, Angelo L. Gaffo, Robert Terkeltaub, Brian F. Mandell, Bagus P.P. Suryana, Claudia Goldenstein-Schainberg, Cèsar Diaz-Torne, Dinesh Khanna, Frederic Lioté, Geraldine Mccarthy, Gail S. Kerr, Hisashi Yamanaka, Hein Janssens, Herbert F. Baraf, Jiunn-Horng Chen, Janitzia Vazquez-Mellado, Leslie R. Harrold, Lisa K. Stamp, Mart A. Van De Laar, Matthijs Janssen, Michael Doherty, Maarten Boers, N. Lawrence Edwards, Peter Gow, Peter Chapman, Puja Khanna, Philip S. Helliwell, Rebecca Grainger, H. Ralph Schumacher, Tuhina Neogi, Tim L. Jansen, Worawit Louthrenoo, Francisca Sivera, And William J. Taylor

ABSTRACT. ***Objective.*** To identify a comprehensive list of features that might discriminate between gout and other rheumatic musculoskeletal conditions, to be used subsequently for a case-control study to develop and test new classification criteria for gout.

Methods. Two Delphi exercises were conducted using Web-based questionnaires: one with physicians from several countries who had an interest in gout and one with patients from New Zealand who had gout. Physicians rated a list of potentially discriminating features that were identified by literature review and expert opinion, and patients rated a list of features that they generated themselves. Agreement was defined by the RAND/UCLA disagreement index.

Results. Forty-four experienced physicians and 9 patients responded to all iterations. For physicians, 71 items were identified by literature review and 15 more were suggested by physicians. The physician survey showed agreement for 26 discriminatory features and 15 as not discriminatory. The patients identified 46 features of gout, for which there was agreement on 25 items as being discriminatory and 7 items as not discriminatory.

Conclusion. Patients and physicians agreed upon several key features of gout. Physicians emphasized objective findings, imaging, and patterns of symptoms, whereas patients emphasized severity, functional results, and idiographic perception of symptoms. (First Release Feb 15 2013; J Rheumatol 2013;40:498–505; doi:10.3899/jrheum.121037)

Key Indexing Terms:
GOUT CLASSIFICATION CRITERIA PATIENTS PHYSICIANS

From the University of Otago, Dunedin, New Zealand; University of Auckland, Auckland, New Zealand; Veterans Affairs Healthcare System, University of California, San Diego, California, USA; University of Sheffield, Sheffield, UK; Veterans Affairs Medical Center and University of Alabama at Birmingham, Birmingham, Alabama, USA; CCF Lerner College of Medicine of Case Western Reserve University, The Cleveland Clinic, Cleveland, Ohio, USA; Brawijaya University and Dr. Saiful Anwar Hospital, Malang, Indonesia; Faculdade de Medicina da Universidade de São Paulo e Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; University of Michigan, Ann Arbor, Michigan, USA; University Paris Diderot, Sorbonne Paris Cité and Hôpital Lariboisière, Paris, France; University College Dublin, Dublin, Ireland; Veterans Affairs Medical Center, Georgetown and Howard Universities, Washington, DC, USA; Tokyo Women's Medical University, Tokyo, Japan; Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; The Center for Rheumatology and Bone Research, Arthritis and Rheumatism Associates, Wheaton, Maryland, USA; China Medical University, China Medical University Hospital, Taichung, Taiwan; Hospital General de Mexico, Mexico City, Mexico; University of Massachusetts Medical School, Worcester, Massachusetts, USA; University of Otago, Christchurch, New Zealand; Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, The Netherlands; Department of Rheumatology, Rijnstate, Arnhem, The Netherlands; University of Nottingham, Nottingham, UK; VU University Medical Center, Amsterdam, The Netherlands; University of Florida, Gainesville Florida, USA; Counties-Manukau District Health Board, Auckland, New Zealand; Canterbury District Health Board, Christchurch, New Zealand; University of Leeds, Leeds, UK; University of Otago, Wellington, New Zealand; University of Pennsylvania and Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA; Boston University School of Medicine, Boston, Massachusetts, USA; Department of Rheumatology, Radboud University Nijmegen Medisch Centrum, Nijmegen, The Netherlands; Chiang Mai University, Chiang Mai, Thailand; and Hospital General de Elda and Universidad Miguel Hernandez, Alicante, Spain.

