

Perspective on Fibroblast Activation Protein–Specific PET/CT in Fibrotic Interstitial Lung Diseases: Imaging Fibrosis—A New Paradigm for Molecular Imaging?

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Interstitial lung diseases (ILDs) are a heterogeneous group of parenchymal pulmonary disorders. Their hallmark is pulmonary infiltration by immune-competent cells followed by lung fibrosis (1). Depending on the subtype of ILD, its prognosis varies. However, several of these disease entities present with a chronic, irreversible, and progressive clinical course and are associated with worsening lung function, impaired quality of life, and limited life expectancy. Despite the possibility of detecting ILDs with the current standard imaging technique high-resolution CT (HRCT) and pulmonary function tests, monitoring of disease activity remains challenging, since the course of disease, such as in systemic sclerosis-associated ILD, is highly variable (2).

To date, HRCT is the mainstay to establish the diagnosis of ILDs since certain morphologic disease patterns indicate specific disease entities. However, morphologic imaging using HRCT is not capable of determining tissue remodeling. Furthermore, the measurement of functional decline by pulmonary function tests requires long-term follow-up. Molecular imaging of ILDs for the assessment of disease activity is so far based on the use of ^{18}F -FDG PET/CT. However, ^{18}F -FDG PET/CT can generally assess only the level of inflammation, not the degree of fibrotic activity in ILDs and other fibroinflammatory diseases (3). Hence, novel noninvasive diagnostic approaches to evaluating disease activity and monitoring treatment of ILDs are of considerable interest. Persistent activation and local accumulation of myofibroblasts play a key role in the development of fibrotic diseases of the lung such as in systemic sclerosis-associated ILD or idiopathic pulmonary fibrosis (4). Fibroblast activation protein α (FAP) is a type II transmembrane protease with dipeptidyl peptidase and endopeptidase activity and is induced in fibroblasts on activation and is negligible or absent in resting fibroblasts or other cell types (5). The recently developed radiolabeled quinoline-based PET tracers binding to FAP demonstrate tracer uptake in various tumor entities as well as in fibrotic diseases and are a major advance for molecular imaging (6).

In a translational exploratory study published in this issue of *The Journal of Nuclear Medicine*, Röhrich et al. evaluated the static and dynamic imaging properties of ^{68}Ga -FAP inhibitor (FAPI)-46 PET/CT in 15 patients with fibrotic ILD (fILD) and suspected lung cancer (LC) (7). They performed static PET/CT scans on 12 patients and dynamic scans on another 3 patients. SUVs were measured for a total of 55 CT-morphologically typical fibrotic lesions and 3 LC lesions. Furthermore, the FAP immunohistochemistry of 4 human fILD biopsy samples and of fibrotic lungs of *Nedd4-2^{-/-}* mice was performed. fILD and LC lesions had considerably elevated uptake at each of the static imaging time points. The SUV_{max} and SUV_{mean} of both fILD and LC lesions decreased over time, with a more pronounced decrease in fILD lesions compared with LC lesions. In contrast, because of the decreasing background activity over time, fILD manifestations demonstrated relatively stable target-to-background ratios, whereas target-to-background ratios of LC manifestations tended to increase during the sequential PET examinations. These findings highlight the potential use of quantitative PET imaging at sequential time points to differentiate between malignant and fibrotic lesions. Analogous results were obtained in the dynamic PET acquisitions: although fILD lesions showed an early peak in tracer accumulation with a slowly decreasing signal intensity over time, LC manifestations presented an increasing time-activity curve with a delayed peak and gradual washout. Interestingly, the peak of the tracer uptake in LC lesions was between 10 and 30 min with a corresponding fast blood clearance resulting in high target-to-background ratios. These findings suggest that, for ^{68}Ga -FAPI-46, the optimal imaging time point might be earlier than the current standard 60 min after injection for LC and fibrosis imaging being applied for ^{18}F -FDG. Immunohistochemistry of both human fILD biopsies and whole lung sections of *Nedd4-2^{-/-}* mice serving as a gold standard were evaluated for FAP expression. FAP-positive areas were localized in the transition zone between healthy lung tissue and fibrotic areas in human fILD sections. In *Nedd4-2^{-/-}* mice, healthy lung parenchyma demonstrated only low FAP expression, but fibrotic lesions exhibited FAP upregulation. These impressive results suggest a promising role for FAP imaging in fibrotic lung diseases for evaluation of disease activity. The early peaks in tracer uptake of LC and fibrotic lesions between 10 and 30 min allow for early image acquisition, which is currently an important logistic advantage at the current time, at a time when there is an increasing number of PET/CT examinations.

