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)

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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

Variable	Results	
	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.

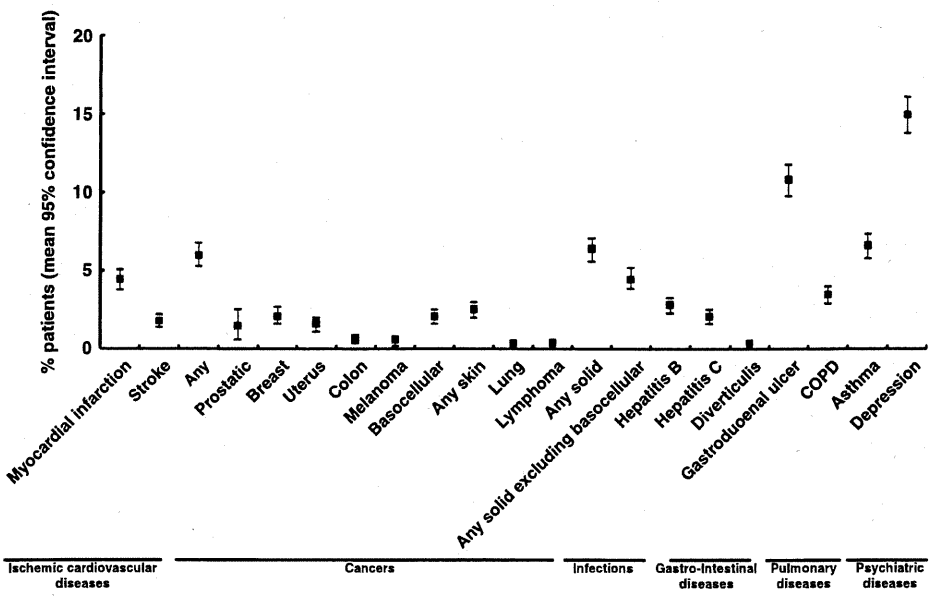

Figure 1 Prevalence of evaluated comorbidities in the 3920 patients with rheumatoid arthritis. COPD, chronic obstructive pulmonary disease.

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

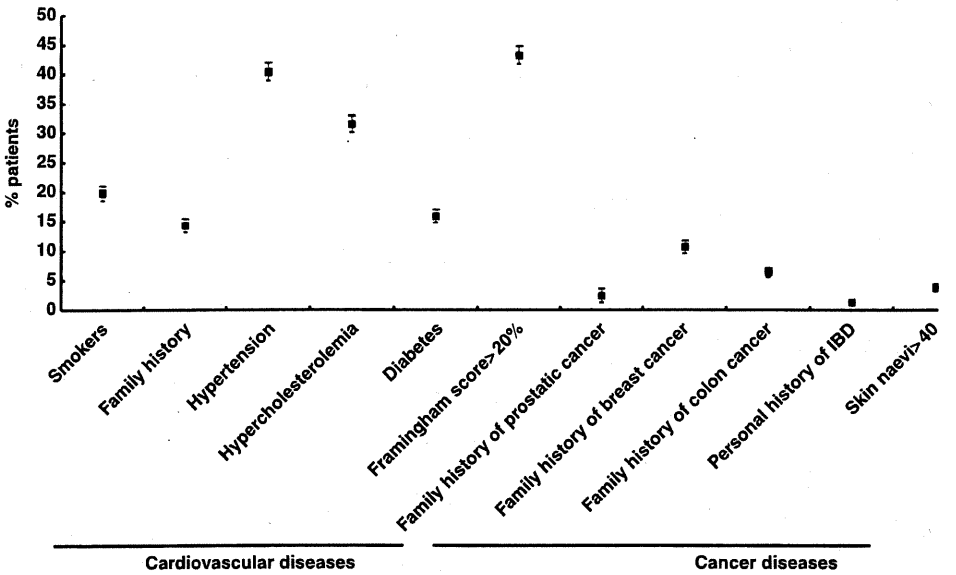

Figure 2 Prevalence of risk factors for cardiovascular and cancer diseases in the 3920 patients with rheumatoid arthritis. IBD, inflammatory bowel disease.

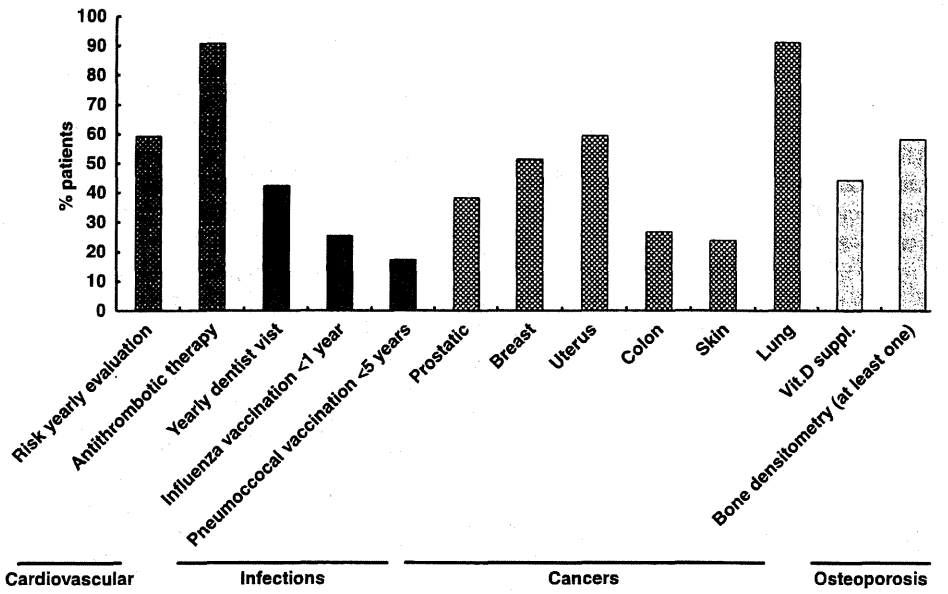

Figure 3 Percentage of patients optimally monitored with respect to some comorbidities. Vit.D suppl., vitamin D supplementation.

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.

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ORIGINAL ARTICLE

Elevation of KL-6 serum levels in clinical trials of tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a report from the Japan College of Rheumatology Ad Hoc Committee for Safety of Biological DMARDs

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Abstract
Objective The associations between elevated levels of serum Krebs von den Lungen-6 (KL-6) and treatment of rheumatoid arthritis (RA) with tumor necrosis factor (TNF) inhibitors were investigated in five Japanese clinical trials.

Methods Percentages and incidence rates were calculated for elevated serum KL-6 levels. Adverse events associated with elevated levels of serum KL-6 were investigated.
Results In RISING, a clinical trial for infliximab, 15.6 % of the enrolled patients met criterion B (KL-6 $\geq$500 U/ml and >1.5-fold increase over the baseline value) by week 54. In HIKARI, 7.8 % of the certolizumab pegol (CZP) group and 0 % of the placebo group met criterion B during the double-blind (DB) period ($p = 0.003$). In J-RAPID, 8.4 % of the methotrexate (MTX) + CZP and

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3.9 % of the MTX + placebo groups met criterion B during the DB period. In GO-MONO, 1.8 % of the golimumab (GLM) and 1.3 % of the placebo groups met criterion B during the DB period. In GO-FORTH, 7.1 % of the MTX + GLM and 0 % of the MTX + placebo groups met criteron B during the DB period ($p = 0.017$). No adverse events accompanied the elevation of serum KL-6 levels in 95.7 % of these patients.