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R.L. Prowse, BSc, University of Otago; N. Dalbeth, MD, University of Auckland; A. Kavanaugh, MD, Veterans Affairs Healthcare System, University of California; A.O. Adebajo, MD, University of Sheffield; A.L. Gaffo, MD, MPH, Veterans Affairs Medical Center, University of Alabama at Birmingham; R. Terkeltaub, MD, Veterans Affairs Healthcare System, University of California; B.F. Mandell, MD, CCF Lerner College

of Medicine of Case Western Reserve University, The Cleveland Clinic; B.P.P. Suryana, MD, Brawijaya University, Dr. Saiful Anwar Hospital; C. Goldenstein-Schainberg, MD, Faculdade de Medicina da Universidade de São Paulo, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; C. Diaz-Torne, MD, Hospital de la Santa Creu i Sant Pau; D. Khanna, MD, MS, University of Michigan; F. Lioté, MD, University Paris Diderot, Sorbonne Paris Cité, Hôpital Lariboisière; G. McCarthy, MD, University College Dublin; G.S. Kerr, MD, Veterans Affairs Medical Center, Howard Universities; H. Yamanaka, MD, Tokyo Women's Medical University; H. Janssens, MD, Department of Primary and Community Care, Radboud University Nijmegen Medical Centre; H.F. Baraf, MD, The Center for Rheumatology and Bone Research, Arthritis and Rheumatism Associates; J-H. Chen, MD, China Medical University, China Medical University Hospital; J. Vazquez-Mellado, MD, Hospital General de Mexico; L.R. Harrold, MD, MPH, University of Massachusetts Medical School; L.K. Stamp, MD, University of Otago; M.A. van de Laar, MD, Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente; M. Janssen, MD, Department of Rheumatology, Rijnstate; M. Doherty, MD, University of Nottingham; M. Boers, MD, VU University Medical Center; N.L. Edwards, MD, University of Florida; P. Gow, MBChB, Counties-Manukau District Health Board; P. Chapman, MD, Canterbury District Health Board; P. Khanna, MD, University of Michigan; P.S. Helliwell, MD, PhD, University of Leeds; R. Grainger, MBChB, PhD, University of Otago; H.R. Schumacher, MD, University of Pennsylvania, Veterans Affairs Medical Center; T. Neogi, MD, MPH, Boston University School of Medicine; T.L. Jansen, MD, Department of Rheumatology, Radboud University Nijmegen Medisch Centrum; W. Louthrenoo, MD, Chiang Mai University; F. Sivera, MD, Hospital General de Elda, Universidad Miguel Hernandez; W.J. Taylor, MBChB, PhD, University of Otago.

Address correspondence to Prof. W. Taylor, Department of Medicine, University of Otago Wellington, PO Box 7343, Wellington 6242, New Zealand. E-mail: Will.taylor@otago.ac.nz

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Gout is characterized by synovial and tissue deposition of monosodium urate crystals[1]. The gold standard diagnostic test for gout is the presence of monosodium urate (MSU) crystals within joint fluid or tissue and this should normally be the preferred approach to diagnosis in clinical practice[2]. However, in some research settings, examination of synovial fluid is impractical. For example, in epidemiological studies or in studies of patients recruited from primary care, there may not be access to synovial fluid microscopy. In such situations, classification criteria that aim to mimic the diagnostic gold standard are needed[3].

Classification criteria for gout that do not rely upon MSU crystal identification have previously been developed but may not be sufficiently accurate. Malik, *et al*[4] examined the validity of the non-crystal-dependent aspects of these criteria in a hospital-based population, using the gold standard of MSU crystal identification as a comparison group; they found imperfect specificity and sensitivity for the Rome, New York[5], and American Rheumatism Association (ARA)[6] criteria. Janssens, *et al* found limited accuracy of the ARA criteria, with a sensitivity of 80% and specificity of 64% in patients presenting to family practitioners with potential gout symptoms[7]. Both the Rome and New York criteria are heavily dependent on verifying the presence of tophi or MSU crystals within a joint, which is not always achievable in research settings. The rising prevalence of gout[8] and its association with the metabolic syndrome[9] and cardiovascular disease[10] make it important to study the disorder accurately. Therefore better classification criteria for gout are required.

A modification of the ARA criteria, termed the Clinical Gout Diagnosis (CGD) criteria set, was shown to have very high sensitivity (97%) and specificity (96%) in a group of rheumatology clinic patients with crystal-proven gout and other rheumatic diseases (osteoarthritis, spondyloarthritis, rheumatoid arthritis)[11]. However, the non-gout cases in that study did not undergo synovial fluid analysis and the high rate of tophi (81%) in the cohort limit the general applicability. Another novel approach based in primary care has been reported, with a positive predictive value of 80%[12]. This approach is somewhat limited by the inclusion of items associated with gout such as cardiovascular disease and male sex, rather than items intrinsic to the disease.

