

Editorial

Molecular Imaging of Inflammation/Infection: The Future of Disease Management

Abstract: In the field of inflammation/infection imaging, nuclear medicine techniques offer non-invasive tools to detect early pathophysiological changes before the development of anatomical changes detected by radiological procedures and, often, before clinical onset of symptoms. This field has been recently developed with several new radiopharmaceuticals for SPECT and PET used to define new strategies for imaging immune cells as well as pathogens.

In particular, we count now several dozens of new radiopharmaceuticals designed for bacterial imaging and new peptides and antibodies for imaging neutrophils, T-cells, B-cells and macrophages.

These may have important applications not only for diagnostic purposes but also for prognostic purposes, therapy decision making and for early follow-up of therapy efficacy, thus allowing us to define specific therapies for each individual patient.

Inflammatory disorders, infections and cancer, have a tangible impact for health and social costs. For this reason, it is advisable to establish, in each hospital, a multi-disciplinary team of experts for the management of patients with chronic inflammatory/infectious diseases, as well as for cancer patients, to optimize diagnostic protocols, therapy decision and follow-up. Nowadays, among the several imaging modalities available, nuclear medicine techniques play a secondary role after radiation-free methods such as ultrasound (US) and Magnetic Resonance Imaging (MRI). Nevertheless, a multidisciplinary approach combining radiology and nuclear medicine often represents a suitable diagnostic, prognostic, and monitoring tool in patient management. Nuclear medicine techniques, in particular, offer non-invasive tools to detect early pathophysiological changes before the development of anatomical changes detected by radiological procedures and often before clinical onset of symptoms.

Hence, this monographic issue is well-timed for providing clinicians current knowledge on molecular imaging in inflammatory disorders and infections, since an early and accurate diagnosis represents an important step to prevent serious or long-lasting complications as well as to monitor therapeutic responses.

Functional imaging with radiopharmaceuticals has been shown to detect inflammatory processes with high sensitivity and specificity and constitute the basis of molecular imaging with Positron Emission Tomography (PET) or Single-Photon Emission Computed Tomography (SPECT).

These techniques are also of great importance for therapy decision making and in monitoring response to therapy. Thanks to the possibility of deeply understanding the nature of an inflammatory process and what cells or cytokines are present in the inflamed site we are now able to decide the most appropriate therapy and to verify its efficacy.

As an example, I could mention the role of ^{99m}Tc -anti-TNF α antibodies [1-5] or ^{99m}Tc -anti-CD20 antibodies [6, 7] or ^{99m}Tc -octreotide [8, 9] in patients with rheumatic diseases, or the role of ^{99m}Tc -Interleukin-2 in patients with Type 1 diabetes [10, 11], or the role of ^{99m}Tc -labelled antibiotics in defining the nature of pathogen causative of an infection [12], or other radiopharmaceuticals in neuro-inflammation [13] and heart inflammation [14].

Along this line, many other radiopharmaceuticals have been developed and studied including those for targeting chemotaxis, cell recruitment, matrix metalloproteinase production, macrophage metabolism, angiogenesis, and several other specific against cells and soluble antigens involved in inflammatory and infective diseases as reviewed in this issue by Signore *et al.* [15] and Sollini *et al.* [16]. The approach of specific imaging of bacteria has been reviewed by Ebenhan *et al.* [17] whereas the new radiopharmaceuticals labelled with ^{68}Ga for PET imaging have been reviewed by Vorster *et al.* [18].

It must be clarified, however, that in some pathological condition it is not so relevant to use a highly specific radiopharmaceutical, being more relevant its high sensitivity or even the strategy used for image acquisition that could improve the disease specificity of a non-highly specific radiopharmaceutical as clearly explained by S. Skehan and M. Peters in early 2000 [19, 20] and others [21].