Conclusion Serum KL-6 levels may increase during anti-TNF therapy without significant clinical events. In these patients, continuing treatment with TNF inhibitors under careful observation is a reasonable option.

Keywords Biological disease modifying antirheumatic drug · KL-6 · Rheumatoid arthritis · Interstitial pneumonia · *Pneumocystis jirovecii* pneumonia

Introduction

During the last decade, the introduction of tumor necrosis factor (TNF) inhibitors for the treatment of rheumatoid arthritis (RA) has completely changed the treatment strategy and management of this intractable disease. In Japan, four TNF inhibitors have been approved for the treatment of RA and are widely used in clinical practice: infliximab (IFX) in 2003, etanercept (ETN) in 2005, adalimumab (ADA) in 2008, and golimumab (GLM) in 2011. Certolizumab pegol (CZP) is now under clinical development, and phase 3 and phase 2/3 trials have already been completed. For IFX, ETN, and ADA, post-marketing surveillance (PMS) programs have revealed short-term safety profiles of these biological disease-modifying antirheumatic drugs (DMARDs) in Japanese RA patients [1, 2]. Infection was the most frequently reported adverse drug reaction for IFX and ETN, and the second most for ADA. About half of these infectious events developed in the respiratory system. The results of the PMS and other clinical studies indicated that clinically important pulmonary infections in Japanese RA patients given TNF inhibitors encompassed bacterial pneumonia, tuberculosis, and *Pneumocystis jirovecii* pneumonia (PCP) [1–4].

The Krebs von den Lungen-6 (KL-6) antigen is a mucinous high-molecular-weight glycoprotein primarily derived from a lung adenocarcinoma cell line and classified as a cluster 9 mucin-1 of lung tumors and differentiation antigens [5]. KL-6 is produced by type II alveolar epithelial cells and is reported to be elevated in patients with idiopathic interstitial pneumonia (IIP), interstitial pneumonia (IP) associated with collagen diseases, other interstitial lung diseases, PCP, and malignancies [6–14]. Among the clinical trials for biological DMARDs, the "impact on Radiographic and clinical response of Infliximab therapy concomitant with methotrexate in patients with rheumatoid arthritis by the trough Serum level in the dose-escalatING study" (the RISING study) [15] systematically measured serum KL-6 levels for the first time. In a report to the Pharmaceuticals and Medical Devices Agency of Japan, the RISING study describes its findings of an abnormal elevation of this serum marker in RA patients receiving IFX without any development or exacerbation of pulmonary disease or malignancies. However, no peer review journal report of the details of the elevation of serum KL-6 has been published, and it has not been determined whether this adverse event is truly related to treatment with IFX, is common among treatment with TNF inhibitors or other biological DMARDs, or is related to treatment with MTX. A report of elevated serum KL-6 levels in three RA patients treated with ADA has been recently published [16].

In Japan, the measurement of serum KL-6 levels is an officially approved and widely used clinical laboratory test in the field of rheumatology. The Japan College of Rheumatology convened an ad hoc committee for the safety of biological DMARDs to investigate the abnormal elevation of serum KL-6 levels in RA patients given biological DMARDs. The committee implemented two studies to investigate this issue, one for clinical trial data and the other for clinical practice data. The results from the analyses of the clinical trial data are reported here; those from the study of clinical practice data will be reported separately.

Patients and methods

Clinical trials

Serum KL-6 levels were measured in clinical trials in Japan for three TNF inhibitors, IFX, CZP, and GLM. For our analyses, we utilized the RISING study for IFX [15], a pHase 3 study to assess the effIcacy, safety and phamacoKinetics of CDP870 (CZP) in rheumatoid ArthRItis patients (HIKARI; ClininalTrials.gov, NCT00791921) and the Japanese RA PreventIon of structural Damage (J-RAPID; ClininalTrials.gov, NCT00791999) for CZP, and the GO-MONO [17] and GO-FORTH [18] for GLM. Although the study period of these clinical trials lasted more than 1 year, including extension studies for CZP and GLM, our study evaluated data only for 54 weeks of the RISING study and 52 weeks for the other four clinical trials. The measurement of serum KL-6 levels was originally scheduled in RISING, HIKARI, and J-RAPID, and the protocols and informed consent forms of GO-MONO and GO-FORTH were amended during these clinical trials to measure serum KL-6.

RISING study

The first clinical trial of biological DMARDs that included serum KL-6 as a laboratory test was RISING [15]. Electronic Supplementary Material (ESM) Fig. S1 shows the design and ESM Table S1 shows the baseline characteristics of the patients enrolled in RISING. In this trial, established RA patients with mean disease duration of 8.2 years received IFX for 54 weeks with concomitant stable doses of MTX. After a screening period, 327 patients entered the open-label period (3 mg/kg at weeks 0, 2, and 6) and 307 patients proceeded to the double-blind (DB) trial period. These patients were randomly allocated to 3, 6, or 10 mg/kg IFX groups and received an infusion of IFX every 8 weeks through to week 54. The percentage of patients with elevated serum KL-6 levels higher than 500 U/ml at baseline was 3.1 %.

HIKARI and J-RAPID

Two clinical trials for CZP have been implemented in Japan—HIKARI (phase III) and J-RAPID (phase II/III). In HIKARI, 230 RA patients who had an inadequate response to or who were intolerant of MTX were DB randomly assigned either to placebo or CZP without MTX for 24 weeks, followed by an open extension period until approval of the drug (ESM Fig. S2-A). In J-RAPID, 316 RA patients who had inadequate response to treatment with MTX were DB randomly allocated either to the placebo or to one of three dosage groups of CZP with concomitant MTX at stable dosages for 24 weeks, followed by an open extension period until approval of the drug (ESM Fig. S2-B). Both trials allowed for early escape (EE) at week 16 if a patient did not meet ACR20 response criteria at both weeks 12 and 14. Demographic characteristics of the enrolled patients to these trials were similar, with a mean disease duration of about 6 years (ESM Table S2). The percentage of patients with IP in HIKARI was 12.2 % and in J-RAPID 2.2 %. The percentage of patients with elevated serum KL-6 levels of $\geq$500 U/ml at baseline was 8.8–11.2 % in HIKARI and 2.4–6.1 % in J-RAPID (ESM Table S3).

GO-MONO and GO-FORTH

Serum KL-6 levels were evaluated in two randomized controlled trials of GLM implemented in Japan—GO-MONO [17] and GO-FORTH [18]. Patients who participated in either of these studies and who gave consent for measurements of serum KL-6 level were enrolled in our study. In GO-MONO, 308 RA patients who had an inadequate response to DMARDs were DB randomly assigned to placebo, GLM 50 mg, or GLM 100 mg monotherapy for 16 weeks, followed by an open extension period until week 116 (ESM Fig. S3-A). In GO-FORTH, 261 RA patients who had an inadequate response to MTX were DB randomly assigned to placebo, GLM 50 mg, or GLM 100 mg with concomitant MTX at stable dosages for 24 weeks, followed by an open extension period until week 152 (ESM Fig. S3-B). Baseline characteristics of the enrolled patients are summarized in Table ESM S4. The mean disease duration of the enrolled patients was about 9 years and patients with IP were not eligible for either study. At baseline for GO-MONO, 3.8 % of the patients in the GLM 50 mg group, 0 % in the GLM 100 mg group, and 1.3 % in the placebo group had KL-6 levels of >500 U/ml. In GO-FORTH, 2.9 % of the patients in the MTX + GLM 50 mg group, 0 % in the MTX + GLM 100 mg group, and 4.2 % in the MTX + placebo group had KL-6 levels of >500 U/ml (ESM Table S5).