Traditionally, potential items for classification criteria are identified by physicians on the basis of clinical experience and knowledge of the pathology of the disease. The opinions of patients about the disease in question are rarely sought, yet patients have firsthand knowledge of how a disease is manifest and may be able to identify important clinical diagnostic pointers that could be overlooked by physicians. Patient involvement in outcome measurement[13,14], teaching health professionals[15], and self-management[16] are well described and so it was thought to be potentially useful to also include patients' perceptions regarding classification criteria in this study.

It is important to emphasize that the purpose of the overall project and for classification criteria in general is accurate case ascertainment for clinical research so that populations that are relatively homogeneous (with respect to the disease under study) are recruited. This is distinct from diagnostic criteria, which may be used for the diagnosis of individual patients in clinical practice. Nevertheless, it is usually the case that classification criteria are formed by a restricted set of items that are also used for diagnosis. In our study, we did not wish to restrict the range of items to be elicited, and thus framed questions in terms of diagnosis rather than classification, even though classification criteria are the ultimate aim. Also, in clinical practice, examination of tissue or synovial fluid is the preferred diagnostic approach for gout. In the case of rheumatology care, all rheumatologists should be able to obtain synovial fluid and examine it for the presence of MSU crystals because that is part of the training curriculum[17]. Classification criteria do not replace this diagnostic approach. Even in primary care, classification criteria do not necessarily replace the recommended diagnostic approach but can be useful aides to recalling the key features of the disease.

The objective of our study was to identify a comprehensive list of clinical, laboratory, and imaging features that could potentially discriminate between gout and other forms of arthritis or rheumatic musculoskeletal disease in a

primary healthcare setting. This study used the Delphi technique to anonymously obtain opinions from both physicians and patients, and then give them the opportunity to revise their opinion in light of the group's average. This information will serve as the basis for a planned multinational case-control study that aims to create and validate new classification criteria for the identification of gout that is designed for the setting of clinical research independent of patient care. As noted, such criteria should not be used for the diagnosis of individual patients in ordinary clinical care.

MATERIALS AND METHODS

Eighty-one physicians from multiple countries who were interested in gout were identified from an e-mail list accumulated from previous gout studies, and 87 patients with gout were identified from patient registers at 3 New Zealand rheumatology services. Nearly all physicians were rheumatologists. Participants were asked to take part in a series of Web-based questionnaires to identify features typical of gout to be used to develop new criteria for the classification of gout. Physicians were invited by e-mail and patients were invited by letter.

Physicians were asked to rate items on the extent to which they believed that particular feature could distinguish gout from other rheumatic musculoskeletal conditions. Items presented to the physicians in the first iteration were identified by literature search and expert opinion. Any extra features identified by physicians as being important were also solicited in the first iteration. Features of gout in the patient survey were obtained from the first iteration using the question, "list as many features of gout as possible that help you and your doctor know you have gout and not some other joint condition." All participants used a 9-point rating scale (1 = not at all discriminatory; 9 = extremely discriminatory). Consensus was defined by the RAND/UCLA disagreement index whereby values > 1 indicated disagreement[18].

Items that had been suggested by physicians in the first iteration, reworded items, items for which there was disagreement, and items that had a median rating of 4–6 (uncertainty) were re-rated in the second and third iterations, if needed.

In the second iteration of the patient survey, all items from the first round were rated using the 9-point agreement scale. In the third round only the items for which there was disagreement or those with a median rating of 4–6 were re-rated. Reminders were sent by e-mail to all participants after a week of each iteration and they were given a further week to complete the survey before they were considered a nonrespondent.

According to the principles of the Delphi method[19], the participants (patients and physicians) remained anonymous to each other throughout the duration of the study. The responses to the surveys were analyzed after each round and the median and 30th and 70th percentiles were made known to each respondent in subsequent rounds. The surveys were carried out for 3 iterations or until consensus was reached, giving participants the opportunity to change their answers in light of the groups' average.

The study protocol was approved by the New Zealand Health and Disability Multiregional Ethics Committee (MEC/11/EXP/077).

