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ORIGINAL ARTICLE



# Current monitoring and treatment of progressive fibrosing interstitial lung disease: a survey of physicians in Japan, the United States, and the European Union

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**ABSTRACT**

**Objective:** To understand assumptions about and approaches to interstitial lung disease (ILD), including those of the progressive phenotype (progressive fibrosing ILD), this multinational survey assessed physicians' attitudes toward, knowledge of, and management strategies for progressive fibrosing ILD.

**Methods:** This internet-based survey of physicians was conducted between November 2018 and February 2019. Practical management strategies for progressive fibrosing ILD, and current approaches to the assessment and treatment of ILD, were compared between countries/regions (Japan vs. United States and European Union) and specialties (pulmonologists vs. rheumatologists).

**Results:** The survey was completed by 574 respondents. Compared with Western countries, the progressive fibrosing phenotype concept was not widely understood by Japanese respondents, with no notable differences in the understanding of this phenotype between pulmonologists and rheumatologists. Across all regions, pulmonary function tests, diffusing capacity of the lungs for carbon monoxide assessments, and pulse oximeter measurements were commonly performed at intervals of ≤6 months. In general, physicians in the United States and European Union preferred physiologic approaches for follow-up, while those in Japan preferred imaging and blood monitoring. Compared with rheumatologists, pulmonologists performed more frequent monitoring of autoimmune ILDs, and the differences between specialties were most pronounced in Japan. Regional differences in treatment approaches were observed, probably reflecting the local availability of agents and healthcare environments.

**Conclusions:** Awareness and management of progressive fibrosing ILD varied between specialties and regions, highlighting an unmet need for standardized diagnosis, treatment guidelines, and specialist education in this area.

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## Introduction

Interstitial lung disease (ILD) comprises over 200 different, uncommon conditions, several of which can cause pulmonary fibrosis[1,2]. For many ILD subtypes, the precise etiology is unknown[1,3], although identified causes include environmental and occupational exposure and, in some cases, autoimmune response[4]. Similarly, the epidemiology of ILDs is not well understood, with existing estimates varying between countries; however, most ILDs are considered rare diseases[5–10].

Chronic and irreversible lung damage can occur in ILD[11]. The clinical course of ILD is defined by several consistent features, including progressive pulmonary fibrosis, declining lung function, worsening symptoms, and premature death; this can occur irrespective of appropriate ILD management based on currently available information or clinical experience (for example, avoiding exposure to the causal antigen for chronic hypersensitivity pneumonitis or using immunomodulatory therapies for autoimmune ILDs)[12–15]. The sole curative treatment option for patients with fibrosing ILDs is lung transplantation, which is feasible in only a subset of individuals[16]. Although the post-transplant mortality rate is lower than that in patients with other lung conditions such as cystic fibrosis[17], survival among ILD patients following lung transplantation is higher than that among patients who do not undergo the procedure[18].

There is increasing recognition of a subgroup of ILDs that have a progressing fibrotic phenotype characterized by progressive fibrosis on high-resolution computed tomography (HRCT), worsening symptoms, impaired quality of life, and

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early death despite treatment with currently available therapies[19–23]. The pathology of progressive fibrosing ILD is diverse but can be divided broadly into cases with and without autoimmune features[20]. Among the non-autoimmune forms of ILD, idiopathic pulmonary fibrosis (IPF) is a common progressive fibrosing ILD, but other forms of ILD may also develop the progressive fibrosing phenotype[20,24] and have been reported to represent 13%–40% of patients with fibrotic ILDs other than IPF[25].

There are difficulties in identifying patients with progressive fibrosing ILD in clinical practice and in estimating accurate prevalence rates. This is because of low levels of awareness and the need for appropriate expertise and access to suitable imaging techniques to make an accurate diagnosis[3,12]. Delays in diagnosis of IPF, a representative disease among PF-ILD, have been attributed to difficulties in accessing medical care, recognizing symptoms, and timely referral to specialized care[26–29]. Current treatment strategies for progressive fibrosing ILD differ depending on the underlying disease diagnosis (especially for ILD resulting from autoimmune diseases such as rheumatoid arthritis, systemic sclerosis [SSc], systemic lupus erythematosus, Sjogren's syndrome, or polymyositis/dermatomyositis), the individual clinician, and the region[13]. Combination treatment with glucocorticoids, immunosuppressants, and N-acetylcysteine was considered as a treatment for IPF, but data from a randomized controlled trial reported harmful effects, including elevated risks of death and hospitalization[30]. Drugs with an immunomodulatory effect, such as immunosuppressants, are currently used for patients with autoimmune features[31,32]. The presence of common pathobiologic mechanisms across all ILDs with a progressive fibrosing phenotype may indicate that these disorders might respond to similar types of treatment[22].

In clinical practice, non-autoimmune ILDs are usually managed by pulmonologists while autoimmune ILDs are managed by pulmonologists and/or rheumatologists. However, given that ILDs are varied and individual forms may not be widely encountered in clinical practice[1,2], specific experience may be limited. The medical environment and health insurance systems differ in the United States, Europe, and Japan; therefore, test methods used in disease management and the cost to the patient differ[33,34], which may affect ILD treatment strategies.

Nintedanib, a tyrosine kinase inhibitor (TKI), was recently approved for the treatment of progressive fibrosing ILD based on the results of the INBUILD trial, in which patients presented with features of diffuse fibrosing lung disease of >10% extent on HRCT and met the progression criteria comprising worsening lung function, worsening respiratory symptoms, and/or evidence of increasing fibrosis on chest imaging, despite appropriate treatment for underlying diseases[21,35]. Pirfenidone, which is approved for the treatment of IPF, was recently evaluated in a phase 2 global study for its efficacy in patients with fibrosing unclassifiable ILD, and might have effectiveness in this population, a subtype of progressive fibrosing ILDs with an unmet need for pharmacological treatment options[36]. Such anti-fibrotic therapies may be initiated as second-line treatment following progression on conventional treatment, while other strategies, such as combined immunosuppression and anti-fibrotic therapy, should be implemented on a case-by-case basis[37].

To gain a better understanding of the knowledge of and approaches to ILD, this multinational survey assessed physicians' attitudes toward and knowledge of progressive fibrosing ILD and strategies used for ILD management, including the progressive fibrosing phenotype, in current clinical practice. Practices were compared among countries/regions (Japan vs. the United States and the European Union) and between specialties (pulmonologists vs. rheumatologists).