Data collection

The chairperson (M.H.) and the committee members (A.T., T.A., M.D., S.H., H.N., and Y.S.) reviewed the data on elevations of serum KL-6 levels in the five Japanese clinical trials. M.H. and A.T. requested that the pharmaceutical companies Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical, UCB Japan, and Janssen Pharmaceutical provide data in a systematic and predetermined format. The data were analyzed by the committee only; the pharmaceutical companies were not involved in data analysis. The committee did not have direct access to the database of the clinical trials. The final version of this report was reviewed by the pharmaceutical companies to enable data validation.

Measurement of serum KL-6 levels

Serum KL-6 levels were centrally measured in each clinical trial. In the RISING study, serum KL-6 levels were measured at weeks 0, 2, and then every 4 weeks until week 54. In HIKARI and J-RAPID, serum KL-6 levels were measured at weeks 0 and 1, every other week (EOW) from weeks 2 to 16, and at weeks 20 and 24 during the double-blind trial period, and every 4 weeks from weeks 28 to 52. Serum KL-6 levels were retrospectively measured at weeks 0, 12, 24, 36, and 52 for GO-MONO and GO-FORTH using stored serum samples. Serum KL-6 levels were available for 250 and 212 patients in GO-MONO and GO-FORTH, respectively. Serum KL-6 levels were also measured after week 52 in the clinical trials for CZP and GLM, but these data were not analyzed for our study. Serum KL-6 levels were measured using the Picolumi KL-6 kit (Eidia Co., Tokyo, Japan) in all five clinical trials.

Definition of elevated/reduced serum KL-6 levels

Criteria A, B, and C for the elevation of serum KL-6 levels were developed by the committee and are shown in Table 1. We defined three criteria based on the serum KL-6 value at the initiation of TNF inhibitor therapy and the maximum value thereafter because some patients with RA have elevated serum KL-6 levels due to concurrent pulmonary diseases at baseline. In this study, our primary focus was criterion B. We also defined criterion R for the significant reduction of serum KL-6 levels in RA patients after achieving criterion B (Table 1).

Association of elevated serum KL-6 level with pulmonary events

We analyzed the association of elevated serum KL-6 levels with pulmonary events through week 54 for IFX and week 52 for CZP and GLM. Pulmonary events of this study were defined using preferred terms of the MedDRA ver 12.0 including PCP (10064108), interstitial lung disease (10022611), pulmonary fibrosis (10037383), and pulmonary interstitial emphysema syndrome (10037415). In this study, we used the diagnosis of pulmonary events that were made during the clinical trials by the original investigators. Newly diagnosed or exacerbated pulmonary events between 4 weeks before and 4 weeks after the first elevation of serum KL-6 levels meeting criterion B were counted.

Statistical analysis

Percentages and incidence rates were calculated per 100 patient-years (PY) for patients who met the criteria for elevated serum KL-6 levels. Denominators were: 327 patients who received open-label treatment in RISING; full-analysis-set patients for whom data on KL-6 were available in HIKARI (230 patients) and J-RAPID (316 patients); patients who gave informed consent to serum KL-6 level measurements and for whom available data were available in GO-MONO (250 patients) and GO-FORTH (212 patients).

Because RISING did not have a placebo group and three different doses of IFX were compared for 54 weeks, the primary and secondary endpoints of our study for RISING were percentage and incidence rates per 100 PY of patients who met criterion B by week 54, respectively. Taking the time points when treatments were changed for open extension periods in HIKARI, J-RAPID, GO-MONO, and GO-FORTH into account (ESM Figs. S2, S3), we defined the primary endpoints as percentages of patients who met criterion B by week 28 for HIKARI and J-RAPID, by week 16 for GO-MONO, and by week 24 for GO-FORTH. Secondary endpoints for these four trials were percentages of patients who met criteria A and C and incidence rates per 100 PY of patients who met criteria A, B, and C by the same time points given above, and percentages and incidence rates per 100 PY of patients who met criteria A, B, and C by week 52 in each trial. Percentages among treatment groups were compared using the Fisher's exact probability test for the primary endpoints, but statistical comparisons were not calculated for secondary endpoints. In clinical trials comparing different dosage groups, the TNF inhibitor groups combined were first compared with the placebo group. If a significant difference was observed, each dosage group was then compared with the placebo group. We took these measures to avoid type I errors derived from multiple comparisons.

Ethics

The study protocols of the five clinical trials were approved by the local institutional review board of each study institution and were carried out in accordance with the Helsinki Declaration and Good Clinical Practice. In GO-MONO and GO-FORTH, patients provided additional informed consent after amendment of the study protocols to measure serum KL-6 levels using stored serum samples.

Table 1 Criteria for the elevation or reduction of serum KL-6 levels

Criteria	Definition
A	≥500 U/ml and ≥1.25-fold higher than baseline value
B	≥500 U/ml and ≥1.5-fold higher than baseline value
C	≥1,000 U/ml and ≥3-fold higher than baseline value
R	Decrease in serum KL-6 levels to <500 U/ml or less than [baseline + 0.5 × (maximum baseline)] after achieving criterion B and reaching the maximum level of a patient

KL-6 Krebs von den Lungen-6 antigen

Criteria A, B, and C are for the elevation of serum KL-6 levels, and criterion R is for the reduction of serum KL-6 levels after achieving criterion B and reaching the maximum level of a patient

Results

Elevation of serum KL-6 levels in RISING

Among the 327 patients who received open-label treatment with IFX, the percentage (incidence rate/100 PY) of patients by week 54 who met criterion A was 18.7 % (20.0/100 PY), criterion B 15.6 % (16.7/100 PY), and criterion C 1.5 % (1.6/100 PY) (Table 2). The percentages of patients meeting all three criteria in the 3 mg/kg group were not significantly different from those in the 6 or 10 mg/kg groups.