RESULTS

There were 49 respondents to the first physician survey (60% response rate). The mean age was 52.5 (SD 10.5) years, participants had been in specialist practice for 19.9 (SD 10.8) years, and consulted on a mean of 29.7 (SD 32.9) patients with gout per month. Of these, 44 responded to the second round (90%). There were 71 clinical, laboratory, and imaging features identified by literature review and expert opinion for the first iteration of the physician survey. Of these, 13 features were considered not discriminatory for gout and 25 were considered discriminatory. All 38 discriminatory and nondiscriminatory features were excluded from the second iteration. The remaining features with a median rating of 4–6 (30 items) or those for which there was disagreement (2 items) were included in the second iteration, along with 15 additional features nominated by physicians and 8 features from the first iteration for which respondents had requested clarification. There was

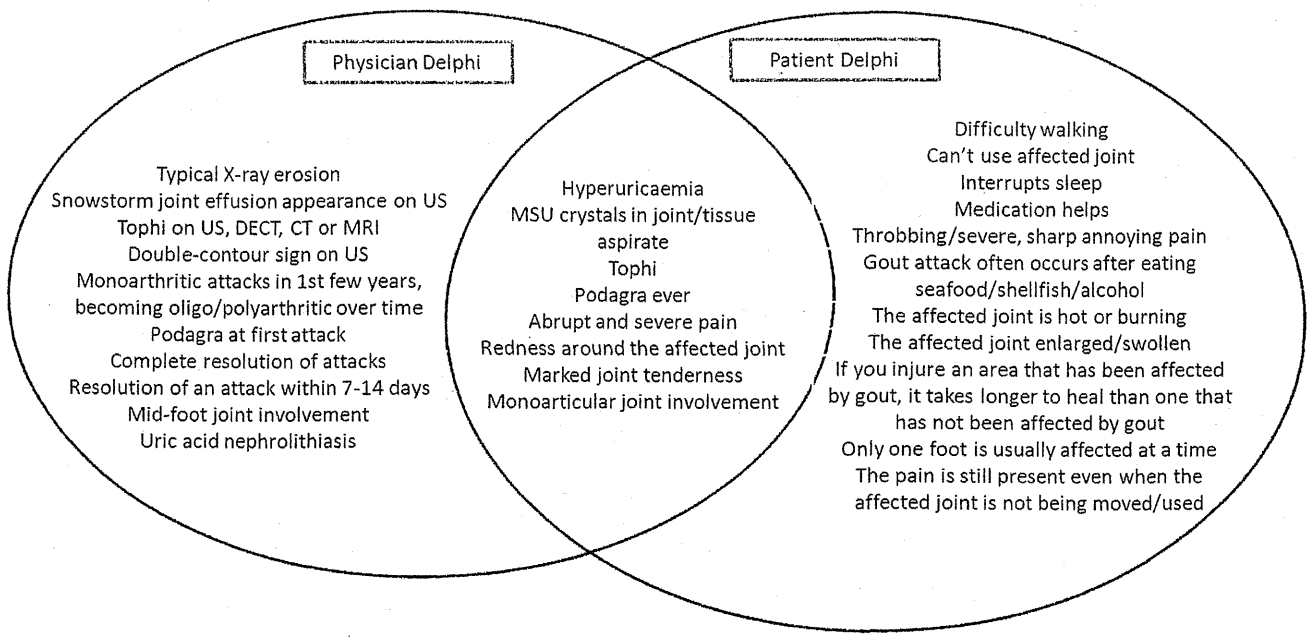

Figure 1. The overlap and differences among features highly rated (median 7–9) by physicians and patients. US: ultrasound; DECT: dual-energy computed tomography; CT: conventional computed tomography; MRI: magnetic resonance imaging; MSU: monosodium urate.

Table 1. Final ratings following the second iteration of the physician survey.

