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Volkmann, ER, Sparks, JA, Hoffmann-Vold, A-M et al. (3 more authors) (2023) Preclinical or subclinical rheumatoid arthritis-associated interstitial lung disease: misleading terms with potentially deleterious consequences. The Lancet Rheumatology, 5 (3). e116-e118. ISSN 2665-9913

https://doi.org/10.1016/s2665-9913(23)00033-4

Preclinical/subclinical rheumatoid arthritis-associated interstitial lung disease: misleading terms with potentially deleterious consequences

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Interstitial lung disease (ILD) is a leading cause of mortality in patients with rheumatic diseases, including rheumatoid arthritis (RA).[1] The 5-year mortality rate is twice as high in RA patients with ILD than without ILD.[2] Moreover, a recent report demonstrated that mortality rates in patients with RA-ILD disease codes remained unchanged from 2005-2018, even though the overall RA mortality rate declined during this time period.[3] Despite the evidence that ILD contributes to premature death in RA, screening for ILD in RA is not routinely performed in clinical practice, and numerous questions remain regarding the management of RA-ILD.[4]

Interstitial lung abnormalities (ILA) are sometimes incidentally observed in patients with RA who undergo imaging for other reasons. The Fleischner Society refers to ILA as specific high-resolution computed tomography (HRCT) findings that are potentially compatible with ILD in patients without clinical suspicion of the disease.[5] A recent Fleischner Society Position Paper recommended that incidentally detected ILA in patients with autoimmune disease, such as RA, should be classified as "preclinical ILD" rather than ILA due to the presence of a strong risk factor for progressive disease.[5] Prior literature has also referred to these radiological changes as "subclinical ILD." One of the obstacles rheumatologists and pulmonologists face is the lack of consensus on the clinical meaning of "preclinical/subclinical" ILD in patients with RA, as these terms are also used at times to describe patients with early ILD, mild ILD, and/or ILD in an asymptomatic patient. These varying definitions not only create semantic confusion, but they also cultivate the misconception that "preclinical/subclinical" ILD is a non-worrisome feature of RA, when in fact, it is associated with 3-fold increased risk of mortality compared to those with normal lung imaging in a study among smokers with RA.[6]

The presence of symptoms related to interstitial changes on HRCT is also variable as some patients with interstitial changes have dyspnea that may or may not be due to the

radiological findings. In addition, ascertaining the presence of respiratory symptoms attributable to ILD is challenging in patients with RA. The extra-pulmonary manifestations may limit exercise tolerance rendering it difficult to evaluate for exertional dyspnea. Moreover, even in patients with well controlled articular disease, many patients will modify their lifestyle to avoid joint pain and/or the sensation of breathlessness. Unless careful probing of past and current physical activity is performed, physicians may erroneously label these patients as asymptomatic. Furthermore, some RA patients may falsely attribute dyspnea to deconditioning and mobility limitations rather than underlying lung disease. Finally, ILD-related symptoms, such as cough, may be attributed to more common causes of cough, such as gastroesophageal reflux disease or post-nasal drip.

In addition to the inherent limitations in evaluating ILD-related symptoms, it is unknown how the outcomes of patients with "preclinical/subclinical" RA-ILD compare to clinical ILD related to RA. Both RA and ILD activity were identified as independent predictors of survival in RA-ILD.[7] Moreover, patients with less extensive ILD can still experience respiratory infections, as well as acute exacerbations, a primary contributor to hospitalizations and mortality in patients with RA-ILD. It is therefore conceivable that some patients with RA diagnosed with preclinical/subclinical ILD could potentially have worse outcomes if both the RA and ILD are not monitored closely.

We herein advocate that any patient with RA and ILD on HRCT, either with or without symptoms, undergoes monitoring for ILD progression. The three pillars of monitoring, derived from the recently published clinical practice guideline on progressive pulmonary fibrosis (PPF),[8] include the following assessments: (1) symptoms; (2) physiology (e.g., declines in forced vital capacity [FVC], and when possible, diffusing capacity for carbon monoxide [DLCO]); (3)

radiological changes on HRCT. The timing of the aforementioned assessments may vary based on an individual patient's risk factors for ILD progression and suspected ILD subtype (e.g., the usual interstitial pneumonia pattern is associated with PPF in RA). Two international groups (American College of Rheumatology and the European Respiratory Society/European Alliance of Associations for Rheumatology) are currently developing clinical practice guidelines for autoimmune ILD, which will provide further guidance on how to monitor for ILD progression in patients with RA.