## Methods

### Study design

This study was an internet-based survey of physicians from Japan, the United States, France, Germany, Italy, Spain, and the United Kingdom conducted between November 2018 and February 2019. Because this was a voluntary survey of physicians, no ethical approval was needed. Personal data were protected, per the General Data Protection Regulation European Union law, and the study complied with all applicable laws in the other participating countries.

### Participants

To be eligible, medical specialists (pulmonologists and rheumatologists) had to meet the following criteria: have 3–35 years of practice in their specialty since graduation; manage ≥6 patients with non-IPF ILD per year; manage or co-manage more than half of their practice's patients with non-IPF ILD; be affiliated with a hospital that has 100 or more beds; spend ≥75% of their professional time in direct patient care; and not currently be affiliated to, employed by (other than involvement in clinical trials), or hold ownership (not including stock ownership) in a pharmaceutical or biotech company, healthcare consulting company, research company, or within the US Food and Drug Administration or any other regulatory bodies. Based on available data, which suggested that development of progressive fibrosing ILD occurs in 18%–32% of patients with non-IPF ILD[38], we considered that a likely progression rate of around 20% combined with a minimum non-IPF ILD patient load of six per year made it possible to assume that all specialists completing the survey should have some experience managing patients with progressive fibrosing ILD.

Internal medicine physicians were included in France and Spain; however, they were excluded from the description of results by specialty. Physicians in the United States, Germany, Spain, and Japan were invited *via* email to complete an online survey. Invitation emails for this survey were sent by the research agency to possible physicians based on the number of IPF diagnoses for pulmonologists, and according to specialty information assembled by the research agency for rheumatologists and internal medicine physicians. For France, the United Kingdom, and Italy, recruitment was *via* email and

Table 1. Characteristics of physicians who responded to the survey.

| | Japan $N = 101$ | United States $N = 132$ | European Union[a] $N = 341$ |
|---|---|---|---|
| Sex | | | |
| Male | 96 (95%) | 108 (82%) | 230 (67%) |
| Female | 2 (2%) | 16 (12%) | 101 (30%) |
| Prefer not to answer | 3 (3%) | 8 (6%) | 10 (3%) |
| Age, years | | | |
| 18–30 | 2 (2%) | 0 (0%) | 2 (1%) |
| 31–40 | 44 (44%) | 15 (11%) | 75 (22%) |
| 41–50 | 24 (24%) | 39 (30%) | 154 (45%) |
| 51–63 | 30 (30%) | 63 (48%) | 107 (31%) |
| >63 | 1 (1%) | 15 (11%) | 3 (1%) |
| Specialty | | | |
| Pulmonology | 60 (59%) | 80 (61%) | 172 (50%) |
| Rheumatology | 41 (41%) | 52 (39%) | 128 (38%) |
| Internal medicine | – | – | 41 (12%) |
| Practice setting | | | |
| Specialist ILD center[b] | – | 13 (10%) | 44 (13%) |
| Specialist ILD center outside a hospital (GER only) | – | – | 1 (<1%) |
| Specialist systemic sclerosis center[b] | – | 3 (2%) | 16 (5%) |
| Specialist systemic sclerosis center outside a hospital (GER only) | – | – | 1 (<1%) |
| Academic hospital/teaching hospital/research center/university medical college or academy | 32 (32%) | 36 (27%) | 154 (45%) |
| Community hospital (non-academic)/non-teaching hospital | 69 (68%) | 14 (11%) | 77 (23%) |
| Private office/office-based practice | – | – | 48 (14%) |
| Private practice, community hospital affiliation (US only) | – | 66 (50%) | – |
| Median time in practice, years | 15.0 | 18.0 | 14.8 |
| Mean number of patients with non-IPF ILD seen per year (respiratory medicine) | 41.6 | 130.2 | 87.2 |
| Mean number of patients with non-IPF ILD seen per year (rheumatology) | 52.7 | 202.3 | 58.5 |

Abbreviations. GER, Germany; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; US, United States. Data are shown as *n* (%) unless otherwise stated.
[a]GER, France, United Kingdom, Italy, and Spain; [b]Within a hospital (GER only).

telephone contact for initiation, and respondents were then sent the survey *via* email. Up to three rounds of reminder emails and/or telephone calls were used at 1- or 2-day intervals in the United States, and several reminders in Italy and Spain were sent at 1- or 2-day intervals *via* email and/or telephone. For other countries, several reminders were sent at 7- or 10-day intervals during the survey period *via* email and/or telephone until the planned sample size was achieved.

### Definitions

In this survey, progressive fibrosing ILD was defined as progression in the deterioration of lung function (forced vital capacity [FVC]) and/or worsening of respiratory symptoms, and/or increasing extent of fibrotic changes on chest imaging despite treatment with (unapproved) medication used in clinical practice to treat ILD plus the presence of fibrosis detected by HRCT (i.e. reticular abnormality with traction bronchiectasis, with or without honeycombing). The survey included the following definitions of ILD: idiopathic nonspecific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, hypersensitivity pneumonitis, exposure-associated ILD (e.g. asbestosis and silicosis), sarcoidosis ILD, SSc-ILD, rheumatoid arthritis-associated ILD, and other connective tissue disease ILDs (e.g. systemic lupus erythematosus ILD, Sjogren's syndrome ILD, mixed connective tissue disease ILD, and polymyositis/dermatomyositis ILD [PM/DM-ILD]).

### Survey and analysis

The survey questions in English were translated into local languages, and the accuracy of translation was confirmed by a native language speaker from each country. Physicians in departments that diagnose and treat patients with ILD were selected for inclusion in this survey. The planned and actual sample sizes for each specialty and country are summarized in Supplementary Table 1. Data were collected and analyzed using IBM SPSS Data Collection Base Professional 6.0.1 (IBM, Armonk, NY, USA).