Table 2 Percentage and incidence rate/100 PY of patients meeting the criteria for elevated serum KL-6 levels at least one time by week 54 in RISING

Treatment group	Number of patients	Percentage and incidence rate		
		Criterion A	Criterion B	Criterion C
IFX (3 mg/kg)	99	16.2 % (16.6/100 PY)	14.1 % (14.5/100 PY)	1.0 % (1.0/100 PY)
IFX (6 mg/kg)	104	21.2 % (21.6/100 PY)	15.4 % (15.7/100 PY)	1.0 % (0.98/100 PY)
IFX (10 mg/kg)	104	18.3 % (18.4/100 PY)	16.3 % (16.5/100 PY)	2.9 % (2.9/100 PY)
All patients	327	18.7 % (20.0/100 PY)	15.6 % (16.7/100 PY)	1.5 % (1.6/100 PY)

Criteria A, B, and C for elevation of serum KL-6 levels are defined in Table 1. Among 327 patients who received open-label treatment with IFX (3 mg/kg), 20 patients did not enter the double-blind (DB) period. No significant difference exists in percentages of the patients meeting the three criteria in the 3 mg/kg group compared to the 6 or 10 mg/kg groups by the Fisher's exact probability test. Lengths of exposure were 96.4 PY for the 3 mg/kg IFX group, 101.7 PY for 6 mg/kg IFX group, 103.2 PY for 10 mg/kg IFX group, and 304.6 PY for all patients

IFX infliximab, *PY* patient-year

We analyzed the association between elevated serum KL-6 levels and the predefined pulmonary events described in "Patients and methods". Of the 51 cases meeting criterion B by week 54, three pulmonary events in three patients were reported (ESM Table S6). The serum KL-6 level of a suspected case of PCP at week 12 (withdrawn from the trial before entering the DB period) increased from 269 (week 0) to 996 U/ml (week 14), that of a patient who developed IP at week 6 (withdrawn from the trial before entering the DB period) increased from 468 (week 0) to 935 U/ml (week 6), and that of a patient developing IP at week 50 increased from 205 (week 0) to 1,470 U/ml (week 50). The remaining 48 patients did not develop any of the predefined pulmonary events, and we could not identify other specific reasons, including malignancy, for the elevated KL-6 levels in these patients.

Changes in serum KL-6 levels over time in RA patients meeting criterion B ($n = 51$) are shown in Fig. 1. In 29 (60.4 %) of the 48 RA patients who met criterion B without developing a predefined pulmonary event, serum KL-6 levels spontaneously decreased to meet criterion R by week 54. Of these 48 RA patients, 33 had serum KL-6 data available after reaching their maximum level of whom 29 (87.9 %) met criterion R by week 54.

Elevation of serum KL-6 levels in HIKARI

In HIKARI, patients who entered EE received 200 mg of CZP EOW on and after week 16, while treatments of patients who did not enter EE were changed at week 28 (ESM Fig. S2-A). We therefore performed on-drug analysis for weeks 0–28: the exposure period of patients who entered EE at week 16 included only the first 16 weeks in their originally allocated treatment group. The exposure period of patients who did not enter EE was 28 weeks or until withdrawal from the trial, whichever came first. Between weeks 0 and 28, 16 (13.8 %) of the patients who received CZP 200 mg without MTX satisfied criterion A and 9 (7.8 %) satisfied criterion B, while 4 (3.5 %) and 0 % of patients who received placebo without MTX met criteria A and B, respectively ($p = 0.009$ for criterion A; $p = 0.003$ for criterion B vs. placebo group by the Fisher's exact probability test) (Table 3). By week 52, of the 219 patients, 12.8 % (19.3/100 PY) met criterion A, 9.2 % (13.8/100 PY) met criterion B, and 1.4 % (2.1/100 PY) met criterion C. For this 52-week analysis, the exposure period of patients who were initially assigned to the placebo group included only the period of time they received CZP, that of patients who were assigned to the CZP 200 mg group was counted from weeks 0 to 52, and that of patients who were withdrawn from the clinical trial before week 52 included only the period before withdrawal.

We analyzed the association between elevated serum KL-6 levels and the occurrence of the defined pulmonary events described in "Patients and methods". One case of IP and two cases of PCP were reported among the 21 cases meeting criterion B by week 52. The serum KL-6 levels of the patient who developed IP at week 50 (CZP 200 mg group) increased from 428 (week 0) to 663 U/ml (week 52), those of the patient who developed PCP at week 6 (CZP 200 mg group) increased from 945 (week 0) to 3,610 U/ml (week 6), and those of the patient who developed PCP at week 24 (placebo group, but receiving CZP 200 mg at the development of PCP) increased from 383 (week 0) to 1,600 U/ml (week 30). The remaining 18 patients did not develop the predefined pulmonary events nor could we identify other specific reasons, including malignancy, for the observed elevation in KL-6 levels in these patients.

Changes in serum KL-6 levels in 6 patients in the placebo group and 15 in the CZP 200 mg group meeting criterion B are shown in Fig. 2. All patients from the placebo group met criterion B after their treatments were changed to 200 mg of CZP. In 7 (38.9 %) of the 18 RA patients who met criterion B without developing any of the

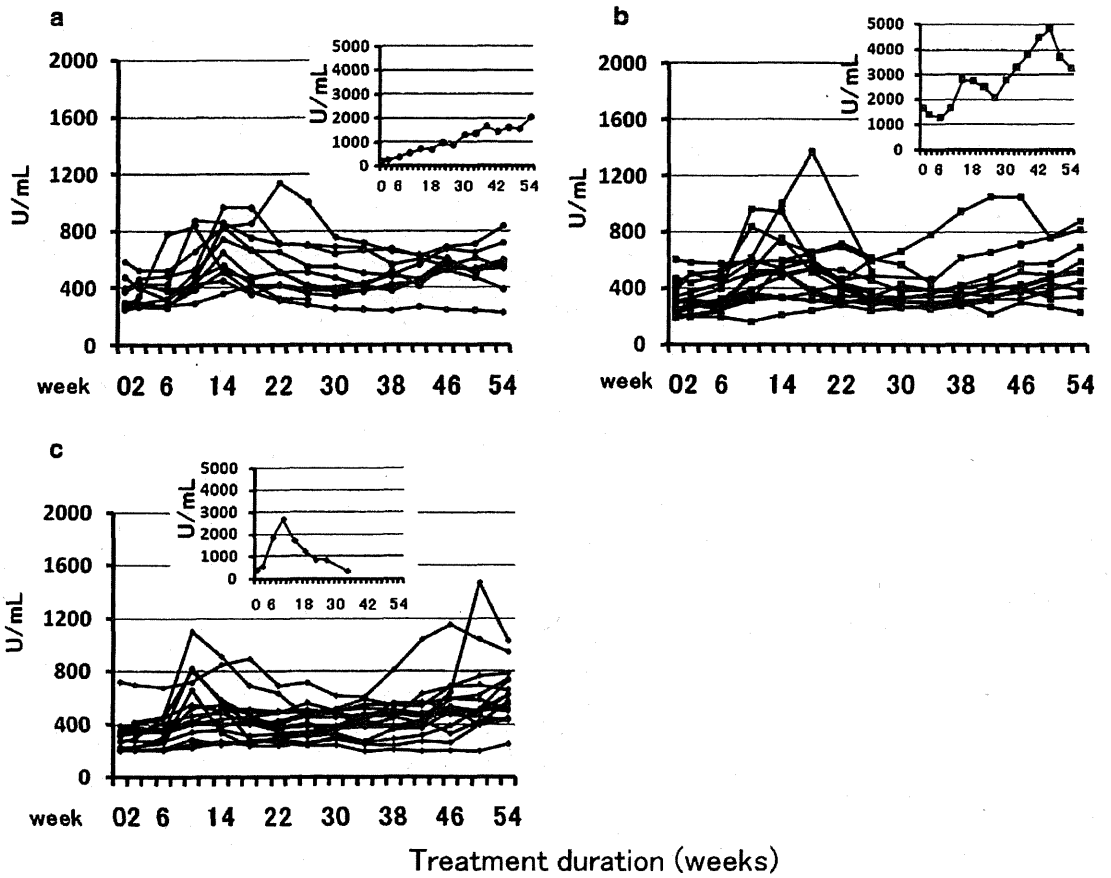

Fig. 1 Changes in serum Krebs von den Lungen-6 (KL-6) antigen levels over time in 51 rheumatoid arthritis (RA) patients who met criterion B at least one time by week 54 in the RISING study. Data from the infliximab (IFX) 3 mg/kg group ($n = 14$) and from patients who did not enter the double-blind (DB) period ($n = 4$) (**a**), data from the IFX 6 mg/kg group ($n = 16$) (**b**), and data from the IFX 10 mg/kg group ($n = 17$) (**c**) are shown separately. Data from patients whose maximum serum KL-6 level reached >2,000 U/ml are shown in the *insets* of the figures. For definition of criterion B, see Table 1