Future studies are needed to improve our ability to risk stratify patients with RA-ILD early in the disease course. While emerging research has augmented our understanding of which patients with RA are more likely to develop ILD,[9,10] longitudinal studies of patients with newly diagnosed RA-ILD may help uncover novel predictive biomarkers. To date, there is no evidence to recommend screening for ILD with HRCT of the chest in all RA patients, but many ILDs are incidentally diagnosed in patients with RA, so clinicians need evidence-based guidance for how to monitor and manage these patients. Future studies are needed to determine whether screening for ILD is justified in specific RA patients, such as smokers or patients with other ILD risk factors. The outcomes of these studies will help us to not only refine our ILD monitoring approach, but also identify patients who may derive the most benefit from specific ILD-targeted therapies. There is undoubtedly a future for precision medicine in RA-ILD, but first, we must ensure that all patients with RA-ILD receive appropriate ILD management.

Contributors

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Names of authors who had the final responsibility for the decision to submit for publication: ERV, JAS, AMHV, TJD, PE, PD

Declarations of interests

The authors report no financial or personal relationships related to the submitted work. Outside of the submitted work, the authors report the following relationships:

ERV is supported by the National Heart, Lung, and Blood Institute (grant number K23 HL150237) and reports the following financial relationships outside of the submitted work on RA-ILD: Consulting and speaking fees (Boehringer Ingelheim); Institutional support received for performing studies on systemic sclerosis for Kadmon, Forbius, Boehringer Ingelheim, Horizon, Prometheus.

JAS is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant numbers R01 AR077607, P30 AR070253, and P30 AR072577), Rheumatology Research Foundation, the R. Bruce and Joan M. Mickey Research Scholar Fund, and the Llura Gund Award for Rheumatoid Arthritis Research and Care. Dr. Sparks has received research support from Bristol Myers Squibb and performed consultancy for AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Inova Diagnostics, Janssen, Optum, and Pfizer unrelated to this work. The funders had no role in the decision to publish or preparation of this

manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard University, its affiliated academic health care centers, or the National Institutes of Health.

AMHV reports the following financial relationships outside of the submitted work on RA-ILD: Consulting fees (ARXX, Boehringer Ingelheim, Genentech, Janssen, Medscape, Roche, Bayer), speaking fees (ARXX, Boehringer Ingelheim, Janssen, Lilly, Medscape, Merch Sharp & Dohme, Roche), grants (Boehringer Ingelheim, and Jannsen), support for attending meetings and/or travel (Boehringer Ingelheim, Janssen), leadership in EULAR.

TJD is supported by the National Heart, Lung, and Blood Institute and reports grant support from Bristol Myers Squibb, consulting fees from Boehringer Ingelheim and L.E.K. consulting, and has been part of a clinical trial funded by Genentech. She also reports support for attending meetings and/or travel and payment for lectures for AURA.

PE reports consulting fees from Bristol Myers Squibb, Boehringer Ingelheim, Galapagos, Eli Lilly, Novartis, Gilead and payments for lectures from Abbvie, Astra-Zeneca, Bristol Myers Squibb, Boehringer Ingelheim, Galapagos, Gilead, Eli Lilly, Novartis. He has received support for attending meetings and/or travel from Eli Lilly and Novartis. He has also participated on a data safety monitoring board or advisory board for Astra Zeneca.

PD is supported by the Société Française de Rhumatologie. Pr. Dieudé has received research support from Bristol Myers Squibb, Galapagos, Chugai and Pfizer and performed consultancy for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Novartis, Galapagos and Pfizer unrelated to this work. He reports participation on a data safety and monitoring board for Bristol Myer Squibb and Boehringer Ingelheim. The funders had no role in the decision to publish or preparation of this manuscript. The content is solely the responsibility of the authors

and does not necessarily represent the official views of Paris cité University, its affiliated academic health care centers, or the Assistance Publique des Hôpitaux de Paris.

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