The understanding of the properties of radiopharmaceuticals and of the most appropriate image acquisition modality, relies on the success of the use of radiolabelled neutrophils [22-24] and on the use of ^{18}F -FDG in certain specific pathological conditions [25-27] as also reviewed by Ankrah *et al.* in case of fungal infections in children [28] or as described by Keidar in case of diabetic infections [29] or by Palestro *et al.* in case of fever of unknown origin [30].

REFERENCES

- [1] Lambert B, Carron P, D'Asseler Y, *et al.* (^{99m}Tc)-labelled S-HYNIC-certolizumab pegol in rheumatoid arthritis and spondyloarthritis patients: A bio-distribution and dosimetry study. *EJNMMI Res* 2016; 6(1): 88.
- [2] Carron P, Lambert B, Van Praet L, *et al.* Scintigraphic detection of TNF-driven inflammation by radiolabelled certolizumab pegol in patients with rheumatoid arthritis and spondyloarthritis. *RMD Open* 2016; 2(1): e000265.
- [3] Lopes FP, de Souza SA, Dos Santos Teixeira Pde F, *et al.* ^{99m}Tc -Anti-TNF- α scintigraphy: A new perspective within different methods in the diagnostic approach of active Graves ophthalmopathy. *Clin Nucl Med* 2012; 37(11): 1097-101.
- [4] Vis R, Malviya G, Signore A, *et al.* ^{99m}Tc -anti-TNF- α antibody for the imaging of disease activity in pulmonary sarcoidosis. *Eur Respir J* 2016; 47(4): 1198-207.
- [5] Galli F, Lanzolla T, Pietrangeli V, *et al.* *In vivo* evaluation of TNF-alpha in the lungs of patients affected by sarcoidosis. *Biomed Res Int* 2015; 2015: 401341.
- [6] Malviya G, Anzola KL, Podestà E, *et al.* (^{99m}Tc)-labeled rituximab for imaging B lymphocyte infiltration in inflammatory autoimmune disease patients. *Mol Imaging Biol* 2012; 14(5): 637-46.
- [7] Malviya G, Conti F, Chianelli M, Scopinaro F, Dierckx RA, Signore A. Molecular imaging of rheumatoid arthritis by radiolabelled monoclonal antibodies: New imaging strategies to guide molecular therapies. *Eur J Nucl Med Mol Imaging* 2010; 37(2): 386-98.
- [8] Anzola-Fuentes LK, Chianelli M, Galli F, *et al.* Somatostatin receptor scintigraphy in patients with rheumatoid arthritis and secondary Sjögren's syndrome treated with Infliximab: A pilot study. *EJNMMI Res* 2016; 6(1): 49.
- [9] Migliore A, Signore A, Capuano A, *et al.* Relevance of ^{99m}Tc -HYNIC-tir-octreotide scintigraphy in a patient affected by sarcoidosis with lung and joints involvement and secondary Sjogren's syndrome treated with infliximab: Case report. *Eur Rev Med Pharmacol Sci* 2008; 12(2): 127-30.