Table 3 Percentage and incidence rate/100 PY of patients who met the criteria for elevated serum KL-6 levels at least one time by week 28 in HIKARI

Treatment group	Number of patients[a]	Percentage and incidence rate		
		Criterion A	Criterion B	Criterion C
CZP (200 mg)	116	13.8 % (29.9/100 PY)*	7.8 % (16.8/100 PY)**	1.7 % (3.7/100 PY)
Placebo	114	3.5 % (10.6/100 PY)	0 % (0.0/100 PY)	0 % (0.0/100 PY)

Criteria A, B, and C for elevation of serum KL-6 levels are defined in Table 1. The exposure period of patients who entered early escape (EE) at week 16 was considered to be 16 weeks. The exposure period of patients who did not enter EE was considered to be 28 weeks or until withdrawal from the trial. Lengths of exposure were 53.5 PY for the CZP 200 mg group and 37.8 PY for the placebo group

CZP certolizumab pegol

Significance: * $p = 0.009$, ** $p = 0.003$ (CZP vs. placebo groups, by the Fisher's exact probability test)

[a] All patients assigned to each group with available data for serum KL-6 levels were evaluated

predefined pulmonary events, serum KL-6 levels spontaneously decreased to meet criterion R by week 52. Of these 18 RA patients, 14 had serum KL-6 data available after reaching their maximum levels of whom 7 (50.0 %) met criterion R by week 52.

Elevation of serum KL-6 levels in J-RAPID

Patients in J-RAPID who entered EE received 200 mg of CZP EOW with MTX on and after week 16, while treatments of patients who did not enter EE were changed at

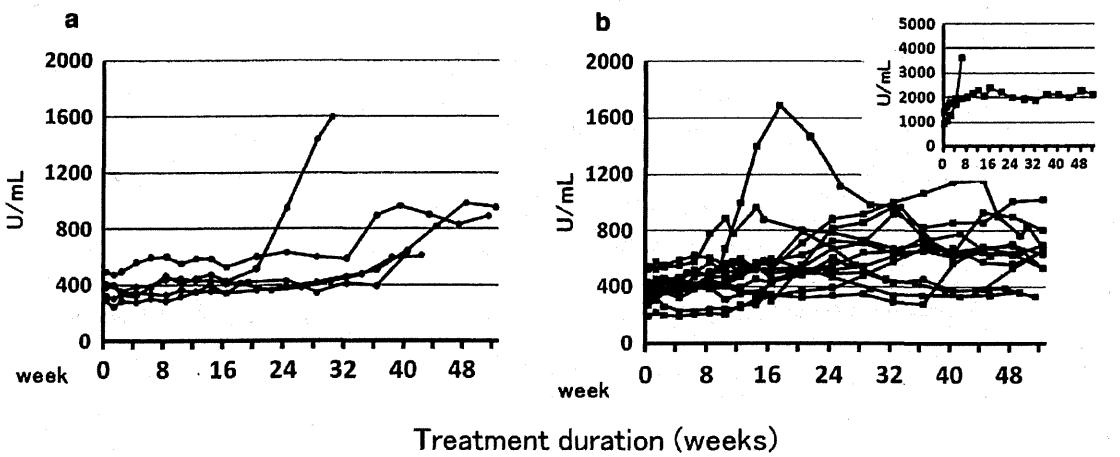

Fig. 2 Changes in serum KL-6 levels over time in 21 RA patients given certolizumab pegol (CZP) who met criterion B at least one time by week 52 in the HIKARI study. Data from the placebo group ($n = 6$) (**a**) and the CZP 200 mg group ($n = 15$) (**b**) are shown separately. The treatment for each patient was changed as described in ESM Fig. S2-A. Data from patients whose maximum serum KL-6 level surpassed 2,000 U/ml are shown in the *insets* of the figures

Table 4 Percentage and incidence rate/100 PY of patients who met the criteria for elevated serum KL-6 levels at least one time by week 28 in J-RAPID

Treatment group[a]	Number of patients[b]	Percentage and incidence rate		
		Criterion A	Criterion B	Criterion C
CZP (100 mg)	72	11.1 % (24.1/100 PY)	5.6 % (12.0/100 PY)	2.8 % (6.0/100 PY)
CZP (200 mg)	82	12.2 % (25.5/100 PY)	9.8 % (20.4/100 PY)	2.4 % (5.1/100 PY)
CZP (400 mg)	85	9.4 % (20.0/100 PY)	9.4 % (20.0/100 PY)	2.4 % (5.0/100 PY)
CZP (combined)	239	10.9 % (23.1/100 PY)	8.4 % (17.8/100 PY)	2.5 % (5.3/100 PY)
Placebo	77	6.5 % (18.0/100 PY)	3.9 % (10.8/100 PY)	0 % (0.0/100 PY)

Criteria A, B, and C for elevation of serum KL-6 levels are described in Table 1. The exposure period of patients who entered EE at week 16 was considered to be 16 weeks. The exposure period of patients who did not enter EE was taken to be 28 weeks or until withdrawal from the trial. Lengths of exposure were 33.2 PY for the MTX + CZP 100 mg group, 39.3 PY for the MTX + CZP 200 mg group, 39.9 PY for the MTX + CZP 400 mg group, and 27.7 PY for the MTX + placebo group. Percentages of the patients meeting the three criteria in the CZP groups combined did not differ significantly from the placebo group by the Fisher's exact probability test

MTX methotrexate

[a] All patients received placebo, CZP 100, 200, or 400 mg with concomitant MTX. CZP (combined) refers to the total of all CZP treatment group patients

[b] All patients who were assigned to each group with available data for serum KL-6 level were evaluated

week 28, the same as in HIKARI (ESM Fig. S2-B). We therefore performed on-drug analysis for weeks 0–28 as described for HIKARI. Between weeks 0 and 28, 4 (5.6 %) patients from the MTX + CZP 100 mg group, 8 (9.8 %) from the MTX + CZP 200 mg group, 8 (9.4 %) from the MTX + CZP 400 mg group, and 20 (8.4 %) from the MTX + CZP groups combined met criterion B, while 3 (3.9 %) patients from MTX + placebo group met criterion B (Table 4). No significant difference was found between the CZP groups combined and the placebo group. By week 52, of the 309 patients, 12.0 % (15.5/100 PY) met criterion A, 9.7 % (12.6/100 PY) met criterion B, and 2.6 % (3.4/100 PY) met criterion C. For this 52-week analysis, the exposure periods were the same as those described for HIKARI.