## Results

### Participant details

Details of the physicians who participated in the study are summarized in Table 1. A total of 9247 invitation emails were sent (1216 for the United States, 3233 for Japan, and 4798 for the European Union [i.e. France, Germany, Italy, Spain, and the United Kingdom]), and 574 physicians completed the survey (101 from Japan, 132 from the United States, and 341 from the European Union). The ratio of respondents in Japan was lower than that for the United States and the European Union; however, the median years of practice among Japanese physicians was comparable with that of the overall study population (Table 1). Slightly more pulmonologists than rheumatologists completed the survey. Notably, rheumatologists were only involved in the management of autoimmune ILDs. The majority of respondents were male, and most were aged between 31 and 63 years. In all countries, respondents were well balanced from across a wide range of geographic regions. The annual mean number of patients with non-IPF ILD in Japan, the US, and Europe was 41.6, 130.2, and 87.2, respectively, for pulmonologists and 52.7, 202.3, and 58.5, respectively, for rheumatologists.

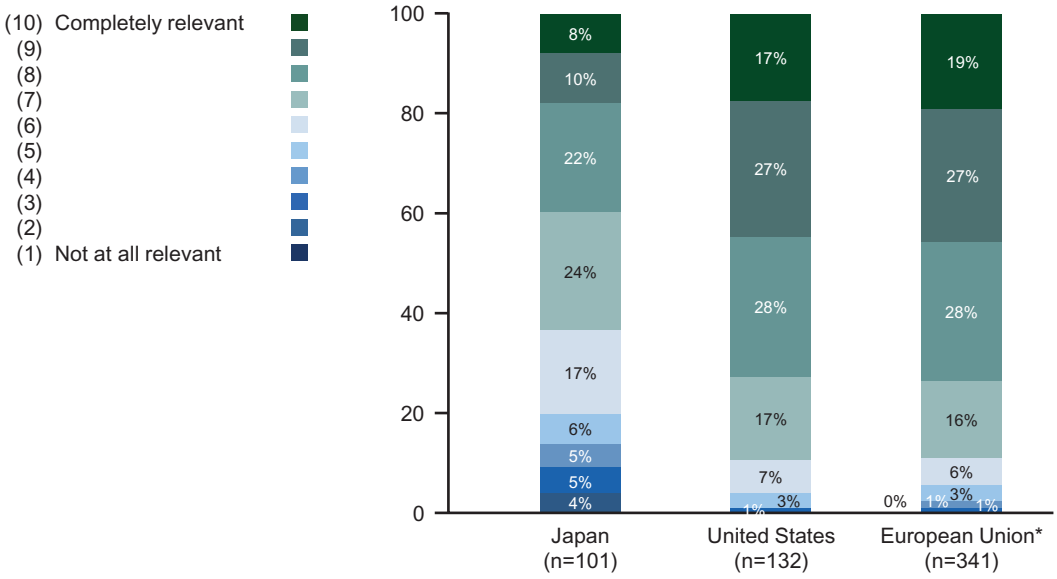


**Figure 1.** Relevance of the progressive fibrosing phenotype of interstitial lung disease (ILD) by region (on a scale from 1–10, where 1 is "not at all relevant" and 10 is "completely relevant"). *Germany, France, United Kingdom, Italy, and Spain.
The following questions were asked in this portion of the survey:
For the following course of the interview please carefully read the following definition.
In this research, progressive fibrosing ILD is defined as a phenotype that might occur in different forms of ILD, characterized by:
(1) progression in terms of deterioration of lung function (FVC = forced vital capacity) and/or worsening of respiratory symptoms, and/or increasing extent of fibrotic changes on chest images despite treatment with (unapproved) medication used in clinical practice to treat ILD
AND
(2) the presence of fibrosis detected by high resolution CT (i.e. reticular abnormality with traction bronchiectasis, with or without honeycombing)
The terminology to describe this phenotype is progressive fibrosing ILD (PF-ILD).
How relevant is this definition—patients with a common progressive fibrosing ILD clinical behavior irrespective of different forms of ILD—for you?

### *Understanding of the progressive fibrosing ILD phenotype*

Physician rating of the relevance of the progressive fibrosing phenotype is summarized in Figure 1. Overall, 40% of physicians from Japan, 73% from the United States, and 73% from the European Union reported that the phenotype was relevant (score of 8–10); 9% of physicians from Japan, 1% from the United States, and 1% from the European Union reported that the phenotype was not relevant (score of 1–3). Thus, the progressive fibrosing phenotype concept was considered less relevant by physicians in Japan compared with the other countries. There were no notable differences between pulmonologists and rheumatologists regarding the relevance of the progressive fibrosing phenotype (data not shown).

### *Current assessment of ILD*

Findings regarding monitoring carried out by pulmonologists for non-autoimmune ILDs are summarized in Figure 2(A). Across all countries, pulmonary function tests (PFTs), assessment of diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$), and pulse oximeter measurements were commonly performed at intervals ≤6 months.

In general, pulmonologists in the United States and European Union preferred physiologic approaches for follow-up, while those in Japan preferred imaging, including HRCT, which was performed more frequently in Japan (usually within intervals of ≤3 months or 4–6 months) than in the assessed Western regions. All pulmonologists in Japan reported performing HRCT and chest X-ray at least every 12 months, whereas approximately 30% of pulmonologists from the United States and European Union reported performing these evaluations only when symptoms worsened. The percentage of pulmonologists who preferred to perform chest X-rays every 3 months was approximately 80% in Japan versus approximately 10% in the other regions; corresponding values for the percentages of pulmonologists performing HRCT at ≤3-month intervals were 10%–32% and 2%–12%.

Blood tests, such as serum levels of the interstitial biomarkers Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D), were more widely used in Japan than in the United States and European Union. In Japan, 70% of pulmonologists reported performing blood tests at intervals of ≤3 months compared with 10%–14% of pulmonologists in the other regions (Figure 2(A)). Notably, 37% of pulmonologists in the European Union and 55% in the United States reported never performing a blood test for patients with ILD, with a similar rate reported for their patients with progressive fibrosing ILD.

The six-minute walk test (6MWT) was used more commonly in the United States and European Union than in Japan (Figure 2(A)). If progression was observed, the frequency of testing increased, especially HRCT, PFT, and $DL_{CO}$ in all regions, while 6MWT and pulse oximeter testing was notably increased in the United States and European Union. The follow-up interval was shorter in progressive fibrosing ILD than for all ILDs (data not shown).