- [10] Signore A, Capriotti G, Chianelli M, *et al.* Detection of insulinitis by pancreatic scintigraphy with ^{99m}Tc-labeled IL-2 and MRI in patients with LADA (Action LADA 10). *Diabetes Care* 2015; 38(4): 652-8.
- [11] Chianelli M, Parisella MG, Visalli N, *et al.* Pancreatic scintigraphy with ^{99m}Tc-interleukin-2 at diagnosis of type 1 diabetes and after 1 year of nicotine therapy. *Diabetes Metab Res Rev* 2008; 24(2): 115-22.
- [12] Auletta S, Galli F, Lauri C, Martinelli D, Santino I, Signore A. Imaging bacteria with radiolabelled quinolones, cephalosporins and siderophores for imaging infection: A systematic review. *Clin Transl Imaging* 2016; 4: 229-252.
- [13] Gargiulo S, Coda AR, Panico M, *et al.* Molecular imaging of neuroinflammation in preclinical rodent models using positron emission tomography. *Q J Nucl Med Mol Imaging* 2017; 61(1): 60-75
- [14] Juneau D, Erthal F, Alzahrani A, *et al.* Systemic and inflammatory disorders involving the heart: The role of PET imaging. *Q J Nucl Med Mol Imaging* 2016; 60(4): 383-96.
- [15] Signore A, Anzola KL, Auletta S, Varani M, Galli F, Lauri C. Current status of molecular imaging in inflammatory and autoimmune disorders. *Curr Pharm Des* 2018; 24(7): 743-53.
- [16] Sollini M, Lauri C, Boni R, Lazzeri E, Erba PA, Signore A. Current status of molecular imaging in infections. *Curr Pharm Des* 2018; 24(7): 754-71.
- [17] Ebenhan T, Elena Lazzeri E, Gheysens O. Imaging of bacteria: Is there any hope for the future based on past experience? *Curr Pharm Des* 2018; 24(7): 772-86.
- [18] Vorster M, Buscombe J, Saad Z, Sathegke MM, Past and future of Ga-citrate for infection and inflammation imaging. *Curr Pharm Des* 2018; 24(7): 787-94.
- [19] Skehan SJ, White JF, Evans JW, *et al.* Mechanism of accumulation of ^{99m}Tc-sulesomab in inflammation. *J Nucl Med* 2003 Jan;44(1):11-8.
- [20] Skehan SJ, White JF, Evans JW, *et al.* Mechanism of Accumulation of ^{99m}Tc-Sulesomab in Inflammation. *J Nucl Med* 2005; 46(1): 382-383.
- [21] Malherbe C, Dupont AC, Maia S, *et al.* Estimation of the added value of ^{99m}Tc-HMPAO labelled white blood cells scintigraphy for the diagnosis of infectious foci. *Q J Nucl Med Mol Imaging* 2017; doi: 10.23736/S1824-4785.17.02964-8.
- [22] Love C, Marwin SE, Tomas MB, *et al.* Diagnosing infection in the failed joint replacement: A comparison of coincidence detection 18F-FDG and ¹¹¹In-labeled leukocyte/^{99m}Tc-sulfur colloid marrow imaging. *J Nucl Med* 2004; 45(11): 1864-71.
- [23] Erba PA, Glaudemans AW, Veltman NC, *et al.* Image acquisition and interpretation criteria for ^{99m}Tc-HMPAO-labelled white blood cell scintigraphy: results of a multicentre study. *Eur J Nucl Med Mol Imaging* 2014; 41(4): 615-23.
- [24] Heiba S, Knešarek K. Evaluation of diabetic foot infection in nuclear medicine. *Q J Nucl Med Mol Imaging* 2017; 61(3): 283-91.
- [25] Jamar F, Buscombe J, Chiti A, *et al.* EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. *J Nucl Med* 2013; 54(4): 647-58.
- [26] Bucerius J. Monitoring Vasculitis with 18F-FDG PET. *Q J Nucl Med Mol Imaging* 2016; 60(3): 219-35.
- [27] Erthal F, Juneau D, Lim SP, *et al.* Imaging of cardiac sarcoidosis. *Q J Nucl Med Mol Imaging* 2016; 60(3): 252-63.
- [28] Ankras AO, Klein HC, Span LFR, *et al.* The role of PET in monitoring therapy in fungal infections. *Curr Pharm Des* 2018; 24(7): 795-805.
- [29] Keidar Z. FDG PET/CT imaging in diabetic patients - A special emphasis on imaging of infection. *Curr Pharm Des* 2018; 24(7): 806-13.
- [30] Palestro CJ, Love C. Nuclear Medicine imaging in fever of unknown origin: The new paradigm. *Curr Pharm Des* 2018; 24(7): 814-20.

Alberto Signore

Nuclear Medicine Unit
Department of Medical-Surgical Sciences and
Translational Medicine
Faculty of Medicine and Psychology
“Sapienza” University of Rome, Rome
Italy

Paola Anna Erba

Regional Center of Nuclear Medicine
Department of Translational Research and
New Technologies in Medicine
University of Pisa, Pisa
Italy