We analyzed the association between elevated serum KL-6 levels and the pulmonary events defined in "Patients and methods". Among the 32 cases meeting criterion B by week 52, no patients developed any of the predefined pulmonary events. We could not identify any other specific reasons, including malignancy, for the elevation of KL-6 serum levels in these 32 patients.

Changes in serum KL-6 levels in these 32 patients in the MTX + placebo (5 patients), the MTX + CZP 100 mg group (8), the MTX + CZP 200 mg group (9), and in the MTX + CZP 400 mg group (10) meeting criterion B are

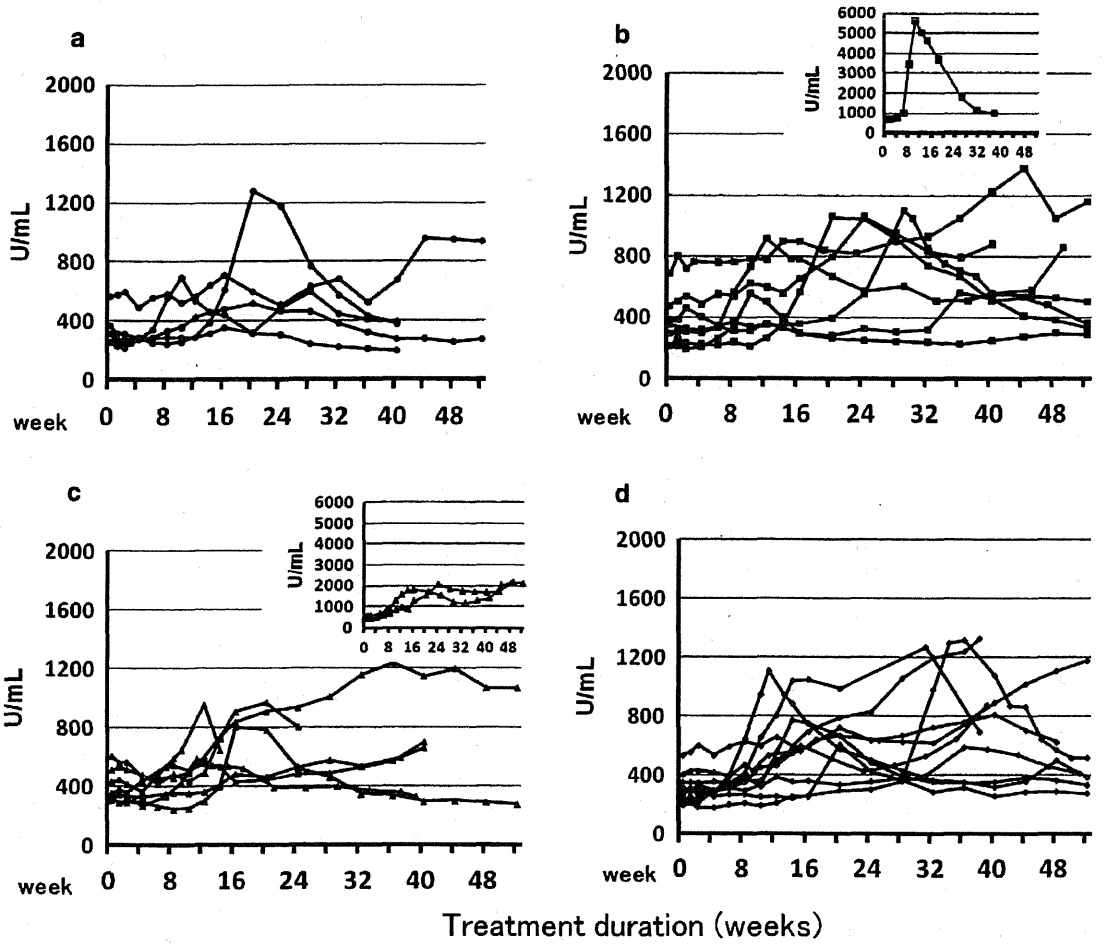

Fig. 3 Changes in serum KL-6 levels over time in 32 RA patients given CZP who met criterion B at least one time by week 52 in the J-RAPID study. Data from the methotrexate (MTX) + placebo group ($n = 5$) (**a**), MTX + CZP 100 mg group ($n = 8$) (**b**), MTX + CZP 200 mg group ($n = 9$) (**c**), and MTX + CZP 400 mg group ($n = 10$) (**d**) are shown separately. The treatment for each patient was changed as described in ESM Fig. S2-B. Data from patients whose maximum serum KL-6 level surpassed 2,000 U/ml are shown in the *insets* of the figures

depicted in Fig. 3. Three patients from the MTX + placebo group met criterion B while they were receiving placebo and 2 patients met criterion B after their treatments were changed to 200 mg of CZP. In 19 (59.4 %) of the 32 patients who met criterion B, serum KL-6 levels spontaneously decreased to meet criterion R by week 52. In these 32 RA patients, 27 had serum KL-6 data available after reaching their maximum level of whom 19 (70.4 %) met criterion R by week 52.

Elevation of serum KL-6 levels in GO-MONO

In GO-MONO, study blindness was maintained until week 16 and there was no EE. Patients from the placebo group started 50 mg GLM on and after week 16 (ESM Fig. S3). By week 16, 1 (1.3 %) patient in the GLM 50 mg group, 2 (2.2 %) patients in the GLM 100 mg group, 3 (1.8 %) patients in the GLM groups combined, and 1 (1.3 %) patient in the placebo group met criterion B (Table 5). No significant difference between the GLM groups combined and the placebo group was found. By week 52, of the 250 patients, 8.0 % (8.8/100 PY) met criterion A, 6.8 % (7.5/100 PY) met criterion B, and 0.8 % (0.9/100 PY) met criterion C. For this 52-week analysis, the exposure period of patients who were initially assigned to the placebo group was counted only for the period when they received GLM and the exposure period of patients who were assigned to the GLM groups was counted from weeks 0 to 52. The exposure period of patients who were withdrawn from the clinical trial before week 52 included only the period before withdrawal.

We analyzed the association between elevated serum KL-6 levels and the pulmonary events described in "Patients and methods". Among the 17 cases meeting

Table 5 Percentage and incidence rate/100 PY of patients who met the criteria for elevated serum KL-6 levels at least one time by week 16 in GO-MONO

Treatment group[a]	Number of patients[b]	Percentage and incidence rate		
		Criterion A	Criterion B	Criterion C
GLM (50 mg)	79	1.3 % (4.1/100 PY)	1.3 % (4.1/100 PY)	0.0 % (0.0/100 PY)
GLM (100 mg)	91	2.2 % (7.1/100 PY)	2.2 % (7.1/100 PY)	0.0 % (0.0/100 PY)
GLM (combined)	170	1.8 % (5.7/100 PY)	1.8 % (5.7/100 PY)	0.0 % (0.0/100 PY)
Placebo	80	1.3 % (4.1/100 PY)	1.3 % (4.1/100 PY)	0.0 % (0.0/100 PY)

Percentages of the patients meeting the three criteria in the GLM groups combined did not differ significantly from the placebo group by the Fisher's exact probability test. Criteria A, B, and C for elevation of serum KL-6 levels are described in Table 1. The exposure period of patients who were withdrawn from the trial before week 16 was counted only for the period until the withdrawal. Lengths of exposure were 24.5 PY for the GLM 50 mg group, 28.2 PY for the GLM 100 mg group, and 24.7 PY for the placebo group