Findings regarding the monitoring of autoimmune ILDs (mainly collagen disease) are summarized in Figure 2(B). The choice of the type of monitoring test was similar to that for

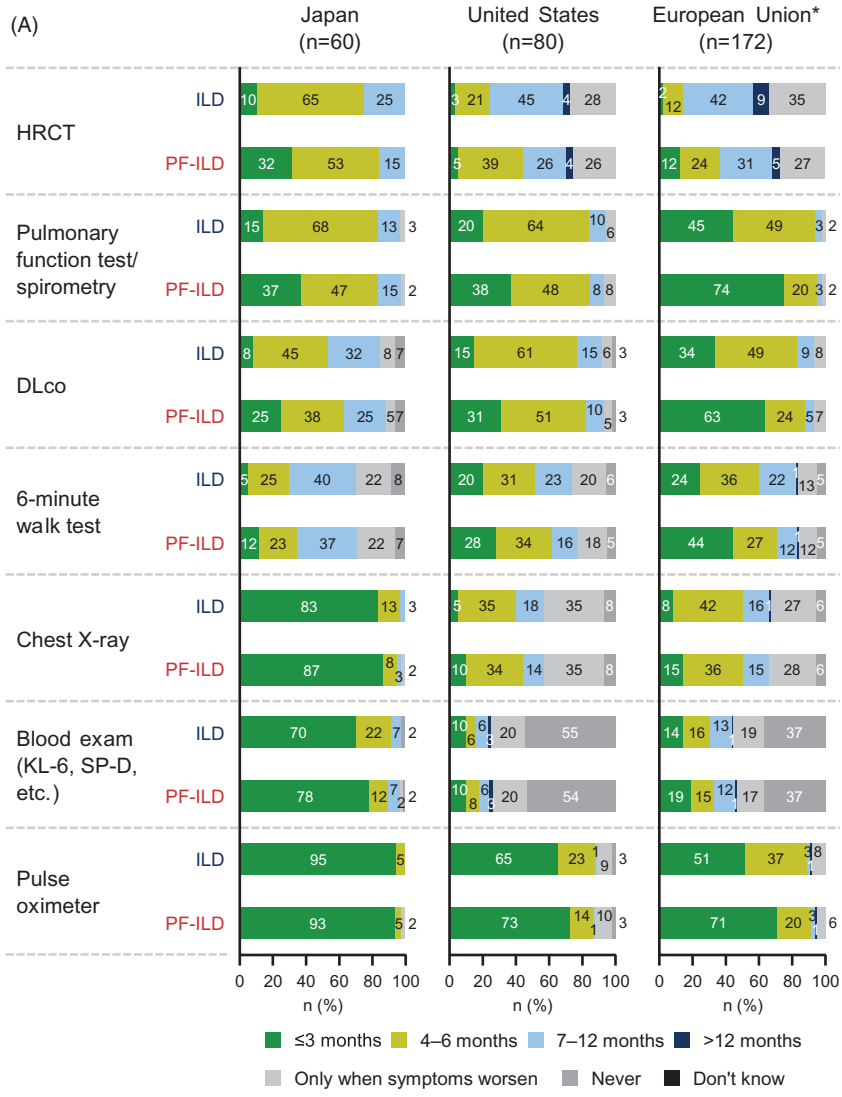


**Figure 2.** Monitoring tests for the progression of ILD with non-autoimmune (asking pulmonologists only) (A) and autoimmune (B) backgrounds. *Germany, France, United Kingdom, Italy, and Spain. For each monitoring test, the upper bars refer to patients with ILD and lower bars to those with progressive fibrosing ILD. Abbreviations. $DL_{CO}$, diffusing capacity of the lungs for carbon monoxide; HRCT, high resolution computed tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; PF-ILD, progressive fibrosing interstitial lung disease; SP-D, surfactant protein-D.

The following questions were asked in this portion of the survey:

This section aims to get a deeper understanding on monitoring (of patient's lung disease) and current treatment of your ILD patients.

In this section we would be interested in your patients with a non-autoimmune/autoimmune ILD. Once an ILD is diagnosed in patients with a non-autoimmune ILD that is NOT IPF/autoimmune ILD, typically, how frequently would the following tests be repeated on average for monitoring of the patient's lung disease?

*Non-autoimmune ILD covers for example: Idiopathic nonspecific interstitial pneumonia (NSIP), unclassifiable idiopathic interstitial pneumonia, hypersensitivity pneumonitis, exposure-associated ILD (e.g. asbestosis, silicosis), sarcoidosis-associated ILD.*

Please select one answer per row (per test).

Please specify the frequency if you do serial tests OR choose "a test would only be repeated if symptoms worsen" OR "never."

non-autoimmune ILDs, but the frequency of monitoring was lower in autoimmune ILDs than in non-autoimmune ILDs. More physicians answered "never" or "don't know" regarding monitoring of autoimmune ILDs compared with that of non-autoimmune ILDs. This may be partly explained by different rates of test selection by specialty, as described below.

Findings regarding progressive fibrosing ILD monitoring by specialty are summarized in Figures 3(A) (pulmonologists) and 3(B) (rheumatologists). A trend was observed regarding more frequent monitoring by pulmonologists than by rheumatologists for autoimmune ILD management in all monitoring tests; this trend was most pronounced in Japan. In Japan, PFT, $DL_{CO}$, and 6MWT were less often used by rheumatologists than by pulmonologists, whereas the frequency of use of X-rays, blood tests, and pulse oximetry was similar between the two specialties. In rheumatology departments, tests are performed based on symptoms. Although similar for all regions, this was most pronounced in Japan.

## *Current treatment of ILDs*

Responses regarding the treatment of autoimmune ILDs by specialty are summarized in Figures 4(A) (pulmonologists) and 4(B) (rheumatologists). Some of the differences seen reflect the specific immunosuppressants available in each region; for example, mycophenolate mofetil (MMF) and


**Figure 2.** Continued

rituximab were used in the United States and European Union, except Germany, and tacrolimus was used in Japan. The low treatment rate for ILD highlights the limited number of treatments approved for this indication. More stable ILD cases tend to be maintained with low-dose steroids (although the specific steroid utilized could not be discerned from the survey). Steroids were used by both specialties, and immunosuppressants were used more often by rheumatologists (Figure 4(B)) than by pulmonologists (Figure 4(A)).

## Discussion

The results of the present survey highlight differences in the awareness and management of progressive fibrosing ILD between specialties and regions, underlining the need for standardized diagnosis, treatment guidelines, and specialist education in this field.