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Although the current imaging standard HRCT is not capable of determining disease activity, ^{18}F -FDG PET/CT is of limited use for the assessment of response to antifibrotic drugs (8). This is not surprising since ^{18}F -FDG PET/CT visualizes increases in glucose metabolism caused by inflammatory processes, but not the activity of activated fibroblasts that play a key role in the development of lung fibrosis. Recently, Bergmann et al. reported the use of ^{68}Ga -FAPI-04 PET/CT in 21 patients with systemic sclerosis-associated ILD and showed that FAP imaging directly visualizes activated fibroblasts in vivo (9). Furthermore, ^{68}Ga -FAPI-04 uptake was higher in patients with extensive disease, with previous ILD progression, or with higher European Scleroderma Trials and Research Group activity scores than in those with limited disease, previously stable ILD, or low European Scleroderma Trials and Research Group activity scores. Increased ^{68}Ga -FAPI-04 uptake at baseline was associated with progression of ILD independently of extent of involvement on HRCT scans and of the forced vital capacity at baseline. Moreover, changes in ^{68}Ga -FAPI-04 uptake were concordant with the observed response to the fibroblast targeting antifibrotic drug nintedanib (9).

To date, FAP PET/CT is the only clinically available imaging approach that can directly visualize and quantify the activity of activated fibroblasts in fibrotic and tumor diseases. In contrast to other techniques, such as pulmonary function tests or HRCT, which measure the cumulative result of tissue damage, ^{68}Ga -FAPI PET/CT can directly assess the dynamic of this process. ^{68}Ga -FAPI PET/CT might improve risk assessment of patients with fibrotic diseases and allow earlier and more accurate treatment as well as dynamic monitoring of the molecular response to fibroblast-targeting therapies.

FAP imaging might open a completely new perspective for the nuclear medicine community. This was also demonstrated in a publication on FAPI PET/CT in IgG₄-related disease (10). IgG₄-related disease is a paradigm of the inflammation-versus-fibrosis dichotomy and is characterized by autoimmune inflammation associated with tumefactive tissue fibrosis. The disorder has a predilection for the pancreas, the biliary tree, the salivary glands, the kidney, and the aorta, among others. Histopathology studies and clinical correlations have suggested progression of IgG₄-related disease from a proliferative to a fibrotic phase. Although in the proliferative IgG₄-related disease phase dense lymphoplasmacytic infiltrates occur, the fibrotic phase has relatively sparse cellular infiltrates and a greater degree of tissue fibrosis. The response of fibrotic lesions to antiinflammatory treatment with rituximab was far less pronounced than that of inflammatory lesions. The

conclusion of this study was that FAP-specific PET/CT permits discrimination between inflammatory and fibrotic activity in IgG₄-related disease. This finding may profoundly change the management of certain forms of immune-mediated disease, such as IgG₄-related disease, as subtypes dominated by fibrosis may require approaches to controlling disease progression different from those required by subtypes that are predominantly inflammatory. For example, in the former, specific antifibrotic agents rather than broad-spectrum antiinflammatory treatments might be useful.

The above-reviewed evidence has demonstrated that imaging of active fibrotic processes has become feasible. Future clinical research will reveal whether the new paradigm of imaging-activated fibroblasts by PET is of clinical utility in ILDs and other rheumatic disorders.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. *Rheumatol Int*. 2017;37:853–863.
2. Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med*. 2020;8:304–320.
3. Chen DL, Cheriyan J, Chilvers ER, et al. Quantification of lung PET images: challenges and opportunities. *J Nucl Med*. 2017;58:201–207.
4. Distler JH, Györfi A-H, Ramanujam M, et al. Shared and distinct mechanisms of fibrosis. *Nat Rev Rheumatol*. 2019;15:705–730.
5. Wenlong L, Leilei Y, Wei F, et al. Luciferase expression is driven by the promoter of fibroblast activation protein- α in murine pulmonary fibrosis. *Biotechnol Lett*. 2015;37:1757–1763.
6. Lindner T, Loktev A, Altmann A, et al. Development of quinoline-based theranostic ligands for the targeting of fibroblast activation protein. *J Nucl Med*. 2018;59:1415–1422.
7. Röhrich M, Leitz D, Glatting FM, et al. Fibroblast activation protein-specific PET/CT imaging in fibrotic interstitial lung diseases and lung cancer: a translational exploratory study. *J Nucl Med*. July 16, 2021 [Epub ahead of print].
8. Bondue B, Castiaux A, Van Simaey G, et al. Absence of early metabolic response assessed by ^{18}F -FDG PET/CT after initiation of antifibrotic drugs in IPF patients. *Respir Res*. 2019;20:10.
9. Bergmann C, Distler JH, Treutlein C, et al. ^{68}Ga -FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. *Lancet Rheumatol*. 2021;3:e185–e194.
10. Schmidkonz C, Rauber S, Atzinger A, et al. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. *Ann Rheum Dis*. 2020;79:1485–1491.