GLM Golimumab

[a] GLM (combined) refers to the total of all GLM treatment group patients

[b] Number of patients who gave consent to measure serum KL-6 levels and had available data

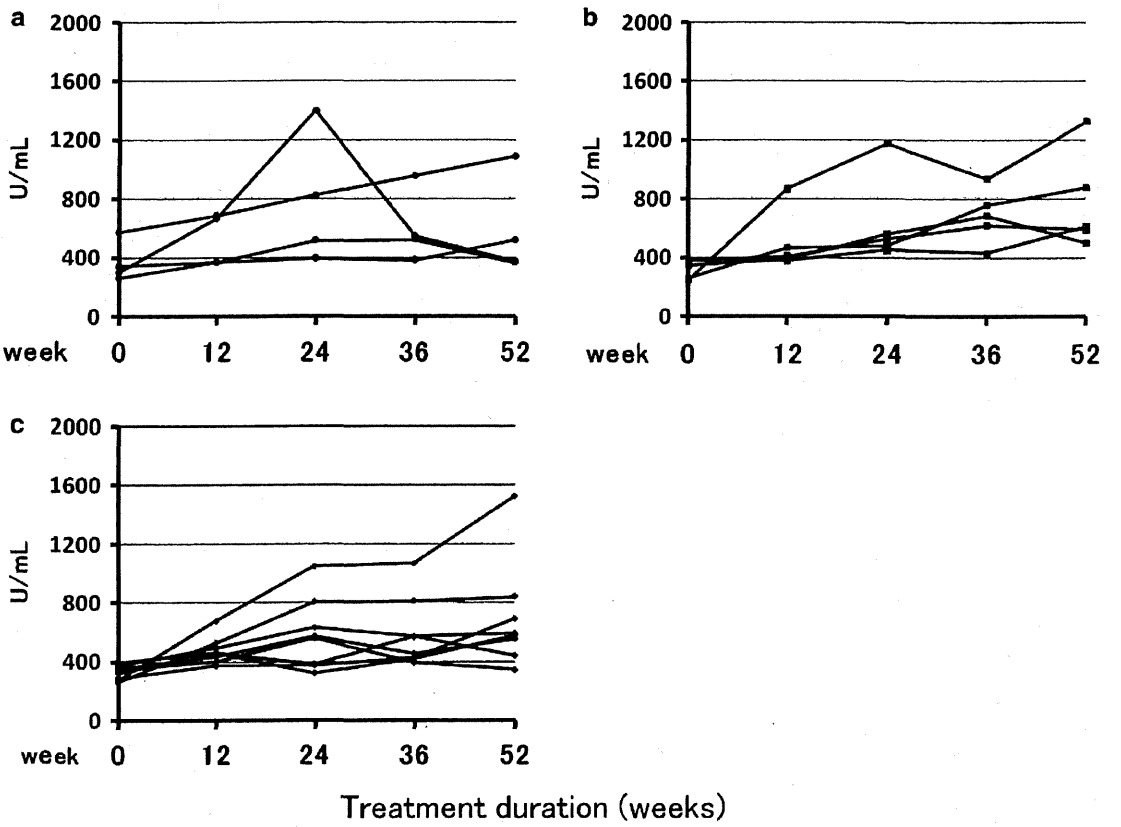

Fig. 4 Changes in serum KL-6 levels over time in 17 RA patients given golimumab (GLM) who met criterion B at least one time by week 52 in the GO-MONO study. Data from the placebo group ($n = 4$) (**a**), GLM 50 mg group ($n = 5$) (**b**), and GLM 100 mg group ($n = 8$) (**c**) are shown separately. The treatment for each patient was changed as described in ESM Fig. S3

criterion B by week 52, no patients developed the predefined pulmonary events, but one case of organizing pneumonia was reported by week 52. We could not identify other specific reasons, including malignancy, for the elevation of KL-6 serum levels in these 17 patients.

Changes in serum KL-6 levels over time in these 17 RA patients meeting criterion B in the placebo group (4 patients), the GLM 50 mg group (5), and the GLM 100 mg group (8) are shown in Fig. 4. One patient from the placebo group met criterion B when receiving placebo, while 3

patients met criterion B after their treatments were changed to 50 mg of GLM. Serum KL-6 levels spontaneously decreased to meet criterion R by week 52 in 6 (35.3 %) of the 17 RA patients. Of these 17 RA patients, 7 had serum KL-6 data available after reaching their maximum level of whom 6 (85.7 %) met criterion R by week 52.

Elevation of serum KL-6 levels in GO-FORTH

Patients in GO-FORTH who entered EE at week 16 from the MTX + placebo group received 50 mg of GLM with MTX and the MTX + GLM 50 mg group received 100 mg. All patients in the MTX + placebo group who did not enter EE received 50 mg of GLM at week 24 (ESM Fig. S3). We therefore performed on-drug analysis for weeks 0–24. The exposure period of patients who entered EE at week 16 included only the first 16 weeks in their originally allocated treatment group. The exposure period of patients who did not enter EE was 24 weeks or until withdrawal from the trial, whichever came first. Between weeks 0 and 24, 3 (4.4 %) patients from the MTX + GLM 50 mg group, 7 (9.7 %) patients from the MTX + GLM 100 mg group, and 10 (7.1 %) patients from MTX + GLM groups combined satisfied criterion B, while no patients from the MTX + placebo group met criterion B ($p = 0.017$ for GLM groups combined and $p = 0.013$ for GLM 100 mg group using the Fisher's exact probability test) (Table 6). By week 52, of the 212 patients, 9.4 % (10.9/100 PY) met criterion A, 9.0 % (10.4/100 PY) met criterion B, and 0 % (0/100 PY) met criterion C. For this 52-week analysis, the exposure periods were the same as those described for GO-MONO.

We analyzed the association between elevated serum KL-6 levels and pulmonary events as defined in "Patients and methods". Among the 19 cases meeting criterion B by week 52, no patients developed the predefined pulmonary events. We could not identify other specific reasons, including malignancy, for the elevation of KL-6 serum levels in these patients.

Changes in serum KL-6 levels over time in these 19 RA patients meeting criterion B in the MTX + placebo (6 patients), the MTX + GLM 50 mg group (5), and the MTX + GLM 100 mg group (8) are depicted in Fig. 5. All patients from the MTX + placebo group met criterion B after their treatments were changed to 50 mg of GLM with MTX. Serum KL-6 levels spontaneously decreased to meet criterion R by week 52 in ten (52.6 %) of these 19 RA patients. Of these 19 RA patients, 11 had serum KL-6 data available after reaching their maximum level of whom 10 (90.9 %) met criterion R by week 52.

Discussion

The major findings of our study are that: (1) the use of TNF inhibitors was significantly associated with elevated serum KL-6 levels compared to placebo in two of the four clinical trials studied; (2) 8.0–18.6 % of RA patients given TNF inhibitors met criterion A, 6.8–15.3 % met criterion B, and 0–2.6 % met criterion C by year 1; (3) 134 (95.7 %) of 140 patients who met criterion B did not have any other specific clinical reasons for the elevation of serum KL-6 levels and the serum marker spontaneously decreased in the majority of these patients.