The progressive fibrosing ILD phenotype grouping is a relatively new concept based on the specific progressive fibrosing characteristic across academic classifications or diagnoses of ILD. Therefore, awareness among physicians may be low, and disease categorization may be based on other background disease features including disease behavior[39]. However, the key features are the progressive nature and behavior of the disease[22]. Some clinical trials to assess the efficacy of medications for this subgroup of ILD patients have been conducted and others are ongoing. Inclusion criteria for these studies were based on the features of progressive fibrosing disease, rather than a specific condition or conditions[35,36,40]. Given the current challenges relating to disease classification and nomenclature, this survey provides important insights into the current knowledge relating to progressive fibrosing ILDs and their management, allowing us to highlight knowledge gaps and suggest potential avenues for improved patient care.

Findings from this study reflect the current approach to managing ILD and progressive fibrosing ILD in Japan and Western countries from the viewpoint of both pulmonologists and rheumatologists. The lower response rate for Japanese physicians may be attributable to regional differences among physicians treating ILD patients. In the United States and European Union ILDs are diagnosed and managed

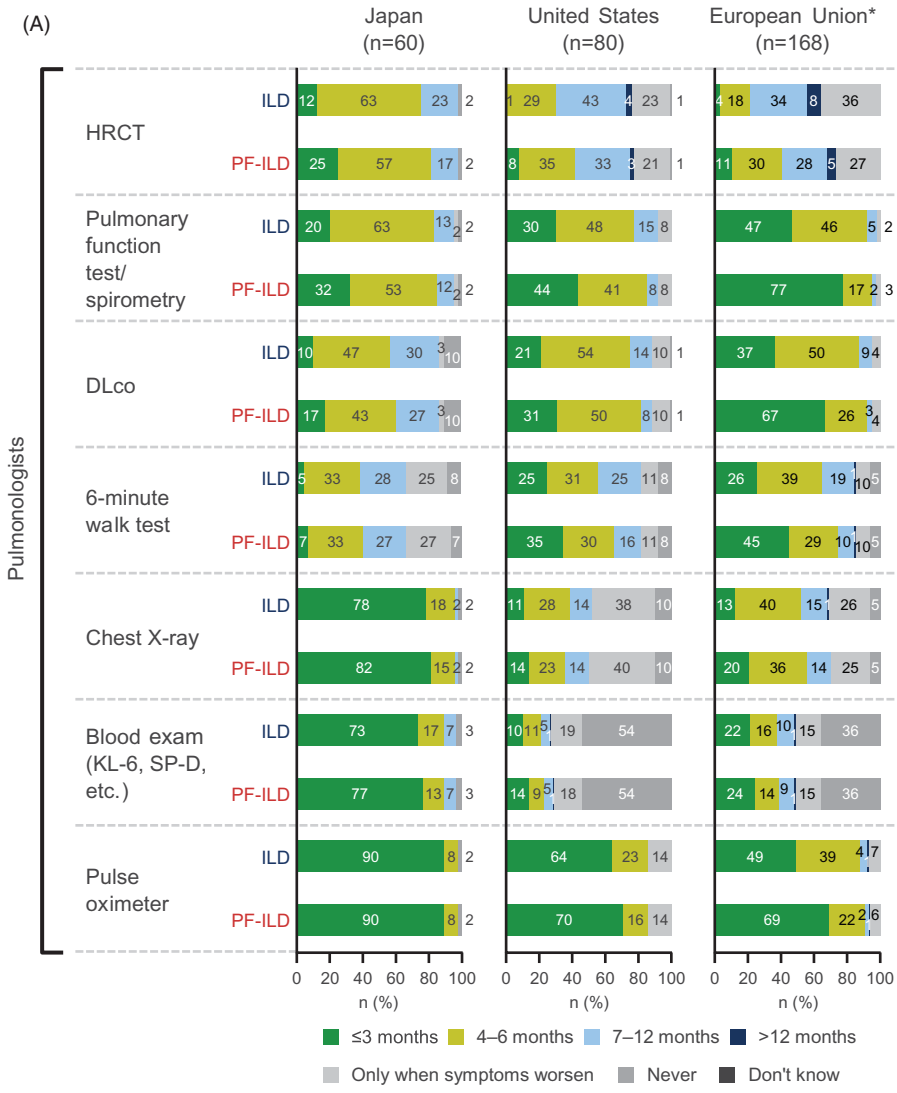


**Figure 3.** Monitoring tests for the progression of ILD with autoimmune backgrounds by physician specialty: pulmonologists (A) and rheumatologists (B). *Germany, France, United Kingdom, Italy, and Spain. For each monitoring test, the upper bars refer to patients with ILD and lower bars to those with progressive fibrosing ILD. Abbreviations. $DL_{CO}$, diffusing capacity of the lungs for carbon monoxide; HRCT, high resolution computed tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; PF-ILD, progressive fibrosing interstitial lung disease; SP-D, surfactant protein-D.
The following questions were asked in this portion of the survey:
Do you change the way you do your monitoring once a patient has been detected for progressive fibrosing ILD (according to the given PF-ILD phenotype)?
Please specify how frequently these tests would typically be repeated in patients with progressive fibrosing ILD.
Please select one answer per row (per test).
Please specify the frequency if you do serial tests OR choose "a test would only be repeated if symptoms worsen" OR "never."

by ILD experts at ILD centers or specific affiliate centers, while in Japan this is the responsibility of pulmonologists/ rheumatologists involved in the management of other diseases. Some important differences in the management of ILD and progressive fibrosing ILD were observed between the two specialties, even in the same region. Rheumatologists were less likely to conduct PFT, $DL_{CO}$, and 6MWT than pulmonologists. As there are specific requirements to ensure the reliability of PFT results[41], rheumatologists are likely to encounter some barriers in the use of these tests (e.g. lack of availability of maintained PFT facilities or experienced technicians).

