

# FAPI PET/CT Immune-Fibrosis Imaging for New Insights into Rheumatologic Disorders

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Immune-mediated diseases are associated with substantial activation of tissue-resident fibroblasts resulting in fibrosis and organ damage (1). Despite the overall low incidence of fibrotic diseases, fibrotic tissue responses across different diseases have been estimated to account for up to 45% of deaths in high-income countries, causing socioeconomic costs of tens of billions of U.S. dollars per year (2). Although the detection of active inflammation by, for example, <sup>18</sup>F-FDG PET/CT is implemented in the clinical routine, the in vivo visualization of immune-mediated tissue remodeling has not been possible until recently (3,4). With the development of radiolabeled quinoline-based tracers suitable for PET that act as fibroblast-activation protein inhibitors (FAPIs), noninvasive characterization of rheumatologic disorders is now available. Clinical assessments of disease activity in immune-mediated rheumatologic disorders such as rheumatoid arthritis or systemic sclerosis (SSC)–associated interstitial lung disease usually include physical examinations and evaluation of functional parameters, as well as the patient’s self-reporting of disease activity and quality of life (5). Progression of disease is defined as tissue destruction between 2 patient examinations, meaning that disease activity is measured only indirectly by progression of existing tissue damage. Direct measurement of disease activity is not established in clinical practice. Instead, PET/CT imaging using FAPIs may serve as a reliable, reproducible, and objective indicator of disease activity (6). Activated fibroblasts that are located in the lining and sublining of the synovium contribute to pannus formation and bone destruction in rheumatoid arthritis, whereas fibroblasts in the lung tissue react to stimulation by an excessive release of extracellular matrix, resulting in progressive tissue fibrosis. To date, PET with <sup>18</sup>F-FDG or MRI is the method of choice for the detection and quantification of inflammation; however, this method does not allow for visualization of mesenchymal stromal activation and the subsequent process of tissue destruction.

## RHEUMATOID ARTHRITIS

An impressive example of the use of FAPI PET/CT for the detection and quantification of disease in rheumatoid arthritis was

given by Luo et al. (7). These authors performed a prospective dual-tracer PET/CT study using <sup>68</sup>Ga-FAPI and <sup>18</sup>F-FDG PET/CT in 20 patients with rheumatoid arthritis. They found that both imaging modalities were able to detect disease-affected joints; however, FAPI PET/CT was more sensitive in this regard than <sup>18</sup>F-FDG PET/CT. Furthermore, SUV<sub>max</sub> correlated with clinical and laboratory disease activity and radiographic progression of joint damage. Further studies that directly compare the use of FAPI PET/CT and the actual standard MRI are warranted to determine the potential role of this novel molecular medicine tool for therapy planning. A possible future therapeutic approach in patients with rheumatoid arthritis guided by FAPI PET/CT was evaluated by Dorst et al. (8). They used anti-fibroblast activation protein–targeted photodynamic therapy on rheumatoid synovial explants and found an upregulation of cell death markers, whereas no significant side effects were noted on the macrophages of neighboring fibroblasts. With this novel therapeutic approach, aberrant synovial cells previously identified using FAPI PET/CT could selectively be targeted without any systemic side effects.

## LUNG FIBROSIS

In contrast to rheumatoid arthritis, which is characterized by a strong inflammatory component, in SSC interstitial lung disease the activation of fibroblasts leads to excessive fibrosis of the lungs. Pulmonary fibrosis is often a severe and progressive condition, and despite the possibility of detecting interstitial lung diseases with the current standard imaging technique high-resolution CT and pulmonary function testing, monitoring of disease activity remains challenging, since the course of disease is highly variable (9). Furthermore, current diagnostic approaches do not predict the course of pulmonary fibrosis and do not enable appropriate risk stratification. In a single-center pilot study, Bergmann et al. studied a group of 21 patients with SSC interstitial lung disease who underwent FAPI PET/CT (6). Bergmann et al. could demonstrate that FAPI uptake was increased in patients with higher clinical activity scores and that the magnitude of tracer accumulation correlated with progression of disease independently of the extent of involvement on CT scans and lung function at baseline. Additionally, in consecutive FAPI PET/CT scans, changes in tracer uptake were concordant with response to the targeting antifibrotic drug nintedanib. These data demonstrated for the first time that fibroblast activation protein imaging is the only imaging method available that

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can directly assess the dynamics and potential treatment response in SSC interstitial lung disease. Besides pulmonary fibrosis, myocardial fibrosis is also a factor of poor prognosis in SSC. Treutlein et al. examined in a proof-of-concept trial patients with SSC-associated myocardial fibrosis who underwent FAPI PET/CT and MRI as well as clinical and serologic investigations (10). With FAPI PET/CT, dynamic changes in tracer uptake associated with changes in SSC-related myocardial fibrosis were observed that could not be detected by MRI. Further larger trials are warranted to evaluate the potential use of FAPI PET/CT to directly monitor cardiac fibroblast activity in vivo, which might enable 1-stop-shop imaging of patients with SSC with both heart and lung involvement. Since inflammatory processes in immune-mediated disease can already be detected by <sup>18</sup>F-FDG PET/CT, one may ask whether FAPI radioligands can provide additional information on the chronic inflammation process that often occurs in that kind of disease.

## IGG4-RELATED DISEASE

IgG4-related disease is a paradigm of the inflammation-versus-fibrosis dichotomy that affects the pancreas and biliary tree, the salivary glands, the kidneys, the aorta, and other organs. During the course of disease, there is a typical progression from a proliferative phenotype that is characterized by dense lymphoplasmacytic infiltrates to a fibrotic phenotype with a greater degree of fibrosis. Immune-targeted therapies effectively inhibit inflammation but may not be suited to tackle fibrotic tissue changes, requiring detection of whether IgG4-related disease is based primarily on inflammatory or fibrotic lesions in an individual patient. In a cross-sectional study, 27 patients with IgG4-related disease underwent both <sup>18</sup>F-FDG and FAPI PET/CT as well as MRI and histopathologic assessment (1). <sup>18</sup>F-FDG-positive lesions showed dense lymphoplasmacytic infiltrations of IgG4-positive plasma cells, whereas FAPI-positive lesions harbored abundant activated fibroblasts. Interestingly, dual-tracer follow-up imaging revealed that antiinflammatory treatment of IgG4 manifestations significantly reduced <sup>18</sup>F-FDG uptake whereas fibrotic lesions demonstrated only a partial reduction in uptake on <sup>68</sup>Ga-FAPI PET/CT. Furthermore, constant fibrotic activity resulted in progression of the fibrotic lesion mass, suggesting that patients with FAPI-positive lesions require different forms of treatment. In view of the development of specific treatments for fibrotic diseases—treatments such as pirfenidone or inhibitors of the transcription factor

purine-rich box1—FAPI-04 PET/CT might be an ideal tool for evaluating the treatment response in IgG4-related disease (11). In summary, FAPI PET/CT offers a completely new view on immune-fibrosis imaging in rheumatologic disorders. This novel imaging modality is the only noninvasive method available for the visualization and quantification of the tissue remodeling process and assessment of treatment response to antifibrotic therapies. To fully exploit the potential of FAPI PET/CT in rheumatologic disorders, further prospective high-quality trials that require the collaboration of the nuclear medicine community are needed.

## DISCLOSURE

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

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