While we have presented data for serum KL-6 levels during treatment with TNF inhibitors from five clinical trials in a similar manner in our attempt to compare these trials, it should be noted that the frequency of the

Table 6 Percentage and incidence rate/100 PY of patients who met the criteria for elevated serum KL-6 levels at least one time by week 24 in GO-FORTH

Treatment group[a]	Number of patients[b]	Percentage and incidence rate		
		Criterion A	Criterion B	Criterion C
GLM (50 mg)	68	4.4 % (9.8/100 PY)	4.4 % (9.8/100 PY)	0.0 % (0.0/100 PY)
GLM (100 mg)	72	9.7 % (20.9/100 PY)	9.7 % (20.9/100 PY)**	0.0 % (0.0/100 PY)
GLM (combined)	140	7.1 % (15.6/100 PY)	7.1 % (15.6/100 PY)*	0.0 % (0.0/100 PY)
Placebo	72	1.4 % (3.4/100 PY)	0.0 % (0.0/100 PY)	0.0 % (0.0/100 PY)

Criteria A, B, and C for elevation of serum KL-6 levels are defined in Table 1. The exposure period of patients who entered EE at week 16 was considered to be 16 weeks. The exposure period of patients who did not enter EE was considered to be 24 weeks or until withdrawal from the trial. Lengths of exposure were 30.7 PY for the MTX + GLM 50 mg group, 33.5 PY for the MTX + GLM 100 mg group, and 29.8 PY for the MTX + placebo group

Significance * $p = 0.017$ (the GLM groups combined vs. placebo group), ** $p = 0.013$ (the GLM 100 mg vs. placebo group) by the Fisher's exact probability test

[a] In GO-FORTH, patients received placebo, GLM 50 mg, or GLM 100 mg with concomitant MTX. GLM (combined) refers to the total of all GLM treatment group patients

[b] Number of patients who gave consent to measure serum KL-6 levels and for whom data were available

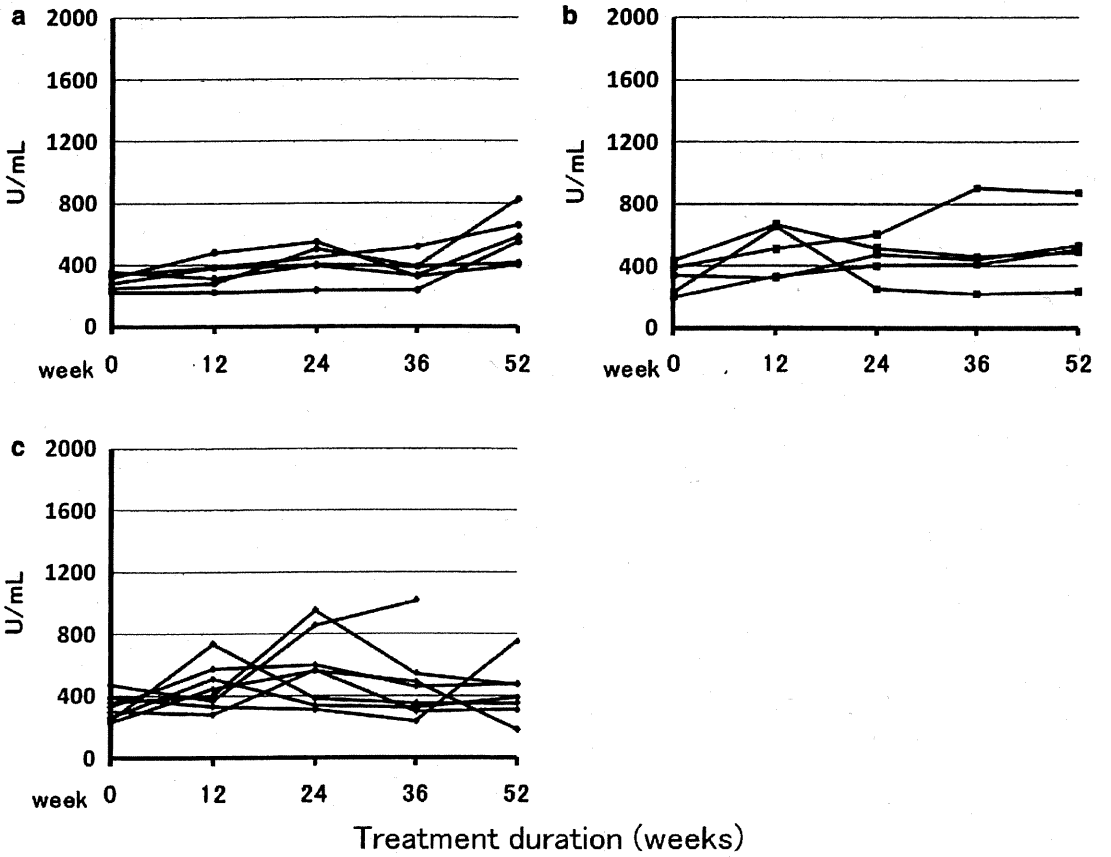

Fig. 5 Changes in serum KL-6 levels over time in 19 RA patients given GLM who met criterion B at least one time by week 52 in the GO-FORTH study are shown. Data from the MTX + placebo group ($n = 6$) (**a**), MTX + GLM 50 mg group ($n = 5$) (**b**), and MTX + GLM 100 mg group ($n = 8$) (**c**) are shown separately. The treatment for each patient was changed as described in ESM Fig. S3

measurement of serum KL-6 levels differed among these clinical trials and that the designs of the trials varied in terms of length of placebo-controlled and DB periods, EE, and treatment changes after the DB periods (ESM Figs. S1, S2, S3). The frequency of KL-6 measurement was highest in HIKARI and J-RAPID, followed by RISING, GO-MONO, and GO-FORTH. Because the spontaneous reduction of serum KL-6 levels was observed in all clinical trials, less frequent measurements may result in lower percentages of patients meeting the criteria for elevation of serum KL-6 levels. It should also be noted that the patient populations were different among the five clinical trials because of their mutually independent eligibility criteria. These differences should be considered when our findings are interpreted.

In HIKARI and J-RAPID, serum levels of pulmonary surfactant protein D (SP-D), another marker for interstitial lung disease [19], were retrospectively measured and visually compared with changes in serum KL-6 levels over time in some patients who met criterion B and had relatively high serum KL-6 levels. Both serum markers increased in parallel in about half of these patients (data not shown). Serum lactate dehydrogenase levels were also measured in these patients, but these did not correlate with serum KL-6 levels. These data indicate that the elevation of serum KL-6 levels in RA patients given TNF inhibitors was not a non-specific fluctuation, but may be associated with subclinical interstitial changes in the lung or that TNF may have a physiological role in regulatory pathways common to both serum markers.

In Japan, PCP is one of the most clinically important opportunistic infection in RA patients during treatment with TNF inhibitors [3, 4, 20]. Because serum KL-6 levels frequently increase in patients with PCP [10], the elevation of serum KL-6 levels in RA patients given TNF inhibitors may be explained by subclinical PCP. However, chest X-ray or thoracic computed tomography has not supported this hypothesis (data not shown). Serum levels of beta-D-glucan (BDG), a marker for PCP [21], were prospectively measured in HIKARI and J-RAPID. Of 21 patients who met criterion B by week 52 in HIKARI, an abnormal elevation of serum BDG levels (≥11.0 pg/ml) was observed