The survey also found differences in the acceptance of the progressive fibrosing definition and in the monitoring and treatment of patients with progressive fibrosing ILD between regions. The proportion of physicians who thought that the progressive fibrosing phenotype was relevant was much lower in Japan than in the other regions; this may indicate that the concept of the progressive fibrosing phenotype in ILD was not widely accepted in Japan at the time of the survey. This might be attributable to an increased focus on making individual ILD diagnoses and choosing specific treatments for each, rather than grouping together conditions with similar characteristics. A cautious approach by Japanese physicians is consistent with previous publications reporting the management of idiopathic interstitial pneumonias (IIPs); the rate of diagnosis of unclassifiable IIPs was higher in Japan compared with that in the United States and

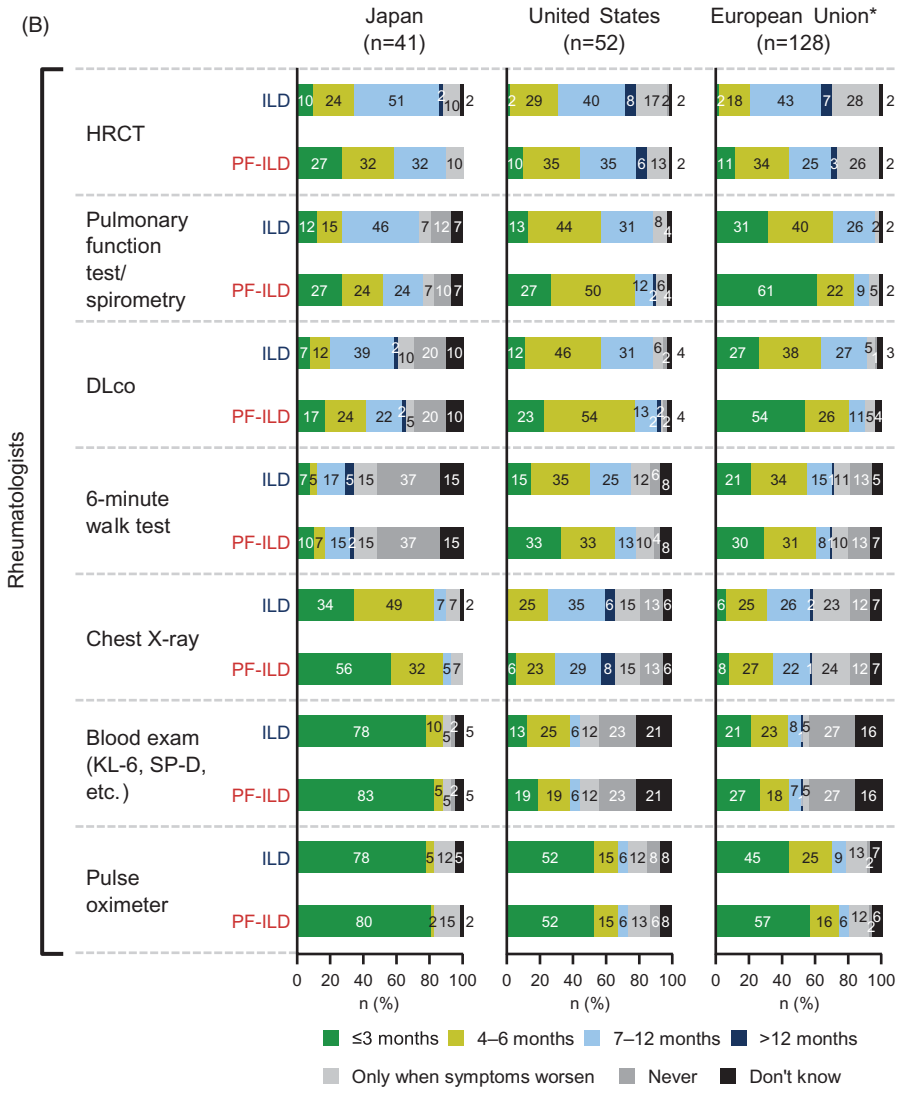


**Figure 3.** Continued

European Union, and the percentage of patients receiving a definitive diagnosis differed from region to region[42–47]. Lower acceptance of the progressive fibrosing ILD phenotype in Japan might also be attributable to the clinical diagnosis of "collagen disease" or "collagen vascular disease" rather than the documentation of individual cases of autoimmune ILDs in Japan. Cases of autoimmune ILD are heterogeneous in terms of underlying pathophysiology and clinical course, including outcome and treatment response, and encompass a spectrum of diseases and conditions including progressive fibrosing ILD and ILD, which are predominately attributable to inflammation without apparent irreversible fibrosis. This finding may also reflect hesitancy among Japanese physicians regarding a definitive diagnosis of this phenotype, because no standardized international consensus for defining ILD progression currently exists. Furthermore, the low physician rating of the relevance of the progressive fibrosing phenotype among Japanese respondents suggests that acceptance of the phenotype concept and imaging alone may not result in the diagnosis of progression. In real-world clinical settings, image analysis tends to be considered as a before/after comparison, meaning that, compared with acute changes, chronic changes may be difficult to identify using frequent testing. Although the appropriate frequency of imaging remains a topic of discussion, comparison with previous images (first test data or data obtained several years previously) would be required to identify such changes where relatively frequent imaging is performed.

Differences between regions were seen regarding the types and frequencies of monitoring tests performed for non-autoimmune ILDs. For instance, imaging and blood testing[48] were performed more frequently in Japan than in the United States and European Union, whereas the 6MWT was used more frequently in Western regions than in Japan. Different rates of blood biomarker testing might reflect differences between regions in access and reimbursement. The use of imaging (HRCT and chest X-ray) was much higher in Japan, in line with the previously reported high prevalence of CT assessment in Japan[49], meaning that the risk of radiation exposure needs to be considered when ordering frequent imaging studies. Although the choice of monitoring test for autoimmune ILDs was similar to that of non-

