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EDITORIAL

FAPI PET/CT in infectious, inflammatory, and rheumatological diseases: "watch it like a hawk" or "one swallow does not make a summer"?

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Radiolabelled fibroblast activation protein inhibitors (FAPI) are emerging as promising radiopharmaceuticals for positron emission tomography (PET) [1, 2]. FAPI are molecules able to bind to fibroblast activation protein (FAP), a membrane serine protease that is highly expressed on activated fibroblasts present in a wide range of pathophysiological conditions, such as wound-healing, inflammation, immune response, and tumors [1–4]. The role of FAPI PET/CT in oncology has been evaluated in several studies and preliminary results are promising for some tumors in comparison to [^{18}F]FDG PET/CT [1–4].

As radiolabelled FAPI uptake has been demonstrated in several benign conditions [5] (thus underlining an issue related to the specificity of FAPI uptake for tumor lesions, similar to that of [^{18}F]FDG), some recently published clinical studies suggested a role of FAPI PET for the assessment of some infectious, inflammatory, and rheumatological diseases, characterized by radiolabeled FAPI uptake related to fibroblast activation in tissue remodeling (Table 1) [6–14].

Overall, these articles (mainly "pilot" or "proof-of-concept" studies on heterogeneous diseases) have the great merit to open new windows on the possible future applications of FAPI PET in non-oncological conditions, stimulating the clinical research in this setting. However, available data are currently not sufficient to translate this research into clinical practice, suggesting more studies on FAPI PET in infectious, inflammatory, and rheumatological diseases ("one swallow does not make a summer").

The study with the largest sample size was recently published on the EJNMMI journal by Wang and colleagues [6]. The authors performed a retrospective study to assess the diagnostic efficiency of FAPI PET/CT in discriminating between periprosthetic joint infection and aseptic loosening in 103 patients with symptomatic hip arthroplasty. Two PET image interpretation criteria were used, the intensity of FAPI uptake (measured as SUV_{max}) and the uptake pattern, and validated criteria for diagnosis of periprosthetic infection were used as reference standard. Diffuse uptake of radiolabelled FAPI between the entire acetabulum and prosthesis or between the entire femur and prosthesis, radiopharmaceutical uptake along the longitudinal axis of femoral stem neck, or involving the soft tissues were used as positive criteria for periprosthetic infection. The sensitivity, specificity, and accuracy of FAPI PET/CT using the uptake pattern were 100%, 93.1%, and 95%, respectively, with a better performance compared to the intensity of uptake using a SUVmax cut-off (cut-off value: 7.53). Furthermore, radiomics analysis showed different clusters among periprosthetic infection and aseptic loosening [6].

The different uptake of radiolabelled FAPI in prosthetic joint infection and aseptic loosening could be explained by the presence of different membranous structures generated between the interface of bone and prosthesis in loosening (a fibrous membrane) and infection cases (biofilm). Both membranes have activated fibroblasts with increased FAP expression, but the biofilm has a higher degree of inflammation than the fibrous membrane caused by loosening, explaining the different findings on FAPI PET/CT in these conditions [6].

This article is part of the Topical Collection on Infection and inflammation

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Table 1 Clinical studies about the role of radiolabelled FAPI PET/CT in patients with infectious, inflammatory, or rheumatological diseases published until January 2023 (case reports including less than 5 patients or studies related to other conditions such as renal or myocardial fibrosis are not reported)

Authors	Publication year	Country	Topic on infectious or inflammatory diseases	No. of patients	Main findings
Wang et al. [6]	2023	China	Periprosthetic hip joint infection	103	[^{68} Ga]Ga-FAPI PET/CT seems promising in the diagnosis of periprosthetic joint infection using the diagnostic criteria of the uptake pattern of the radiopharmaceutical
Chen et al. [7]	2023	China	Crohn's disease	16	[^{68} Ga]Ga-FAPI PET/CT seems a promising method for assessing disease activity in Crohn's disease. FAPI PET/CT correlated well with endoscopic, computed tomography enterography, and disease biomarkers. It was highly sensitive in the detection of different classes of lesions in all intestinal segments
Treutlein et al. [8]	2023	Germany	Systemic sclerosis	14	[^{68} Ga]Ga-FAPI PET/CT may be a diagnostic option to monitor cardiac fibroblast activity being able to visualize myocardial fibrosis related to systemic sclerosis
Yang et al. [9]	2023	China	Interstitial lung diseases	83	[^{68} Ga]Ga-FAPI PET/CT can assess the profibrotic activity of interstitial lung diseases. Radiolabelled FAPI uptake was significantly related to lung function decline in patients with interstitial lung diseases
Röhrich et al. [10]	2022	Germany	Interstitial lung diseases	15	[^{68} Ga]Ga-FAPI PET/CT is a promising method for detecting fibrotic interstitial lung diseases and associated lung cancer
Wang et al. [11]	2022	China	Light-chain amyloidosis	30	[^{68} Ga]Ga-FAPI PET/CT is feasible in detecting myocardial fibroblast activation in patients with light-chain cardiac amyloidosis in correlation with myocardial remodeling. Radiolabelled FAPI uptake was significantly correlated with cardiac magnetic resonance, echocardiography, and clinical biomarkers
Sviridenko et al. [12]	2022	Austria	COVID-19	6	[^{68} Ga]Ga-FAPI PET/CT may detect pulmonary fibrosis in patients with long-term CT abnormalities after severe COVID-19
Luo et al. [13]	2021	China	IgG-4 related disease	26	[^{68} Ga]Ga-FAPI PET/CT might be promising for the assessment of IgG4-related disease showing higher detection rate compared to [^{18}F]FDG PET/CT
Schmidkonz et al. [14]	2020	Germany	IgG-4 related disease	27	The combination of [^{18}F]FDG and [^{68} Ga]Ga-FAPI PET/CT may enable the discrimination between inflammatory and fibrotic activity in IgG4-related disease

The findings reported in this research article are very interesting; however, they should be confirmed by future large prospective studies, in particular comparing the diagnostic performance of FAPI PET/CT with that of radiolabelled white blood cell scintigraphy, which is currently considered the best nuclear medicine imaging modality to discriminate among periprosthetic joint infection and aseptic loosening [15].

Even if literature data on the applications of FAPI PET/CT in infectious, inflammatory, or rheumatological diseases are relatively lower in number compared to the oncological field, there is great attention by the scientific community on these applications ("watch it like a hawk"). The desirable increased availability of FAPI radiotracers worldwide will surely increase the research studies on these topics likely leading to the possible use of FAPI PET/CT in the clinical practice for selected infectious, inflammatory, or rheumatological conditions in the next years.

Author contribution All authors contributed to the manuscript writing. All authors read and approved the final manuscript.

Declarations

Competing interests The authors declare no competing interests.

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