Survey Items	Median (30th to 70th percentile)†	Disagreement Index††
Items agreed by physicians to be discriminatory		
MSU crystals present in joint aspirate/tissue	9 (9 to 9)	0
Tophi (especially in typical sites such as hands, helix of the ear, olecranon bursa, and Achilles tendon)	9 (8 to 9)	0.13
MSU crystals still present in the joint fluid despite the patient being asymptomatic	9 (7 to 9)	0.29
Radiographic erosions with sclerotic margins and overhanging cortical edges	8 (8 to 8)	0
First metatarsophalangeal joint (podagra) involved at the very first episode	8 (7 to 8)	0.16
Abrupt onset of an attack that peaks around 12–24 hours	8 (7 to 8)	0.16
Conventional CT tophi (soft-tissue masses of intermediate density)	8 (7 to 8)	0.16
Recurrent stereotypical episodes of attacks	8 (7 to 8)	0.16
MRI tophi (low to intermediate signal intensity on T1-weighted images)	8 (7 to 8)	0.16
MRI tophi (variable intensity on T2-weighted images)	8 (7 to 8)	0.16
Dual-energy CT to detect urate deposits	8 (7 to 8)	0.16
First metatarsophalangeal joint involved ever	7.5 (7 to 8)	0.16
US double-contour sign (hyperechoic band on the surface of articular cartilage)	7.5 (7 to 8)	0.16
Severe pain that is maximal within 4–12 hours	7 (7 to 8)	0.16
US tophi (hyperechoic, heterogeneous lesion surrounded by an anechoic rim)	7 (7 to 8)	0.16
Serum uric acid elevated during the intercritical period*	7 (7 to 8)	0.16
Attacks are monoarthritic in the first few years and become oligoarthritic and polyarthritic over time*	7 (7 to 8)	0.16
Between attacks, the patient appears well with no signs of pain or obvious inflammation	7 (6 to 8)	0.37
Redness/erythema around the affected joint observed by the physician	7 (6 to 8)	0.37
Marked joint tenderness — patient protects the affected joint from use or from being knocked	7 (6 to 7)	0.22
Monoarticular joint involvement in acute attacks	7 (6 to 7)	0.22
Resolution of an attack within 7–14 days	7 (6 to 7)	0.22
Raised serum urate level*	7 (6 to 7)	0.22
Joints of the midfoot are affected, observed by the physician*	7 (6 to 7)	0.22
Uric acid nephrolithiasis (kidney stones)	7 (5.1 to 8)	0.62
US joint effusion (snowstorm appearance due to MSU crystals within the synovial fluid)	7 (5 to 7)	0.52
Items agreed by physicians to be of uncertain discrimination		
Patient responds rapidly to low-dose colchicine treatment*	6.5 (6 to 7)	0.22
Swelling resolves once symptoms subside, observed by the physician	6.5 (5 to 7)	0.52
Serum uric acid elevated during acute attack of gout*	6.5 (5 to 7)	0.52
Warmth of skin overlying affected joint, as observed by the physician*	6 (6 to 7)	0.22
Onset of a gout attack is generally at night*	6 (6 to 7)	0.22
MRI erosion (a sharply marginated bone lesion with cortical bone defect)*	6 (6 to 7)	0.22
Conventional CT to detect urate deposits*	6 (6 to 7)	0.22
Conventional CT to detect erosion*	6 (6 to 7)	0.22
Swelling of associated bursa, observed by the physician	6 (5.3 to 7)	0.42
Other joints affected that are typical of gout (midfoot, ankle, knee)	6 (5.1 to 7)	0.48
Swelling in the joint, as observed by the physician*	6 (5 to 7)	0.52
Redness/erythema around the affected joint, as observed by the patient*	6 (5 to 7)	0.52
Precipitation of an episode by purine-containing food (such as seafood or red meat), alcohol, dehydration, or drugs (such as diuretics)	6 (5 to 7)	0.52
Swelling resolves once symptoms subside, as observed by the patient*	6 (5 to 7)	0.52
Chronic uric acid nephropathy*	6 (5 to 7)	0.52
If the patient is female she is postmenopausal*	6 (5 to 7)	0.52
Patient is unable to wear shoes*	6 (5 to 7)	0.52
Skin peels/scales over the affected area as acute attack is resolving*	6 (5 to 7)	0.52
Previous diagnosis of gout made by another physician*	6 (5 to 7)	0.52
Other joints are affected that are typical of gout such as ankle and knee, observed by the physician*	6 (5 to 6)	0.32
Patient has a history of chronic, heavy alcohol intake*	6 (5 to 6)	0.32
Patient is taking medication such as diuretics*	6 (5 to 6)	0.32
Patient is a male*	6 (5 to 6)	0.32
Patient is an organ graft recipient*	6 (4.3 to 7)	0.81
Synovial fluid cultures of affected joint are negative for organisms (to exclude septic arthritis)*	6 (4.3 to 6)	0.66
Family history of gout*	5.5 (5 to 6)	0.32
Redness of skin with skip area (suggestive of gouty cellulitis), which can eliminate cellulitis (redness of skin without skip area)*	5.5 (5 to 6)	0.32
US erosion (break in the cortical contour)*	5 (5 to 6)	0.32
US tendon pathology (includes tenosynovitis, tendinosis, and intratendinous tophi)*	5 (5 to 6)	0.32
Reduced renal uric acid excretion*	5 (4.3 to 6)	0.66