Radiological usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: prognostic does not mean treatment-predictive

Dear Editor,

Radiological usual interstitial pneumonia (UIP) is one of the most influential findings in rheumatoid arthritis-associated interstitial lung disease (RA-ILD). It is associated with adverse outcomes and increasingly informs monitoring and treatment discussions. Yet an important methodological distinction is easily overlooked: a marker that predicts outcome is not necessarily a marker that predicts treatment benefit. A prognostic marker is associated with outcome irrespective of treatment, whereas a treatment-predictive marker identifies patients in whom the relative effect of a treatment differs according to marker status; formally, this requires evidence of a treatment-by-marker interaction (1).

The prognostic relevance of UIP in RA-ILD is well established, although its effect is not absolute. In a longitudinal cohort, UIP was associated with shorter survival in unadjusted analyses, whereas baseline forced vital capacity (FVC) and subsequent FVC decline, rather than high-resolution computed tomography pattern, independently predicted mortality after adjustment (2). Thus, UIP is an important risk signal, but it does not fully capture subsequent disease behaviour.

Evidence for UIP as a treatment-predictive marker is considerably weaker. In a multisite cohort of 212 patients treated with azathioprine, mycophenolate, or rituximab, immunosuppression was associated with improved FVC and diffusing-capacity trajectories, and UIP did not significantly modify the treatment-associated response (3). Similarly, in a multicentre abatacept cohort, clinical, functional, and radiological stabilisation was broadly comparable between UIP and non-specific interstitial pneumonia (4). These observational data do not prove that immunomodulation is equally effective across patterns, but neither do they support using UIP alone to exclude it.

The antifibrotic evidence should be interpreted with the same distinction. In the RA-ILD subgroup of INBUILD, nintedanib reduced the annual rate of FVC decline versus placebo (5). This is randomised evidence for nintedanib in progressive fibrosing RA-ILD. It is not, however, evidence that UIP itself selects patients who derive greater relative benefit: 86.5% of the RA-ILD subgroup had a UIP-like fibrotic pattern, and the subgroup was selected for documented progression rather than UIP alone (5). The actionable trial phenotype was progressive pulmonary fibrosis; UIP contributed to risk characterisation but was not validated as a treatment-predictive biomarker.

This distinction is clinically relevant because recent consensus and guideline documents support both immunomodulatory and antifibrotic strategies in RA-ILD according to the clinical context (6, 7). Our recent review further highlighted that RA-associated UIP is morphologically heterogeneous, with variable contributions from parenchymal fibrosis, inflammatory change, and airway-centred disease (8). Such heterogeneity provides biological plausibility for differential treatment responses, but it is not direct evidence that radiological subtype predicts relative treatment benefit.

We therefore suggest using UIP for the question it can currently answer. UIP should heighten prognostic concern, support closer longitudinal assessment, and lower the threshold for considering fibrosis-directed therapy when objective progression is present. It should not, by itself, exclude immunomodulation or dictate a fixed therapeutic pathway. Future comparative studies should stratify by radiological pattern and, crucially, pre-specify formal treatment-by-UIP interaction analyses.

In RA-ILD, UIP may tell us how concerned we should be. It does not yet tell us which treatment will work better.

Acknowledgements

During manuscript preparation, ChatGPT (OpenAI) was used to assist with language refinement and organisation of the manuscript. The author critically reviewed and revised all content and takes full responsibility for the final manuscript.

H. Yamakawa[1,2], *MD, PhD*

[1]Department of Respiratory Medicine, Saitama Red Cross Hospital, Saitama; [2]Department of Internal Medicine, Division of Respiratory Medicine, Jikei University School of Medicine, Tokyo, Japan.

Please address correspondence to:
Hideaki Yamakawa
Department of Respiratory Medicine,
Saitama Red Cross Hospital,
1-5 Shintoshin, Chuo-ku,
Saitama 330-8553, Japan.
E-mail: hide1144@jikei.ac.jp

Competing interests: H. Yamakawa r eports receiving honoraria from Nippon Boehringer Ingelheim, outside the submitted work.

Clin Exp Rheumatol 2026.

© Copyright Clinical and Experimental Rheumatology 2026.

References

1. BALLMAN KV: Biomarker: predictive or prognostic? *J Clin Oncol* 2015; 33(33): 3968-71. https://doi.org/10.1200/JCO.2015.63.3651
2. SOLOMON JJ, CHUNG JH, COSGROVE GP *et al*.: Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2016; 47(2): 588-96. https://doi.org/10.1183/13993003.00357-2015
3. MATSON SM, BAQIR M, MOUA T *et al*.: Treatment outcomes for rheumatoid arthritis-associated interstitial lung disease: a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. *Chest* 2023; 163(4): 861-9. https://doi.org/10.1016/j.chest.2022.11.035
4. ATIENZA-MATEO B, FERNÁNDEZ-DÍAZ C, VICENTE-RABANEDA EF *et al*.: Abatacept in usual and in non-specific interstitial pneumonia associated with rheumatoid arthritis. *Eur J Intern Med* 2024; 119: 118-24. https://doi.org/10.1016/j.ejim.2023.08.025
5. MATTESON EL, ARINGER M, BURMESTER GR, MUELLER H, MOROS L, KOLB M: Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial. *Clin Rheumatol* 2023; 42(9): 2311-9. https://doi.org/10.1007/s10067-023-06623-7
6. SOLOMON JJ, DIEUDÉ P, MATSON SM *et al*.: Rheumatoid arthritis-associated interstitial lung disease: screening, diagnosis, and treatment-an expert group consensus statement. *Lancet Respir Med* 2026; 14(9): 820-36. https://doi.org/10.1016/S2213-2600(26)00094-9
7. ANTONIOU KM, DISTLER O, GHEORGHIU AM *et al*.: ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease. *Eur Respir J* 2026; 67(1): 2402533. https://doi.org/10.1183/13993003.02533-2024
8. YAMAKAWA H, YAMANO Y, TSUBOI H, MAKINO S, TAKEMURA T, OGURA T: Radiological diversity in rheumatoid arthritis associated with usual interstitial pneumonia (RA-UIP) and its therapeutic implications: towards a generalizable framework of interstitial lung disease treatment. *Respir Res* 2026; 27(1): 315. https://doi.org/10.1186/s12931-026-03750-y