Radiolabelled white blood cells or FDG for imaging of inflammation and infection?

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Nuclear medicine plays an important role in the management of patients with inflammatory and infectious diseases, especially when anatomical changes in inflammatory foci are absent or obscured. Several radiopharmaceuticals methods have been used for scintigraphic imaging of infectious and sterile inflammatory foci, including 67Ga-citrate, labelled white blood cells, antibodies, human immunoglobulin and antibiotics. Since the 1970s, scintigraphic imaging with labelled white blood cells has been the most frequently used nuclear imaging method for clinical diagnosis of infection and inflammation worldwide. The success of white blood cell scintigraphy is primarily due to its superb diagnostic accuracy. White blood cell scintigraphy comprises the isolation of autologous leukocytes, the \textit{ex vivo} labelling of these cells with either $^{99m}$Tc-HPMAO or $^{111}$In-oxine and reinjection of the labelled cells into the patient. The preparation of the radiopharmaceutical is the Achilles's heel of white blood cell imaging, because it requires a trained technician and special facilities. The procedure is laborious and time-consuming and requires the handling of the patient's blood, which could potentially be contaminated with pathogens. During the preparation of the radiopharmaceutical care should be taken that the leukocytes are not damaged, as this would result in leakage of the radioactivity from the cells, sticking of the labelled leukocytes to the vascular endothelium (especially in the microvasculature of the lungs) and loss of motility. Even when the leucocytes are handled correctly during labelling, release of $^{99m}$Tc-HPMAO from the labelled white blood cells after re-injection into the patient is still observed. The free $^{99m}$Tc-HPMAO is excreted via the hepatobiliary system and the kidneys, which may hamper image interpretation. This phenomenon is not observed with $^{111}$In-oxine labelled leukocytes. Still, $^{99m}$Tc-HPMAO labelled white blood cells are usually preferred for scintigraphy, because the radiation characteristics of $^{99m}$Tc are superior for gamma camera imaging. Despite the aforementioned drawbacks, white blood cell scintigraphy is still considered the method of choice for many applications. Especially when the correct imaging protocol is used (\textit{i.e.} early and delayed white blood cell imaging in combination with colloid imaging), the specificity of this method is very high. Further improvement of the diagnostic accuracy of white blood cell imaging can be achieved using hybrid single photon emission computed tomography (SPECT)-CT systems. By combining the anatomical information from the CT with the func-

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tional information of SPECT, the location of the inflammatory or infectious lesion can be pinpointed in a more precise manner. This would allow, for example, the discrimination between bone and soft tissue inflammation, which can have a significant impact on patient management.

In the last decade, the distribution of PET and hybrid PET-CT cameras and the availability of $[^{18}F]$FDG have strongly increased, due to the reimbursement of fluorodeoxyglucose (FDG) positron-emission tomography (PET) in oncology. One of the disadvantages of $[^{18}F]$FDG in oncology is its lack of specificity. The tracer not only accumulates in tumours, but also in activated leukocytes that are present in inflammatory lesions. The accumulation of $[^{18}F]$FDG in leukocytes is being exploited more and more for infection and inflammation imaging. In fact, FDG PET is now increasingly replacing conventional imaging methods for infection and inflammation, including white blood cell scintigraphy, because FDG PET may have some intrinsic advantages over the conventional scintigraphic imaging techniques. With the exception of a few organs, physiological uptake of $[^{18}F]$FDG is low and clearance from non-target tissue is fast. Consequently, high-contrast images of inflammatory or infectious lesions can already be obtained with FDG PET early after tracer injection. Consequently, the diagnostics can be completed within a single visit to the hospital, which makes FDG PET a patient friendly procedure. In addition, the intrinsic characteristics of PET make it the preferred imaging technique over gamma camera imaging and SPECT. As compared to planar imaging and SPECT, PET can provide 3D images with significantly higher spatial resolution images and higher sensitivity, because image acquisition does not require the use of a lead collimator.

The entrance of FDG PET to the centre stage of inflammation and infection imaging has raised the question whether FDG PET, or white blood cell scintigraphy is the preferred imaging method. There is currently quite some confusion about the method of choice for infection and inflammation imaging, especially amongst non-experts. In many institutes, however, the selection of the imaging method is governed by the local situation, i.e. the infrastructure of the nuclear medicine department where the study is going to be performed. In many developing countries (but also in some developed countries), PET facilities, cyclotron and advanced radiopharmaceuticals are scarce or not available at all. Consequently, conventional scintigraphic imaging with $^{67}$Ga-citrate or labelled white blood cells are the only options remaining. However, even when the infrastructure is available, selection of the radiopharmaceutical may not be made on basis of scientific evidence, but on economical issues. The costs of FDG PET are much higher than those of labelled leukocytes scintigraphy. In contrast to several oncological applications, the use of FDG PET in the diagnosis of infection and inflammation is not covered by the Social security yet. In addition, one should keep in mind that $[^{18}F]$FDG merely detects enhanced glucose metabolism and therefore cannot discriminate between infection/inflammation and neoplastic disease. Consequently, the specificity of FDG is lower than that of labelled white blood cells and therefore, with exception of vascular prosthesis, the use of white blood cell scintigraphy is still to be considered the gold standard.

In order to combine the best of both worlds, scientists have labelled leukocytes with $[^{18}F]$FDG for white blood cell of infection and inflammation with PET. The preliminary results with this radiopharmaceutical were promising, but $[^{18}F]$FDG was found to be rapidly released from the labelled leukocytes. Labelling cells with $[^{18}F]$FDG is also time consuming and demands expertise, dedicated personnel and special equipment. Thus, this technique is even more expensive than $[^{18}F]$FDG PET. In addition, the physical half-life of fluorine-18 (110 min) is too short for delayed imaging, which might reduce the specificity of the radiopharmaceutical. Still, the combination of labelled white blood cells with PET imaging is an attractive approach, but better labelling agents are required.

In this monographic issue of the Quarterly Journal of Nuclear Medicine and Molecular Imaging, a selection of experts in the field of infection and inflammation imaging have reviewed the literature and analyzed the role of FDG-PET and white blood cell scintigraphy in clinical diagnosis. For many indications, the available literature on FDG PET is still somewhat limited. However, the data published so far suggest that FDG PET and white blood cell scintigraphy could have a complementary, rather than a competitive role in infection and inflammation imaging. For most applications, white blood cell scintigraphy has a superior diagnostic accuracy than FDG PET, but in situations where white blood cell scintigraphy performs poorly (e.g. vasculitis), FDG PET can be of added value. On the other hand, it can be expected that FDG PET will
get a more prominent role in infection and inflammation diagnosis in the future, not because of its diagnostic performance, but simply because it is less labo-
rious and time-consuming than white blood cell scintigraphy.

References