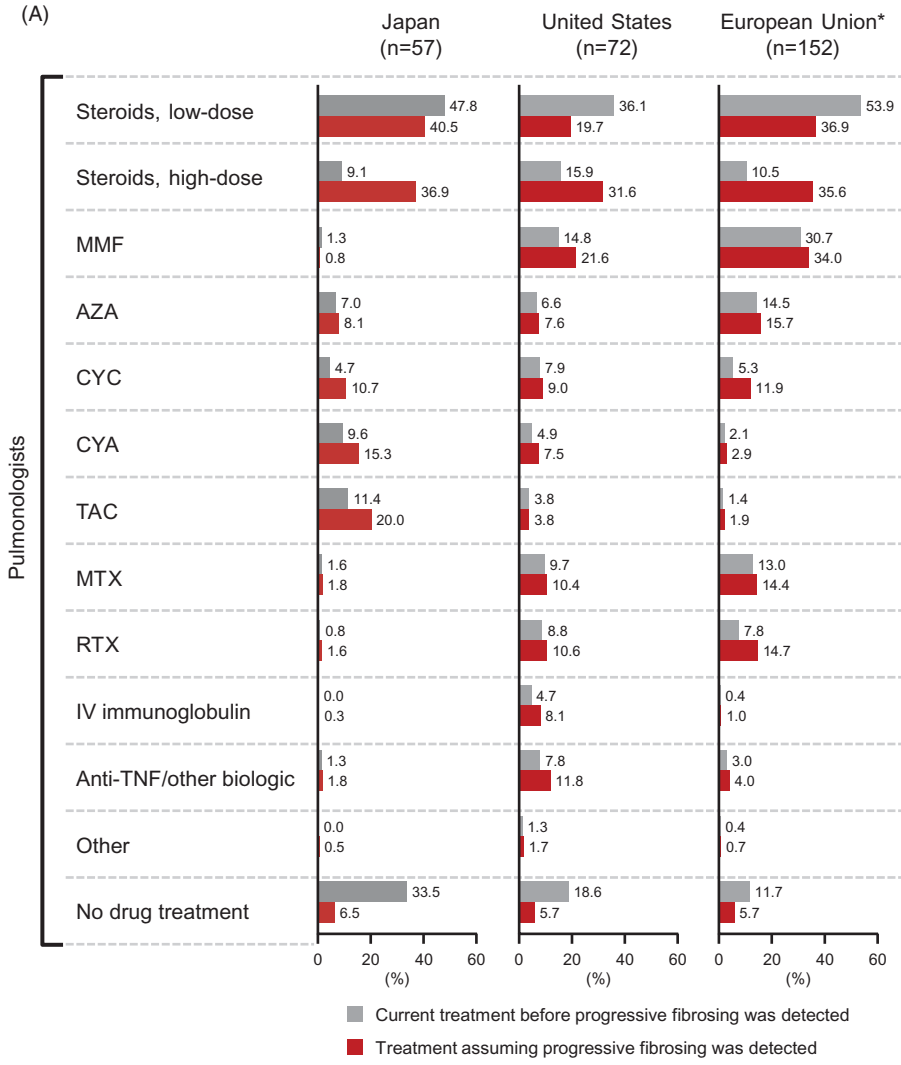


**Figure 4.** Current treatment of autoimmune ILD with or without progression by physician specialty: pulmonologists (A) and rheumatologists (B). *Germany, France, United Kingdom, Italy, and Spain. Abbreviations. AZA, azathioprine; CYA, cyclosporine; CYC, cyclophosphamide; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab; TAC, tacrolimus; TNF, tumor necrosis factor.
The following questions were asked in this portion of the survey:
Please think of your patients who have an ILD with an autoimmune (AI)/connective tissue disease (CTDs) and who do not (yet) have a progressive fibrosing ILD.
How many of these patients receive each of the following drug treatments for their ILD?
*If you plan a combination therapy, please count each treatment component per patient. The sum can be higher than the number of patients.*
How would you change drug treatment once a progressive fibrosing ILD is detected in (all) these patients?
*Please reallocate your patients. If you would not change a patient's therapy, please provide the same numbers as in the previous question.*
*If you plan a combination therapy, please count each treatment component per patient. The sum can be higher than the number of patients.*

autoimmune ILDs across regions, the actual frequency of monitoring of autoimmune ILDs was lower than that of non-autoimmune ILDs. In Japan, frequent imaging and broad access to blood tests is standard, based on ready access to CT imaging plus broad health insurance coverage[49], and might result in low awareness of medical radiation exposure, which may not be the case at ILD reference centers in Western countries. In patients with diffuse disease in Japan, imaging is performed at diagnosis and HRCT is performed at 3 months. Repeat imaging at 3 months may also be considered for cancer screening and to monitor the patient's condition, including progression or acute worsening of disease.

Differences in treatment approaches among regions were also observed, with use of tacrolimus being more common in Japan. This may be at least partly due to the differing availability of agents in each region. For instance, tacrolimus was developed in Japan for the treatment of PM/DM-ILD[50], in which some patients may develop a progressive phenotype, and is therefore more familiar to Japanese physicians. Additionally, immunosuppressants including MMF are not approved for the treatment of ILDs worldwide, but rather are used to attempt systemic management or as part of clinical trials, for example in SSc-ILD[51,52]. Differences in medical environments including health insurance systems are likely to have contributed to the findings of inter-regional differences, not only pertaining to treatment approaches, but also regarding the selection and frequency of monitoring tests.

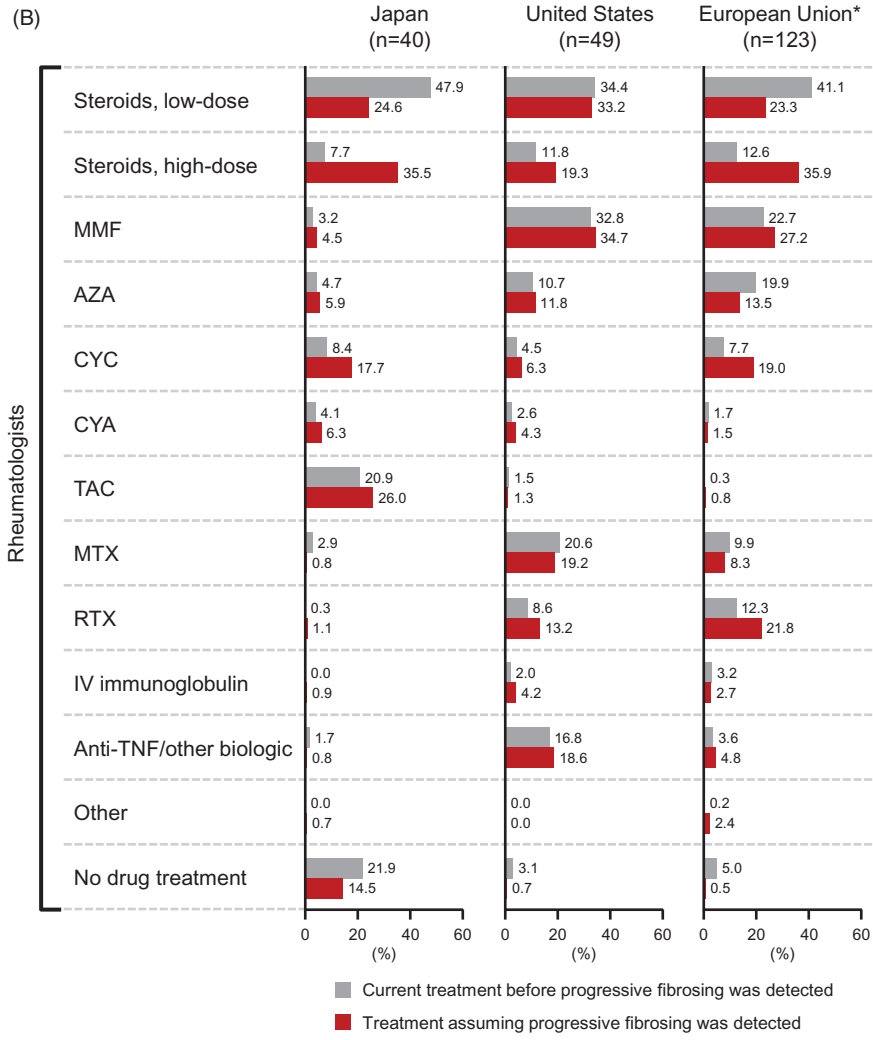


**Figure 4.** Continued

The findings from our survey provide further understanding of treatment selection by specialists from a similar recent survey of physicians from Japan, the United States, and Europe[38]. In that study, it was reported that pulmonologists generally initiated treatment in patients with progressive fibrosing ILD, with the most commonly prescribed treatment being corticosteroids; the authors also noted that 25%–50% of patients did not receive any treatment. However, the percentage of patients without drug treatment in the present study was below 10%. This discrepancy might be attributable to differences in the awareness of progressive fibrosing ILDs in the different survey periods (i.e. May–June 2017 vs. November 2018–February 2019) or to differences in the approach to questioning (i.e. physicians directly questioned regarding treatment for progressive fibrosing ILDs vs. physicians questioned using a list of general names of medications).

Our findings highlight a lack of specific tests (including biomarkers), standardized diagnostic criteria, and treatment for progressive fibrosing ILD[48]. An official international guideline that includes the definition, diagnosis, and management of progressive fibrosing ILD is required. Moreover, improved treatment options are urgently needed because progressive fibrosing ILD negatively affects patients' daily activities and functioning, reduces quality of life[53], and is thought to increase healthcare utilization[54]. Our findings also suggest that collaboration between specialties and a multidisciplinary approach to the management of ILD is required[55–57].

Clinical study findings should provide useful information to help better define the future management of progressive fibrosing ILD[21,34,35]. For instance, recent results from the phase 3 INBUILD study, which specifically included patients with a progressive fibrosing ILD phenotype, and from the regions covered by our survey, reported a significant reduction in the annual rate of FVC decline in patients treated with the small-molecule TKI nintedanib compared with placebo[35]. Recent data from a phase 2 study in patients with progressive fibrosing unclassifiable ILD indicated that pirfenidone treatment may be a safe and effective treatment option in this patient population and should be investigated further[36]. Although data are lacking on the use of immunosuppressive therapy in ILD, some insights might be available from the trial conducted for SSc-ILD[58] and ongoing trials investigating the efficacy and safety of anti-fibrotic therapies in combination with immunosuppressants such as mycophenolate mofetil (e.g. the SLS III study, NCT03221257).

The limitations of our study include the potential for sampling bias based on the characteristics of physicians who responded to the survey, the potential for respondents to have interpreted questions and definitions differently, the influence of the country of origin (potential uncertainty of diagnosis given the different criteria used for progressive fibrosing ILD), treatment/test availability, potential influences of formulary restrictions or insurance coverage limitation on physician responses, and differences in the severity of ILD between patients treated by pulmonologists and those treated by rheumatologists. Furthermore, data on the use of multidisciplinary team diagnosis, regarded as the diagnostic reference standard for ILD, were not collected.

### Conclusions and future directions

Our survey of pulmonologists and rheumatologists from Japan, the United States, and the European Union found between-specialist and inter-regional differences in the perception of progressive fibrosing ILD relevance and in management strategies for patients with ILD. These findings highlight the unmet need for an international guideline for the definition, diagnosis, and management of ILD. Education of specialists about progressive fibrosing ILD could contribute to better understanding and patient management, leading to better outcomes for patients with ILD.

## Transparency

### Declaration of funding

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### Declaration of financial/other relationships

A.T. and M. Kamita are employees of Boehringer Ingelheim. Y.K. has received consulting/advisory fees from Asahi Kasei Pharma Corp., Boehringer Ingelheim, Shionogi Co., Ltd, and Janssen Pharmaceutical K.K., and speaker bureau fees from Asahi Kasei Pharma Corp., Boehringer Ingelheim, Eisai Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Corp., Novartis Pharma K.K., and Shionogi Co., Ltd. M.B. has received advisory board fees from Nippon Boehringer Ingelheim, and consulting and speaker fees from Nippon Boehringer Ingelheim and Shionogi Co., Ltd. M. Kuwana has received research grants from Astellas, Boehringer Ingelheim, and Ono Pharmaceuticals, and consulting fees from Bayer, Boehringer Ingelheim, Chugai, Corbus, CSL Behring, MBL, Mochida, and Reata, and serves on speaker bureaus for Actelion, Astellas, Boehringer Ingelheim, Chugai, GSK, Ono Pharmaceuticals, and Pfizer. Y.I. was a member of the steering committee for the INBUILD study, which was funded by Boehringer Ingelheim, and has received lecture fees from Boehringer Ingelheim and Shionogi. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work. One of these reviewers has disclosed grants and speaker and consultancy fees from Boehringer Ingelheim and Hoffman la Roche. The remaining reviewers have no other relevant financial relationships or otherwise to disclose.

### Author contributions

All authors were involved in the conception and design of the study, interpretation of data and critical revision and final approval of the manuscript, and take responsibility for the accuracy and integrity of the study. M. Kamita was involved in data acquisition.

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### Data availability statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria. Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/. Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants. Clinical Study Reports and Related Clinical Documents can also be requested *via* the link https://trials.boehringer-ingelheim.com/. All requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Researchers should use the https://trials.boehringer-ingelheim.com/ link to request access to study data.

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